16. Appendices

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Celerion Project No.: AA98497

Sponsor Project No.: YPL-001-YJP-130403

IND No.: 114903

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

1. PROTOCOL REVISION HISTORY

DATE/NAME	DESCRIPTION
08-Jun-2016 by Caroline Engel	Final Protocol, Amendment 7 This protocol amendment is generated to allow patients on low dose of aspirin for prophylactic treatment, since acetylsalicylic acid is a reversible non-competive inhibitor. However a washout of 7 days prior the main PK days and the bronchoscopy procedures will be required. Therefore the following sections were updated accordingly with the new text added in bold: 1. Section 13.3.3 Exclusion Criteria – Exclusion criterion #19 was updated as follow: Use of any drugs or substances known to be significant inhibitors (strong or moderate) of UDP-glucuronosyltransferase (UGT) (such as 17-beta-estradiol glucuronide, flavonoids [citrus fruit], silybin [herb supplement milk thistle]) and/or sulfotransferases (SULT) (refer to Appendix 1), within 12 hours prior to Day 1 of the Run-in Period. **The use of low dose of acetylsalicylic acid (e.g., aspirin) will be allowed during the study, but prohibited 7 days prior to the bronchoscopy performed prior to dosing of Day 1 until the last PK blood sample collected on Day 1, and 7 days prior to Day 54 (± 1 day) dosing until completion of the bronchoscopy procedures on Day 56.** Additional sources may be consulted by the PI or medical monitor to confirm lack of PK/PD interaction with study drug. 2. Section 13.3.5.1.1 Prohibited Therapy – bullet #8 was updated as follow: Drugs or substances known to be significant inhibitors (strong or moderate) of UGT and/or SULT, within 12 hours prior to Day 1 of the Run-in Period and through collection of the final PK sample. **The use of low dose of acetylsalicylic acid (e.g., aspirin) will be allowed during the study, but prohibited 7 days prior to the bronchoscopy performed prior to dosing of Day 1 until the last PK blood sample collected on Day 1, and 7 days prior to Day 54 (± 1 day) dosing until completion of the bronchoscopy procedures on Day 56.** 3. Minor editorial corrections were made where applicable.
28-Apr-2016 by Caroline Engel	Final Protocol, Amendment 6 This protocol amendment is generated to change the Sponsor representative, CEO and President, to Su-Jun Park. Therefore Section 2 Sponsor – Signatories was updated accordingly. And to add the following Investigator and clinical site: Faisal Fakih, MD Florida Pulmonary Research Institute, LLC 1788 W. Fairbanks Avenue,Suite B Winter Park, Florida, 32789

DATE/NAME	DESCRIPTION
28-Apr-2016 by Caroline Engel	United States Tel.: +1 407 740-8078 Therefore, Section 3 Investigators Signatures was updated accordingly. Section 4 Additional Key Contacts for the Study was also updated to add the corresponding certified clinical laboratory. In addition, the following changes were made to facilitate the clinical conduct at each investigative site: 1. To allow patients to recover from the bronchoscopy procedure before going through a 12 hours' period of PK blood draws and collect quality samples, a recovery period was added between these procedures; Procedures scheduled on Day -1 will now be performed within 3 days prior to Day 1 (now defined as Check-in procedures). In addition, the PK sampling previously scheduled on Day 56 will be conducted on Day 54 (± 1 day) before the bronchoscopy now scheduled on Day 56, instead of Day 55. Therefore, the following sections were updated acccordingly: • Section 5 Synopsis - Summary of Study Design, Dosage, Dosage Form, Route, and Dose Regimen, and Exploratory Outcome Measures. • Section 6 Study Events Flow Chart • Section 13.1 Overall Study Design and Plan • Section 13.2.4 Treatment Period (Days 1 to 56) • Section 13.2.4.1 Meal Schedule • Section 13.3.5.2 Prohibitions • Section 13.4.1.2 Drug Administration During Treatment Period • Section 14.3.1 Pulmonary Function (Spirometry) • Section 14.3.4.1 Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) • Section 15.1.2 Patients to Analyze • Section 15.1.6.1.1 Plasma • Section 15.1.6.2 Statistical Methods for Pharmacokinetic Analyses 2. To provide flexibility in the schedule of events, electrocardiograms, vital sign and pulse oximetry will be measured within 4 hours of bronchoscopy procedures, instead of 2 hours. Therefore, Section 6 Study Events Flow Chart, Section 14.1.3 Vital Signs, Section 14.1.4 Pulse Oximetry, and Section 14.1.5 Electrocardiogram Monitoring were updated accordingly. 3. Exclusion criterion #9 was updated to clarify that patients withclinically significant cardiac arrhythmia; prostatic hyperplasia; bladder-neck obstruction; urinary retention; and narrow-angle glaucoma that, in the opinion of the PI, would contraindicate the administration of tiotropium, will be excluded.

DATE/NAME	DESCRIPTION
28-Apr-2016 by Caroline Engel	4. To allow flexibility, subjects with a positive alcohol screen or subjects reporting consumption of alcohol within 48 hours prior to testing, an alcohol test may be rescheduled or repeated, at the discretion of the PI if there is sufficient time remaining to perform the visit procedures within the time window specified for this visit (e.g., ± 2 days of Day 15 visit). Therefore exclusion criterion # 13 was split into two exclusion criteria; criteria #13 (alcohol screen) and #14 (drug screen), which were updated accordingly. 5. Exclusion criterion #15 was updated to exclude subject with a positive results for hepatitis C antibodies only if they present with clinically significant liver impairment and/or a viral ribonucleic acid (RNA) titer of > 6.9 ± 0.8log molecules/mL. Section 14.1.6.3 Serology was updated accordingly. Section 17 Reference was updated to include reference #3 as a justification to the titer value selected. 6. The Child-Pugh scale should only be used to classify patients with a diagnosis of hepatic impairment. Thus, exclusion criteria #11 was clarified to exclude patients with diagnosed hepatic impairment and a Child-Pugh class A score or higher. Patients without hepatic impairment with normal laboratory results for bilirubin, albumin, prothrombin time/international normalized ratio (which automatically would fall in a Class A Score of 5) will not be assigned a Child-Pugh score and will thus be allowed to enrol. In addition, to assess the extent of hepatic impairment according to exclusion criterion # 11, a blood sample for prothrombin time/international normalized ratio will be collected at screening. Thus, a new section (14.1.6.9 Additional Tests) was added, and Section 6 Study Events Flow Chart, Section 8 Abbreviations, and Table 5: Blood Volume during Study were updated accordingly. 7. Prescribed vitamin supplement will be allowed, therefore the following sections were updated accordingly: • Section 13.3.5.1.1 Prohibited Therapy • Section 13.3.5.1.2 Permitted Therapy 8. Minor editorial and typographical corrections were made where applicable.
05-Nov-2015 by Caroline Engel	Final Protocol, Amendment 5 This protocol amendment is generated to add the following Investigator and clinical site: Samir Arora, MD Aventiv Research Inc. 99 North Brice Road, Suite 260 Columbus, Ohio 43213 United States Tel: + 1 614 501-6164 Therefore, Section 3 Investigators Signature was updated accordingly. Section 4 Additional Key Contacts for the Study was also updated to add

DATE/NAME	DESCRIPTION
05-Nov-2015 by Caroline Engel	the correcponding certified clinical laboratory. All 3 sites clinical sites will be using the Western Institutional Review Board. Section 4 Additional Key Contacts for the Study was updated accordingly. Minor editorial corrections were made where applicable.
16-Sep-2015 by Caroline Engel	Final Protocol, Amendment 4 This protocol amendment is generated to clarify and adjust study procedures as listed below: 1. Brigham and Women's Hospital Investigator signature and contact information was removed throughout the protocol since the center will not be participating during this study. The following sections were updated accordingly: • Section 3 Investigators Signatures • Section 4 Additional Key Contacts for the Study 2. The age limits were changed from 40 - 80 years of age, inclusively, to 30 - 85 years of age, inclusively. The following sections were updated accordingly: • Section 5 Synopsis - Study Population • Section 13.3.2 Inclusion Criteria – Inclusion criterion #1 3. To provide scheduling flexibility to the patients, a ±2-day window was added to the return visits on Days 15, 29, and 43. The following sections were updated accordingly: • Section 5 Synopsis - Summary of Study Design and Exploratory Outcome Measures • Section 6 Study Events Flow Chart • Section 13.1 Overall Study Design and Plan • Section 13.4.1.2 Drug Administration During Treatment Period • Section 15.1.6.2 Statistical Methods for Pharmacokinetic Analyses 4. Breathalyzer was added as an alternative method to the urine dipstick for the alcohol screen. The following sections were updated accordingly: • Section 6 Study Events Flow Chart • Section 13.3.3 Exclusion Criteria – Exclusion criterion #13 • Section 14.1.6.7 Urine/Breathalyzer Alcohol Screen was added • Section 14.1.6.8 (previously 14.1.6.7) was renamed Urine Drug Screen (previously Urine Drug/Alcohol Screen). 5. Only patients suffering from severe sleep apnea, as assessed by the Berlin Questionnaire, will be excluded from the study; The following

DATE/NAME	DESCRIPTION
16-Sep-2015 by Caroline Engel	sections were updated accordingly: • Section 6 Study Events Flow Chart • Section 13.3.3 Exclusion Criteria - exclusion criterion #8. • Section 14.1.8 Berlin Questionnaire was added. 6. The body mass index upper limit was increased from 32.0 kg/m^2 to 40.0 kg/m^2 inclusively. Therefore inclusion criterion #5 of Section 13.3.2 Inclusion Criteria was revised accordingly. 7. Drug screen false positive will be allowed if they are due to the use of prescription medication following approval from the PI and the medical monitor, the exclusion criterion #13 of Section 13.3.3 Exclusion Criteria was revised accordingly. 8. Smoking restriction prior to the bronchoscopy procedures was removed. Therefore, Section 14.3.2 Bronchoscopy and Bronchoalveolar Lavage (BAL) Biomarkers was updated accordingly. 9. Only strong and moderate inhibitors of UDP-glucuronosyltransferase and/or sulfotransferases are prohibited, therefore to prevent confusion with the list of substrats that was provided in Appendix 1, Appendix 1 was remove and the only 3 inhibitors listed in that table was enumarated in exclusion criterion #18. The list of substrate in appendix 2 (now rename Appendix 1) was also remove. This change will prevent possible confusion with the lists provided in the appendices. Exclusion criterion #18 of Section 13.3.3 Exclusion Criteria was revised accordingly. 10. To be consistent with Section 6 Study Events Flow Chart, pulse oximetry was added to the order of procecedures listed in Section 14.1 Safety Assessments. 11. Typographic and editorial corrections were made where applicable.
23-Apr-2015 by Caroline Engel	Final Protocol, Amendment 3 This protocol amendment is generated to clarify and adjust study procedures as listed below. The changes to the protocol are presented with new text in **bold** font and deleted text in ~~strikethrough~~ font. **Serious Adverse Event Contact Information** Drug Safety Solution's Medical Monitor will be contacted in case of serious adverse events. Hence the information under Sponsor Contact for Serious Adverse Events (Medical Monitor) in Section 4 Additional Key Contacts for the Study was corrected as follows: ~~Primary Contact:~~ ~~Yongnam Lee, Ph.D.~~ ~~Principal Scientist,~~ ~~Yungjin Pharm. CO., LTD.~~ ~~#451-20 Cheonho-3 dong, Gangdong-gu, Seoul, 134-721, Republic of Korea~~

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	~~Tel.: +82-(31) 546-6980 ext. 220~~ ~~Fax: +82-(31) 546-6983~~ ~~E-mail: nami0209@yungjin.co.kr~~ ~~Mobile: +82-(10) 6311-4228~~ ~~Secondary Contact:~~ ~~Kangrae Ha, B.Sc.~~ ~~E-mail: hakr@yungjin.co.kr~~ **Dr. Kathy Smith** **Drug Safety Solution** **Tel.: +1 919 264-5626** **E-mail: ksmith@drugsafety.biz** Section 14.1.8.4 Serious Adverse Events and Section 13.4.3.2 Procedures for Breaking the Blind Prior to Study Completion was also corrected accordingly. **Certified Clinical Laboratory:** Brigham and Women's Hospital and UAB Lung Health Center clinical laboratories contact information were added to Section 4 Additional Key Contacts for the Study. **Clinical Indication:** As indicated in the objectives of the study, the study will examine the pharmacodynamic (PD) effect of YPL-001 in patients with chronic obstructive pulmonary disease (COPD) only. Therefore, to prevent potential confusion and to capture the intended indication of the study specifically “asthma” was removed from the Clinical Indication in Section 5 synopsis and Section 10.1 Purpose of the Study. **Study Population:** As indicated throughout the protocol, patients will be will be adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3). Hence to be consistent with the GOLD Stage standards, the first sentence under Study Population from Section 5, Synopsis was corrected as follow: “Patients will be adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3) with a predominant bronchitic component ~~and a history of frequent (>2/year) COPD exacerbations,~~ between 40 and 80 years of age (inclusive).” **Randomization and Drug Dispensing** Instruction for randomization and drug dispensing are provided in a separate document. To be consistent with this document, which states that two sets of randomization code envelopes will be provided to site pharmacist/study coordinators and patients will received appropriately

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	labeled kits and/or any unused wallets from previously provided kits (when applicable) for YPL-001 home dosing in addition to the containers for tiotropium/albuterol home dosing, the following section were modified accordingly: • Section 5 Synopsis under Summary of Study Design and Study Products • Section 6 Study Event Flow Chart, Day 1 Study Drug Administration at CRU - Footnotes “k” and “p” • Section 6 Study Event Flow Chart, Days 2 to 55 Study Drug Administration at Home – Footnotes “j” and “o” • Section 13.1 Overall Study Design and Plan • Section 13.4.1.2 Drug Administration During Treatment Period • Section 13.4.3.1 Maintenance of Randomization • Section 13.4.3.2 Procedures for Breaking the Blind Prior to Study Completion In addition, and “X” was also added in the “Randomization” row under Day 1 predose in Section 6 Study Events Flow Chart. **Fasting Conditions** As indicated throughout the protocol, subjects will be required to fast for at least 8 hours before and 4 hours after YPL-001/placebo morning administration on Days 1 and 56. For clarity, footnote “q” was added to Day 1 Study Drug Administration at CRU and footnote “k” was added to Day 56 Study Drug Administration at CRU in Section 6 Study Events Flow Chart. **Analytes to be Measured** As indicated throughout the protocol, blood samples will be collected for the analyses of verproside and picroside II in plasma. Hence, the row identified as “Blood for Verproside Phamacokinetics” on Day 56 of Section 6 Study Events Flow Chart, was corrected to read: “Blood for Verproside **& Picroside II PK**”. **End-of-Treatment – Early Termination Procedures** All procedures listed under End-of-Treatment/Early Termination column in Section 6 Study Events Flow Chart are also scheduled to be performed on Day 55 before the bronchoscopy procedures. Therefore, as it is not required to repeat these procedures for two consecutive days, End-of-Treatment procedures were removed on Day 56, however early termination (ET) procedures were listed under the new ET column. Hence, the following sections were corrected accordingly. • Section 6 Study Events Flow Chart • Section 13.2.4.2 End-of-Treatment or Early Termination (Day 56), (renamed Section 13.2.4.2 Early Termination). • Section 13.3.2 Inclusion Criteria – Criterion #16 • Section 13.3.4 Removal of Patients from the Study

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	• Section 13.3.5.1.1 Prohibited Therapy • Section 13.3.5.1.2 Permitted Therapy • Section 14.1.8.2 Monitoring • Section 14.5 Blood Volume for Study Assessments (Table 5: Blood Volume during Study) In addition, the following sentence was added to Section 13.2.4.2 End-of-Treatment or Early Termination (Day 56), (renamed Section 13.2.4.2 Early Termination): "Patients who want to terminate from the study and are not currently on-site will be contacted and asked to return to the CRU to perform the early termination procedures" **Investigator's Brochure Version** In Section 9.1 YPL-001, the Investigator's Brochure version was updated to reflect the reference section and the most recent version of the Investigator's Brochure. **Method of Blood Collection** Throughout the protocol, the option of using an angiocatheter was added. Hence, the following sections were corrected accordingly: • Section 11 Risk/Benefit • Section 14.3.3 Blood Biomarkers • Section 14.4.1 Blood Sampling and Processing • Section 14.5 Blood Volume for Study Assessments **Recording of Meal** To be consistent with clinical sites standard procedures, the last sentence of Section 13.2.4.1 Meal Schedule was corrected as follow: "Meals are not required to be completed by patients ~~and all meals and snacks eaten by patients will be recorded on the CRFs~~.' **Coffee, Tea and Alcohol Prohibition** As indicated in Section 13.3.5.2 Prohibitions, coffee tea, and red wine will be restricted for 7 days prior to Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample. Beer will be restricted for 14 days prior to Day 1 of the Treatment Period through collection of Day 56 last PK sample. Any other product containing xanthines or caffeine will be restricted 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample. Any other alcohol product will be restricted 48 hours prior to each CRU visit, 48 hours prior to dosing on Days 1 and 56 last PK sample. Hence, the xanthines/caffeine prohibition and the alcohol prohibition were corrected as follows for clarification: "Xanthines/caffeine **(other than coffee and tea)**: 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period

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23-Apr-2015 by Caroline Engel	through collection of Days 1 and 56 last PK sample." "Alcohol **(other than red wine and beer)**: 48 hours prior to each CRU visit, 48 hours prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample." **e-Diary** Home dosing will be recorded using a yes/no answer in the e-diary. Therefore the last sentence of the second to last paragraph of Section 13.4.1.2 Drug Administration During Treatment Period was corrected as follows: ***"***Patients will be given instructions on ~~recording of dosing times~~ **how to record their drug administration** in their e-diary on home-dosing days.' In addition, estimation of sputum quantity was added to the list of major symptoms of COPD exacerbation recorded daily by the patients on their e-diary, "color" and "consistency" was moved as example of sputum quality, and a statement indicating that the e-diary device will be return in case of early termination was also added. Hence, the following sections were corrected accordingly: • Section 5 Synopsis under Secondary Outcome Measures • Section 5 Synopsis under Summary of Study Design • Section 6 Study Events Flow Chart – Day 1, Footnote "j" • Section 6 Study Events Flow Chart – Days 2-55, Footnote "i" • Section 6 Study Events Flow Chart – Day 56, Footnotes "g" and "h" • Section 12.2 Study Endpoints • Section 13.1 Overall Study Design and Plan • Section 13.2.3 Run-In Period (Days 1 to 14 [± 2 days]) • Section 13.2.4 Treatment Period (Days 1 to 56) • Section 14.2.1 Electronic Diary • Section 14.2.3 Symptoms of Chronic Obstructive Pulmonary Disease Exacerbation **Treatment Compliance** Drug administration at home will be monitored by HGE Technologies Inc. via the e-diary. Therefore, the last sentence of Section 13.4.4. Treatment Compliance was corrected as follow: "Self-administration by patients at home will be monitored ~~by the CRU~~ via the e-diary and attempted phone calls will be performed to remind patients to take their medication, if they did not record their self-administration on the e-diary." **Oxygen Saturation** For consistency throughout the protocol, "oxygen levels, saturation (%)" was replaced with "oxygen saturation (%)."

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	**Tiotropium Treatment** As indicated in Section 13.3.2 Inclusion Criteria and Section 13.3.5.1.2 Permitted Therapy, tiotropium will be withheld 24 hours prior to pulmonary function (spirometry) measurements. Hence, the 2nd paragraph of Section 14.3.1 Pulmonary Function (Spirometry), was corrected to read: "Short acting β2-agonist and anticholinergic bronchodilators (e.g., albuterol, ipratropium bromide) and long acting β2-agonist and anticholinergic bronchodilators (e.g., salmeterol, tiotropium) agents will be withheld approximately 4 and ~~12~~ **24** hours, respectively, before each pre-bronchodilator spirometry." **Spirometer Across Clinical Site** The 3rd paragraph of Section 14.3.1 Pulmonary Function (Spirometry) was corrected as follow: "Every effort will be made to perform all assessments for a given patient on the same instrument throughout the study~~ and all sites should be using the same brand and model of spirometer for this study~~." **Bronchoalveolar Lavage (BAL) Collection** It is planned that a maximum of 180 mL BAL will be performed during each planned bronchoscopy procedures. Therefore, to prevent confusion, the second sentence of Section 14.3.2.3, Bronchoalveolar Lavage (BAL) was corrected to read: "A **total of** 180 mL BAL**, using 6 x 30 mL aliquots of normal saline warmed to room temperature,** will be performed ~~in~~ **using** each subsegment of the right middle or lower lobe, as deemed appropriate by the Investigator~~, using 6 x 30 mL aliquots of normal saline warmed to room temperature~~." **Blood Volume for Clinical Safety Laboratory Tests, Pharmacodynamic (PD) Markers and Pharmacokinetic (PK) Samples:** Blood collection volume for PD markers, as indicated in Section 14.3.3 Blood Biomarkers and Section 14.5 Blood Volume for Study Assessments, only accounts for 1 tube. However, 3 tubes will be required to assess CRP (4 mL tube), fibrinogen (3.5 mL tube) and the rest of the PD biomarkers (6 mL tube). The blood volume per time point will be approximately 13.5 mL instead of 4.5 mL. As indicated above, End-of-Treatment listed on Day 56 were removed as the same tests are scheduled on Day 55 before the bronchoscopy procedures. Hence one sample was removed for a total of 3 on-study hematology and serum chemistry tests to be performed throughout the study. In addition, 4 mL of blood will be sufficient for the determination of verproside and picroside II concentration in plasma at each time point. Therefore the total blood volume was corrected to 310.5 mL for males and 317.5 mL for females. Section 14.3.3 Blood Biomarkers, Section 14.4.1 Blood Sampling and Processing, and Section 14.5 Blood Volume for Study

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	Assessments were corrected accordingly. Minor typographic and editorial corrections were made where applicable.
16-Feb-2015 by Caroline Engel	Final Protocol, Amendment 2 This protocol amendment is generated to clarify and adjust study procedures as listed below. **Number of Subjects:** The sample size was revised to 60 subjects as it is sufficient to meet the objectives of the study. In case of dropouts, discontinued patients may be replaced at the discretion of the Sponsor as indicated throughout the protocol. Therefore the following sections were corrected accordingly to indicate that at least 60 subjects are planned to be enrolled and randomized with 20 patients to receive one of the 3 treatments: • Section 5 Synopsis (the 1st sentence of the 2nd paragraph under Summary of Study Design and the 1st and 2nd sentences under Number of Patients). • The 1st sentence of the 2nd paragraph of Section 13.1 Overall Study Design and Plan. • The 1st and 3rd sentences of Section 13.3.1 Number of Patients. • The last sentence of Section 15.1.1 Sample Size Calculation. **Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) and COPD Assessment Test (CAT):** BDI/TDI and CAT questionnaires will not be used as a diagnostic tool to assess the patient's potential to meet all inclusion criteria and none of the exclusion criteria. Therefore these questionnaires are not required at screening. In addition, it is not required to perform them for 2 consecutive days to meet the study objectives and therefore, Day 55 assessments were removed. Section 6 Study Events Flow Chart was corrected accordingly. The first sentence in Section 14.3.4.1 Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) was also corrected to be consistent with Section 6. **Early Termination Procedures:** Weight, and oxygen levels, saturation (%), and heart rate assessed using a pulse oximeter were added to the procedures performed at the end of the Treatment Period on Day 56 or prior to early termination from the study to monitor subject's safety appropriately. A pulmonary function (spirometry) test was also added prior to early termination for safety monitoring. Section 6 Study Events Flow Chart was corrected accordingly.

DATE/NAME	DESCRIPTION
16-Feb-2015 by Caroline Engel	**Recording Concomitant Medication:** Concomitant medication will be recorded at each study visit by the clinical staff in to the electronic data capture system. Therefore, concomitant medications was removed from the list of events that will be recorded by the patients via their e-diary throughout the protocol. The following sections were corrected accordingly: • Footnotes in Section 6 Study Events Flow Chart. • The first sentence of the 4th paragraph of Section 13.2.3 Run-In Period (Days 1 to 14 [± 2 days]). • The 2nd sentence of the 2nd paragraph of Section 13.2.4 Treatment Period (Days 1 to 56). • The 2nd sentence of the first paragraph of Section 14.2.1 Electronic Diary. **Subject Numbering:** The first paragraph of Section 13.4.2 Method of Assigning Patients to Treatment Groups was modified to clarify that the screening number and randomization number are two separate identification number given to each subject at different stages of the study. **Adverse Events Reporting** Footnotes were added to clarify the rating severity definitions in Section 14.1.8.3 Reporting. Minor editorial and typographical corrections were made where applicable.
20-Nov-2014 by Ziv Machnes	Final Protocol, Amendment 1 This protocol amendment is generated to update the study population with regards to smoking frequency, to update the handling procedures for BAL samples, and to clarify other study procedures as listed below. **Study Population:** Section 13.3.2 - Inclusion Criteria, bullet 11 was updated to indicate that the study population will consist only of current and ex-smokers with a history of >10 pack years. As such, the indications for 'packs/year' were replaced with 'pack years' and the allowance for current smokers with <10 pack/years was removed. Wording was added to indicate an approximately equal number of current and ex-smokers will be enrolled, and that each treatment group will consist of an approximately equal number of smokers and ex-smokers. In addition, the stratification criteria for the randomization was updated to consist of either current or ex-smokers. The following sections were affected: • Section 5 – Synopsis (under Study Population and Number of Patients) • Section 13.1 - Overall Study Design and Plan (second paragraph)

DATE/NAME	DESCRIPTION
20-Nov-2014 by Ziv Machnes	• Section 13.3.1 – Number of Patients. • Section 13.4.2 - Method of Assigning Patients to Treatment Groups. **BAL Sample Handling:** Section 14.3.2.3 - Bronchoalveolar Lavage (BAL) was updated to indicate that sample handling, processing and storage procedures will be provided in a separate document. **Follow-up Procedures:** The wording in regards to follow-up procedures to be conducted on 14 days (± 2 day), after the last study drug administration, was updated to indicated a phone-call and not a visit, as indicated correctly in Section 6 – Study Event Flow Chart. Study event were updated accordingly. The following sections were affected: • Section 5 – Synopsis (under Duration of Participation for Patients, and Exploratory Outcome Measures [under Blood Assessments, Pulmonary Assessment, and Quality of Life Assessments]) • Section 13.3.5.2 – Prohibitions (under Alcohol) • Section 14.1.8.2 – Monitoring (first paragraph). **Study Duration:** The total duration of the study indicated in Section 5 – Synopsis (under Duration of Participation for Patients) was corrected to 12 weeks to correspond with the actual study duration as indicated throughout the protocol. **Inflammatory Markers in Blood Samples:** The list of cell types to be evaluated as part of the inflammatory markers in the blood was updated to include monocytes instead of macrophages, as macrophages are not expected to be present in blood. The following sections were affected: • Section 5 – Synopsis (under Study Objectives, fourth exploratory objective, and under Exploratory Outcome Measures [under Pharmacodynamic Assesments, Blood Assessments, first bullet]) • Section 12.1 - Study Objectives (fourth exploratory objective) • Section 12.2 - Study Endpoints (third exploratory endpoint) • Section 14.3.3 - Blood Biomarkers (first bullet) • Section 15.1.5.1 - Biomarkers (third bullet) **Neutrophil Evaluation in BAL Samples** Neutrophils were added to the list of cell types to be evaluated as a percentage of the total cell count in BAL samples. The following sections were affected: • Section 5 – Synopsis (under Study Objectives, second exploratory objective and under Exploratory Outcome Measures [under

DATE/NAME	DESCRIPTION
20-Nov-2014 by Ziv Machnes	Pharmacodynamic Assessments, Bronchoalveolar Lavage Assessments, second bullet]) • Section 12.1 - Study Objectives (second exploratory objective) • Section 12.2 - Study Endpoints (second exploratory endpoint) • Section 14.3.2.4 - Biomarkers (second bullet) • Section 15.1.5.1 – Biomarkers (second bullet) **Location of Study Drug Administration**: Wording was added in Section 6 – Study Events Flow Chart for Day 56, to clarify that the study drug will be administered at the CRU. **Meal Schedule**: The indication for fasting requirement in Section 13.2.4.1 – Meal Schedule, was corrected to indicate patients will fast overnight for at least 12 hours before bronchoscopy and BAL collection on Days -1 and 55 instead of Days -1 and 56, as correctly indicated in Section 6 – Study Events Flow Chart. **ECG Monitoring:** Following an update in Celerion's standard operating procedure, Section 14.1.5 – Electrocardiogram Monitoring was updated to include at least 5 minutes of rest prior to each ECG measurement (instead of at least 1 minute as previously indicated). **Hematology:** The tests included in the hematology panel Section 14.1.6.1 – Hematology were updated to indicate that the red blood cell (RBC) count will include a reticulocytes count, and that the white blood cell (WBC) count with differential will include monocytes but will not include reticulocytes. **Bronchoscopy and BAL:** Due to the sensitivity of YPL-001 components to UV light, a warning was added to protect all samples from exposure to UV light, as indicated for the PK blood samples. The following sections were affected: • Section 14.3.2.2 - Bronchial Brushings • Section 14.3.2.3 - Bronchoalveolar Lavage (BAL) **PK Population:** The indication for measurable concentration of verproside and picroside II in urine was removed from the definition of PK population in Section 15.1.2 - Patients to Analyze, as there is no urine PK sampling planned for this study. Minor typographic and editorial corrections were made where applicable.

DATE/NAME	DESCRIPTION
18-Sep-2014 by Caroline Engel	Final Protocol

2. SPONSOR – SIGNATORIES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

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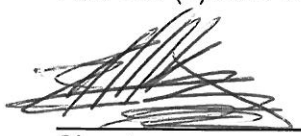

Signature

June 14, 2016

Date

3. INVESTIGATORS SIGNATURES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

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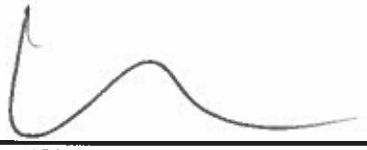

Investigator (Signature)

12/9/16

Date

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Investigator (Signature)

Date

3. INVESTIGATORS SIGNATURES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

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Investigator (Signature) _____ Date 6/10/2016

INVESTIGATORS SIGNATURES (*CONTINUED*)

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

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15 JUN 2016
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Date

INVESTIGATORS SIGNATURES (*CONTINUED*)

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

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Investigator (Signature) _____ 09 JUN 16 Date

4. ADDITIONAL KEY CONTACTS FOR THE STUDY

Sponsor Contact for Serious Adverse Events (Medical Monitor)	Dr. Kathy Smith Drug Safety Solution Tel.: +1 919 264-5626 E-mail: ksmith@drugsafety.biz
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Certified Clinical Laboratories	<u>For Temple University School of Medicine:</u> Yuri Persidsky, MD, Ph.D. Chairperson, Department of Pathology and Laboratory Medicine Professor, Pathology and Laboratory Medicine 3401 N. Broad Street Philadelphia, Pennsylvania, 19140 United States E-mail: Yuri.Persidsky@tuhs.temple.edu <u>UAB Lung Health Center:</u> UAB Hospital Laboratories 619 19th Street South Birmingham, Alabama, 35249 United States <u>Aventiv Research Inc.:</u> Quest Laboratories 6700 Steger Drive, Cincinnati, Ohio, 45237 United States

Certified Clinical Laboratories (continued)	Florida Pulmonary Research Institute, LLC: Quest Diagnostics 4225 E Fowler Avenue Tampa, Florida, 33617 United States Lab Director: Luis A. Diaz-Rosario, MD (FASCCP, FCAP), MT (FASCP) E-mail: luis.a.diaz-rosario@questdiagnostics.com
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Pharmacokinetic and Statistical Analyses	Celerion 100 Alexis-Nihon Boulevard Suite 360 Montreal, Quebec H4M 2N8 Canada Tel.: +1 514 744-9090 Fax: +1 514 744-8700 AND/OR Celerion 621 Rose Street Lincoln, Nebraska 68502 United States Tel.: +1 402 476-2811 Fax: +1 402 476-7598
Institutional Review Board Main Office Location	Western Institutional Review Board 1019 39th Avenue SE, Suite 120 Puyallup, Washington, 98374-2115 United States Tel.: +1 360 252-2500

5. SYNOPSIS

Compound:	YPL-001
Clinical Indication:	Treatment of inflammatory diseases of the respiratory tract such chronic obstructive pulmonary disease (COPD)
Study Type:	Phase 2a, proof of concept
Study Objectives:	The **primary objective** of the study is to assess the safety and tolerability of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients. The **secondary objective** of the study is to assess the number and magnitude of daily respiratory symptoms of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients. The **exploratory objectives** of the study are to evaluate the following in moderate to severe COPD patients: 1. To assess bronchoalveolar lavage (BAL) epithelial brushings for YPL-001 component levels. 2. To compare BAL samples for total cell count (cells/mL) macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; neutrophil, macrophage, lymphocyte and eosinophil counts as absolute inflammatory cell numbers in YPL-001 groups versus placebo group. 3. To compare BAL samples for tumor necrosis factors alpha (TNF-α), interleukin (IL)-1β, IL-4, IL-5, IL-6, IL-8, IL-13, myeloperoxidase (MPO), neutrophil elastase, monocyte chemotactic protein (MCP)-1, and matrix metalloproteinase (MMP)-9 in YPL-001 groups versus placebo group. 4. To compare blood inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) and concentrations of C-reactive protein (CRP), fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9 in YPL-001 groups versus placebo group. 5. To compare spirometric functions (forced expiratory volume in one second [FEV_1], forced vital capacity [FVC], FEV_1/FVC, and inspiratory capacity [IC]) in YPL-001 groups versus placebo group. 6. To compare patient reported outcomes (Baseline Dyspnea Index [BDI]/Transition Dyspnea Index [TDI], COPD Assessment Test [CAT]) in YPL-001 groups versus placebo group. 7. To assess verproside and picroside II concentration in plasma and BAL and verproside and picroside II pharmacokinetics (PK) in plasma following multiple oral doses administration of two YPL-001 dose levels.

Summary of Study Design:	This is a Phase 2a, proof-of-concept, multicenter, randomized, double-blind, double-dummy, 3-treatment, parallel study, with low and high YPL-001 doses (80 mg and 160 mg twice daily [BID]) and a placebo control in moderate to severe COPD patients. At least 60 patients will be enrolled and randomized into 3 treatment groups (20 patients per group). Patients will participate only once. Safety and tolerability will be assessed throughout the study. Assessment of respiratory symptoms and symptom burden in YPL-001 and placebo treatments will be performed daily through patient self-report of peak expiratory flow (PEF), major and minor symptoms of COPD exacerbation, dyspnea, and activity in their electronic diary (e-diary). Spirometry measurement, bronchoalveolar lavage (BAL), and blood samples will be collected for the pharmacodynamic (PD) assessment of YPL-001 and placebo treatments. Serial blood samples will also be collected for PK assessment of verproside (the principal active ingredient of YPL-001) and picroside II. Other components of YPL-001 and its metabolites may also be analyzed in plasma. Following screening, eligible patients will discontinue non permitted respiratory drugs if already receiving them and enter a 14 ± 2 days Run-in Period during which patients will be given albuterol taken on an as required basis and daily tiotropium 18 µg (one capsule inhaled daily in the morning) to be administered at home. On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their daily symptoms throughout the Run-in Period. Patients will return to the clinical research unit (CRU) in the morning within 3 days prior to Day 1 (define hereafter as Check-in) of the Treatment Period to confirm their eligibility and assess their health conditions. If they still meet all of the inclusion criteria and none of the exclusion criteria, they will undergo Check-in scheduled study procedures. Patients will return to the CRU on the morning of Day 1 to be randomized and receive one of the 3 treatments and undergo all scheduled study procedures. Patients will return on the morning of Days 15 (± 2 days), 29 (± 2 days), 43 (± 2 days), 54 (± 1 day), and 56 of the Treatment Period for study drug administration and procedures. Prior to each release from the CRU, patients will receive a properly labeled YPL-001 kit (and/or any unused wallets from previously provided kits [when applicable]) and tiotropium/albuterol container with sufficient doses which will be self-administered by patients at home until the next morning visit at the CRU. Patients will continue recording their daily symptoms via the e-diary throughout the Treatment Period. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff. The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any adverse event (AE) has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary. Patients will be instructed to call the Investigator if breathing worsens or if they need to take more than 8 puffs per day of albuterol for more than 2 consecutive days. If the Investigator determines that the patient is too unstable to continue in the study, he/she will be discontinued. Rescue medication will be used for any patient with an exacerbation of COPD and

	will be administered in accordance with the study center standard of care.
Study Population:	Patients will be adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3) with a predominant bronchitic component, between 30 and 85 years of age (inclusive). An approximately equal number of current and ex-smokers will be enrolled.
Number of Patients:	The study is planned to enroll at least 60 patients. Patients will be divided in 3 treatment groups with 20 patients to receive one of the 3 treatments (i.e., low and high YPL-001 doses [80 mg and 160 mg BID] and a placebo control) as per the randomization schedule. Each treatment group will consist of an approximately equal number of current and ex-smokers.
Duration of Participation for Patients:	The planned length of participation in the study for each patient is approximately 12 weeks (from Day 1 of the Run-in Period through completion of the follow-up procedures on Day 70 [± 2 days]).
Duration of Study Conduct:	The study is planned to take place over approximately 12 to 24 months (from screening of the first patient through completion of all study procedures for the last patient). This time period may change in the event that the study is terminated early, additional time is required to review safety, or a decision is made to complete an unscheduled analysis for a group.
Study Products:	YPL-001 will be supplied as 80 mg tablets for oral administration. Placebo will be supplied as YPL-001 80 mg matching placebo tablets for oral administration. YPL-001 or placebo will be dispensed in accordance with the Randomization and Drug Dispensing Instructions provided in a separate document.
Dosage, Dosage Form, Route, and Dose Regimen:	Treatments are described as follows: Treatment A: Multiple oral YPL-001 80 mg doses (1 x 80 mg tablet + 1 x 1 YPL-001 80 mg matching placebo tablet) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days.. Treatment B: Multiple oral YPL-001 160 mg doses (2 x 80 mg tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Treatment C: Multiple oral matching placebo (2 x 1 YPL-001 80 mg matching placebo tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. In all treatments, one tiotropium (Spiriva® HandiHaler®) 18 µg capsule will also be administered QD every morning prior to study drugs administration. Albuterol will be administered on an as needed basis. Each dose of Treatments A, B, and C will be administered orally with approximately 240 mL of water.

Stopping Rules:	A decision to stop or suspend the study will be made jointly by the Sponsor and the Investigator following the review of all pertinent safety and tolerability. Together they will make one of the following determinations: 1. To continue with the study as planned. 2. To continue with the study and add additional safety evaluations. 3. To continue with the study by adjusting to a lower dose if 2 patients at any dose level meets any of the following criteria and the patient was determined to have received YPL-001 after unblinding: a. Has a drug–related, unexpected serious adverse event (SAE). b. Experiences drug-related grade ≥ 3 toxicity. 4. The study will be terminated if ≥ 3 patients at any dose level meet any of the following criteria and the patients were determined to have received YPL-001 after unblinding: a. Has a drug–related, unexpected SAE. b. Experience drug related grade ≥ 3 toxicity.
Primary Outcome Measures	Safety and tolerability will be monitored through physical examinations, vital signs, pulse oximetry, ECGs, clinical laboratory tests, and AEs.
Safety and Tolerability Analysis	The following analyses will be performed. Safety analyses will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data, when appropriate. **Medical History:** Medical history will be listed by patient. **Adverse Events:** AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion (e.g., 17.0 or higher) and data will be summarized by System organ class (SOC) and preferred term. The number of treatment-emergent AEs (TEAEs) will be reported. In addition, the number and percent of patients reporting each TEAE will be summarized separately for each treatment. A by-patient AE data listing, including verbatim term, preferred term, treatment, severity, outcome, and relationship to treatment, will be provided. **Physical Examination:** Changes in physical examinations will be described in the text of the final report and significant findings will be reported as AEs. **Clinical Laboratory Tests, Electrocardiograms, Vital Signs, and Pulse Oximetry Measurements:** All clinical laboratory tests, 12-lead ECGs, vital signs, and pulse oximetry measurements and their change from baseline, if applicable, will be summarized by treatment and time point of collection. A shift table describing out-of-normal range shifts will be provided for clinical laboratory results. A normal-abnormal shift table will be presented for ECGs.

Safety and Tolerability Analysis (continued):	**Concomitant Medications:** Concomitant medications will be listed by patient and coded using the most current World Health Organization (WHO) drug dictionary available at Celerion (e.g., 01-MAR-2014 or later).
Secondary Outcome Measures:	PEF, major (e.g., estimated sputum quality [e.g., color, consistency], and quantity) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (Duke Activity Status Index [DASI]) self-reported daily by the patients using an e-diary.
Symptom Monitoring Analysis:	Symptom free days and overall symptom burden will be evaluated and compared across treatment groups. Secondary outcome analysis will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative data and frequency counts will be compiled for classification of qualitative data, when appropriate. **Peak Expiratory Flow and Symptoms of COPD Exacerbation:** PEF measurements and symptoms of COPD exacerbation and their change from baseline will be summarized by treatment and time point of collection. **Dyspnea and Activity:** The Modified Borg Dyspnea Scale and DASI scores will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.
Exploratory Outcome Measures:	**Pharmacodynamic Assessments:** <u>Bronchoalveolar Lavage Assessments:</u> BAL samples will be collected at baseline and again at the completion of the study for PD assessments of biomarkers. Biomarker assessments include: 1. epithelial brushings for YPL-001 component levels; 2. total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells 3. total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers 4. concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9. <u>Blood Assessments:</u> Blood samples will be collected at screening, and throughout the study for PD assessments of biomarkers. Biomarker assessments include: 1. inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) 2. concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9. <u>Pulmonary Assessment:</u> Pulmonary function measurements (spirometry [FEV_1, FVC, FEV_1/FVC, and

Exploratory Outcome Measures (continued):	IC] will be performed at screening, and throughout the study. Quality of Life Assessments: Patient reported outcomes (e-diary, BDI/TDI, CAT) will be performed at baseline, and throughout the study. **Pharmacokinetic Assessments:** Bronchoalveolar Lavage Assessments: BAL samples will be collected at baseline and again at the completion of the study to determine verproside and picroside II concentrations in BAL. Other components of YPL-001 and its metabolites may also be analyzed. Plasma Assessments: Serial blood samples will be collected prior to the initial dosing and through 12 hours following dosing on Days 1 and 54 (± 1 day) to determine verproside and picroside II concentrations in plasma. Predose samples will also be collected in the morning of Days 15 (± 2 days), 29 (± 2 days), 43 (± 2 days) and 54 (± 1 day) for C_{trough} determination. Other components of YPL-001 and its metabolites may also be analyzed. The sampling schedule and/or collection intervals may be modified based on the results as the study progress.
Pharmacodynamic Analysis:	**Blood, Plasma, and Pulmonary biomarkers:** When applicable, the raw data and % change from baseline or placebo, as appropriate, for PD markers (BAL biomarkers, blood biomarkers, and pulmonary biomarker) will be summarized by time point and treatment using descriptive statistics (arithmetic means, standard deviations [SD], coefficients of variation [CV], sample size [N], minimum, maximum, and median). Figures will be created to display mean and individual level or activity as a function of time. **Quality of Life:** The quality of life parameters will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.
Pharmacokinetic Parameters and Analysis:	Noncompartmental PK parameters, including AUC_{0-t}, AUC_{0-inf}, AUC_{τ}, k_{el}, C_{max}, C_{max_ss}, C_{min_ss}, C_{trough}, t_{max}, t_{max_ss}, CL/F, CL_{ss}/F, V_z/F, V_{z_ss}/F, and $t_{1/2}$, as appropriate, will be calculated from plasma concentrations of verproside and picroside II from patients who received YPL-001 only. Additional PK parameters may be calculated if deemed appropriate. Plasma PK parameters may also be calculated for other components of YPL-001 and its metabolites. PK parameters will be summarized by treatment using descriptive statistics. Relative exposure of verproside and picroside II will be assessed between the two YPL-001 dose levels, and steady-state will be assessed by visual inspection in the active treatment groups. Verproside and picroside II concentration in BAL samples from patients who received YPL-001 only will be listed.

6. STUDY EVENTS FLOW CHART

Study Procedures[a]	Screen[b]	Run-in Period		Treatment Period																			
Days →		1	2-14 (±2)	Up to -3 [c]	1																		
Hours →				C-I	Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12
Administrative Procedures																							
Informed Consent	X																						
Inclusion/Exclusion Criteria	X	X																					
Medical History	X																						
Randomization					X																		
Safety Evaluations																							
Physical Examination[d]	X			X[e]																			
Height	X																						
Weight	X			X[e]																			
Chest X-ray[f]	X																						
Berlin Questionnaire	X																						
12-Lead Electrocardiogram	X			X[g]																			
Vital Signs[h]	X			X[g]	X						X		X						X				
Pulse Oximetry	X			X[g]																			
Hem, Chem, and UA[i]	X			X[e]																			
PT/INR	X																						
Serum Pregnancy Test (♀ only)	X			X[e]																			
Serum FSH (postmenopausal ♀ only)	X																						
Urine Drug Screen	X				X																		
Urine or Breathalyzer Alcohol Screen	X				X																		
HIV/Hepatitis Screen	X																						
AE Inquiries																							
AE Monitoring										X													
ConMeds Monitoring	X									X													
Symptoms Monitoring																							
Diary Training		X																					
Diary Use[j]										X													
PEF, COPD exacerbation, dyspnea and activity[k]										X													
Study Drug Administration																							
Tiotropium Administration[l]		X	X	X	X																		

Study Procedures[a]	**Screen**[b]	**Run-in Period**		**Treatment Period**																		
Days →		1	2-14 (±2)	Up to -3 [c]	1																	
Hours →				C-I	Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12
Study Drug Administration at CRU[m,n]						X																X
Pharmacodynamic																						
Pulmonary Function (Spirometry)[o]	X			X[e]																		
Pharmacodynamic																						
Bronchoscopy and BAL Biomarkers[p]				X																		
Blood Biomarkers	X				X						X											
BDI/TDI & CAT				X[e]																		
Pharmacokinetic																						
Blood for Verproside & Picroside II PK					X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[q]
Other Procedures																						
Visit & Return Visits[r]	X	X		X	X																	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.
b. Within 14 days of Day 1 (inclusive) of the Run-in Period.
c. Scheduled procedures may be performed within 3 days prior to Day 1 dosing.
d. A full physical examination will be performed at screening. Symptom-driven physical examinations will be performed at other scheduled times, and may be performed at other times at the Investigator's discretion.
e. To be performed prior to the bronchoscopy procedures.
f. To be performed at screening or within 3 months (inclusive) of screening.
g. ECGs, vital sign and pulse oximetry will be measured within 4 hours of bronchoscopy procedures. During the bronchoscopy procedures and BAL sample collection, patients will be continuously monitored for ECGs, vital signs (blood pressure, heart rate, respiration rate, and body temperature), and oxygen saturation.
h. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
i. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.
j. Patients will be provided with an e-diary device to record their self-administered doses, whether the dose was administered with food, and daily respiratory symptoms.
k. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality [e.g., color, consistency] and quantity) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).
l. Patients will receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. They must return the container (empty or not) at the next schedule visit.
m. Prior to release from the CRU, patients will receive a properly labeled kit with sufficient study drug for their assigned treatment which will be self-administered by patients at home until the next morning visit at the CRU. Patients must return the used and unused wallets at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.
n. On Day 1, patients will be required to fast overnight for at least 8 hours before and 4 hours after YPL-001/placebo morning administration.
o. Pulmonary function will be performed prior to and 20 to 30 minutes after inhalation of approximately 400 µg albuterol.
p. Bronchoscopy and BAL sample collection will be performed following a 12-hour fast.
q. To be performed prior to dosing.
r. Patients will be admitted to the CRU at the time indicated by the CRU.

STUDY EVENTS FLOW CHART *(CONTINUED)*

Study Procedures[a]	**Treatment Period**									
Days →	2-14	15 (± 2)		16-28	29 (± 2)		30-42	43 (± 2)		44-53
Hours →		AM	PM		AM	PM		AM	PM	
Safety Evaluations										
Physical Examination[b]					X[c]					
Weight					X[c]					
12-Lead Electrocardiogram					X[c]					
Vital Signs[d]		X[c]			X[c]			X[c]		
Hem, Chem, and UA[e]					X[c]					
Serum Pregnancy Test (♀ only)		X[c]			X[c]			X[c]		
Urine Drug Screen		X[c]			X[c]			X[c]		
Urine or Breathalyzer Alcohol Screen		X[c]			X[c]			X[c]		
AE Inquiries		X[c]			X[c]			X[c]		
AE Monitoring	X									
ConMeds Monitoring	X									
Symptoms Monitoring										
Diary Use[f]	X									
PEF, COPD exacerbation, dyspnea and activity[g]	X									
Study Drug Administration										
Tiotropium Administration[h]	X									
Study Drug Administration at CRU		X			X			X		
Study Drug Administration at Home[i]	X		X	X		X	X		X	X
Pharmacodynamic										
Pulmonary Function (Spirometry)[j]		X[c]			X[c]			X[c]		
Blood Biomarkers		X[c]			X[c]			X[c]		
BDI/TDI & CAT		X[c]			X[c]			X[c]		
Pharmacokinetic										
Blood for Verproside & Picroside II PK		X[c]			X[c]			X[c]		
Other Procedures										
Return Visits[k]		X			X			X		

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.
b. Symptom-driven physical examinations will be performed at scheduled times, and may be performed at other times at the Investigator's discretion.
c. To be performed or completed prior to dosing.
d. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
e. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.
f. Patients will be provided with an e-diary device to record their self-administered doses, whether the dose was administered with food, and daily respiratory symptoms.
g. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality [e.g., color, consistency] and quantity) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).
h. Patients will receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. They must return the container (empty or not) at the next schedule visit.
i. Prior to release from the CRU on Days 15 (± 2 days), 29 (± 2 days), and 43 (± 2 days) patients will receive a properly labeled kit and/or any unused wallets from previously provided kits (when applicable) with sufficient study drug for their assigned treatment which will be self-administered by patients at home until the next morning visit at the CRU. Patients must return the used and unused wallets at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.
j. Pulmonary function will be performed prior to and 20 to 30 minutes after inhalation of approximately 400 µg albuterol.
k. Patients will be admitted to the CRU at the time indicated by the CRU.

STUDY EVENTS FLOW CHART *(CONTINUED)*

Study Procedures[a]	Treatment Period																				ET[b]	FU[c]
Days →	54 (± 1 day)																		55	56		
Hours →	Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12				
Safety Evaluations																						
Physical Examination[d]																				X[e]	X	
Weight																				X[e]	X	
12-Lead Electrocardiogram																				X[f]	X	
Vital Signs[g]	X						X		X						X			X		X[f]	X	
Pulse Oximetry																				X[f]	X	
Hem, Chem, and UA[h]																				X[e]	X	
Serum Pregnancy Test (females only)																				X[e]		
Urine Drug Screen	X																			X[e]		
Urine or Breathalyzer Alcohol Screen	X																			X[e]		
AE Inquiries	X																			X[e]	X	
AE Monitoring	X																					X
Concomitant Medication Monitoring	X																					
Symptoms Monitoring																						
Diary Use[i]	X																			X[e]	X	
PEF, COPD exacerbation, dyspnea and activity[j]	X																					
Study Drug Administration																						
Tiotropium Administration	X																		X	X		
Study Drug Administration at CRU[k]		X																X				
Study Drug Administration at Home[l]																			X			
Pharmacodynamic																						
Pulmonary Function (Spirometry)[m]																				X[n]	X	
Bronchoscopy and BAL Biomarkers[o]																				X		
Blood Biomarkers	X[p]						X															
BDI/TDI & CAT	X[p]																					
Pharmacokinetic																						
Blood for Verproside & Picroside II PK	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Other Procedures																						
Return Visits[q]	X																			X	X	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.
b. To be performed prior to early termination from the study.
c. The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.
d. Symptom-driven physical examinations will be performed at scheduled times, and may be performed at other times at the Investigator's discretion.
e. To be performed or completed prior to bronchoscopy procedures.
f. ECGs, vital sign and pulse oximetry will be measured within 4 hours of bronchoscopy procedures. During the bronchoscopy procedures and BAL sample collection, patients will be continuously monitored for ECGs, vital signs (blood pressure, heart rate, respiration rate, and body temperature), and oxygen saturation.
g. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
h. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.
i. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff.
j. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality [e.g., color, consistency] and quantity) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).
k. On Day 54 (± 1 day), patients will be required to fast overnight for at least 8 hours before and 4 hours after YPL-001/placebo morning administration.
l. Prior to release from the CRU on Day 54 (± 1 day) patients will receive a properly labeled kit and/or any unused wallets from previously provided kits (when applicable) with sufficient study drug for their assigned treatment which will be self-administered by patients at home until the next morning visit at the CRU. Patients must return the used and unused wallets at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.
m. Pulmonary function will be performed prior to and 20 to 30 minutes after inhalation of approximately 400 µg albuterol.
n. To be completed prior to bronchoscopy procedures.
o. Bronchoscopy and BAL sample collection will be performed following a 12-hour fast.
p. To be performed at predose on Day 54 (± 1 day) or upon early termination.
q. Patients will be admitted to the CRU at the time indicated by the CRU.

Abbreviations: ♀ = Female, AE = Adverse events, AM = Morning, BAL = bronchoalveolar lavage, BDI/TDI = Baseline Dyspnea Index/Transition Dyspnea Index Test, CAT = COPD Assessment Test, Chem = Serum chemistry, C-I = Check-in, COPD = chronic obstructive pulmonary disease, CRU = Clinical research unit, ConMeds = Concomitant medication, DASI = Duke Activity Status Index, ECG = Electrocardiogram, e-diary = electronic diary, ET = Early termination, FSH = Follicle-stimulating hormone, Hem = Hematology, HIV = Human immunodeficiency virus, IL= interleukin, PEF = Peak expiratory flow, PK = Pharmacokinetics, PM = Evening, Preg = Serum pregnancy, PT/INR = Prothrombin time/international normalized ratio, Screen = Screening, UA = Urinalysis.

7. TABLE OF CONTENTS

8. ABBREVIATIONS

Only those uncommon abbreviations specific to this study are listed. Pharmacokinetic (PK) parameter abbreviations and definitions may be found in Section 15.1.6.1.

AE	Adverse event
AHR	Airway hyper-responsiveness
ALD	Approximate lethal dose
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
BALF	Bronchoalveolar lavage fluid
BDI	Baseline Dyspnea Index
BID	Twice daily
BLQ	Below the lower limit of quantification
BMI	Body mass index
bpm	Beat per minute
BUN	Blood urea nitrogen
°C	Degrees Celsius
CAT	COPD Assessment Test
Chem	Chemistry
CFR	Code of Federal Regulations
CK	Creatine kinase
CNS	Central nervous system
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CRO	Contract Research Organization
CRP	C-reactive protein
CRU	Clinical research unit
CS	Clinically significant abnormality
CSC	Cigarette smoking condensate

CXCL	Chemokine (C-X-C motif) ligand
CV	Coefficient of variation
DASI	Duke Activity Status Index
dL	Deciliter
DRF	Dose range finding
e-diary	Electronic diary
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
ERS	European Respiratory Society
F	Female
°F	Degrees Fahrenheit
FDA	Unites States Foods and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FU	Follow-up
FVC	Forced vital capacity
g	gram
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HBsAg	hepatitis B surface antigen
HCO_3	Bicarbonate
HCV	hepatitis C antibodies
HED	Human equivalent dose
Hem	Hematology
HIV	Human immunodeficiency virus
hr	Hour
IC	Inspiratory capacity
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
IL	Interleukin
IND	Investigational New Drug

INR	International normalized ratio
IRB	Institutional Review Board
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
kg	Kilogram
kg/m^2	Kilogram per meter squared
LABA	long acting beta agonist
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
LOQ	Limit of quantitation
LPS	Lipopolysaccharide
LSM	Least-squares means
µg	Microgram
m^2	Square meter
M	Male
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCO	Myeloperoxidase
MCP	Monocyte chemotactic protein
MCV	Mean Corpuscular Volume
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
MIP	Monocyte inhibitory protein
mL	Milliliter
mmHg	Millimeter of mercury
MMP	Matrix metalloproteinase
msec	Millisecond
MTD	Maximum Tolerated Dose
N	Sample size
NCS	Not clinically significant
ng	Nanogram
No.	Number
NOAEL	No observed adverse effect levels

OTC	Over-the-counter
OVA	Ovalbumin
PD	Pharmacodynamic(s)
PEF	Peak expiratory flow
PK	Pharmacokinetic(s)
PT	Prothrombin time
QA	Quality Assurance
QC	Quality Control
QT	Interval between the Q and T waves on the electrocardiogram tracing
QTcF	Corrected QT interval with Fridericia's formula
RBC	Red blood cell
RDW	Red cell distribution width
Resp	Respiration
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SABA	Short-acting β2-agonist
SAD	Single ascending dose
SAE	Serious adverse event
SAMA	Short-acting anticholinergic agent
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SULT	Sulfotranferase
TBIL	Total bilirubin
TDI	Transition Dyspnea Index
TEAE	Treatment-emergent adverse event
Th	T helper
TNF-α	Tumor necrosis factors alpha
UA	Urinalysis
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

9. INTRODUCTION AND BACKGROUND

This study is being conducted as the third in a series of studies for the clinical development of YPL-001. The trial will be conducted in compliance with the protocol, GCP, and applicable regulatory requirements. The patient population will be comprised of moderate to severe (GOLD Stage 2-3) COPD patients.

9.1 YPL-001

YPL-001 drug product is an oral dosage form of an herbal extract from the aerial parts of the plant Speedwell (*Pseudolysimachion rotundum* subsp. *Subintegrum*). *Pseudolysimachion* (*Veronica*) is a perennial herb which has been used as a traditional medicine in Korea and China for the treatment of inflammatory diseases of the respiratory tract such as asthma and COPD.

As a botanical drug product, the drug substance is a mixture of chemical species (iridoids [including verproside] and other related compounds) and biological activity is considered to be from the mixture and not from an individual component. It is unknown if the total activity from individual components is additive or synergistic. Five active constituents, classified as iridoids, have been identified in the herbal extract: verproside, picroside II, catalpolside, isovanilloyl catalpol, and 6-*O*-veratroylcatalpol. Recent experimentation has revealed that the principal active ingredient in *Pseudolysimachion* is verproside, a dihydroxylated catalpol derivative.

YPL-001, containing verproside and other active ingredients, is being developed as a potential oral treatment for long term inflammatory diseases of the respiratory tract such as asthma or bronchitic COPD. Current long term control medications include corticosteroids, cromolyn sodium, immunomodulators, long acting beta agonists, (LABAs), methylxanthines, and leukotriene modifiers. YPL-001 belongs most closely with the leukotriene modifier class of drug.

A brief overview of available information regarding YPL-001 follows below. Details can be found in the YPL-001 Investigator's Brochure of June 3, 2014. [1]

9.1.1 Preclinical Trials

9.1.1.1 Pharmacology

Five *in vivo* primary pharmacology studies have been completed.

In ovalbumin-sensitized mice, an animal model for asthma, YPL-001 reduced elevated immunoglobulin E (IgE), IL-4, IL-5, IL-13, airway hyper-responsiveness, and mucus hyper-secretion.

In the lipopolysaccharide (LPS)- and cigarette smoking condensate (CSC)-induced COPD mice model, verproside and roflumilast treatment inhibited the accumulation of neutrophils in Bronchoalveolar lavage fluid (BALF) as well as the increase of several proinflammatory cytokines and chemokines. Neutrophil infiltration induced by LPS and CSC treatments was associated with a significant increase in BALF levels of the chemoattractants, TNF-α, chemokine (C-X-C motif) ligand (CXCL)-1, and monocyte inhibitory protein (MIP)-2. These data also demonstrated that the effect of YPL-001 and

verproside involves down-regulation of the influx of neutrophils and production of TNF-α, CXCL-1, and MIP-2 molecules which play a major role in tissue remodeling.

YPL-001 significantly suppressed the increase of inflammatory cell counts, particularly neutrophils in BALF and also effectively suppressed elevated levels of TNF-α, CXCL-1 and MIP-2 with the reduction in airway inflammatory responses in CSC- and LPS-induced COPD mice.

YPL-001 also effectively suppressed the increased inflammatory cell count, particularly neutrophils in BALF and also significantly inhibited elevated levels of TNF-α, IL-1β and IL-6 with the reduction in reactive oxygen species (ROS) production and elastase activity in cigarette smoke- and LPS-induced COPD mice.

In the LPS- and cigarette smoke-induced COPD rats model, YPL-001 significantly inhibited the increase of inflammatory cell count, particularly neutrophils in BALF and also effectively suppressed elevated levels of TNF-α, IL-1β, IL-6, MIP-2 and CRP.

YPL-001 effectively inhibited development of both T helper (Th)2 and Th1/Th17 type asthma in these murine models. These effects resulted from inhibition of cytokine and chemokine production by infiltrated inflammatory cells and antigen specific T cells in lymph nodes. YPL-001 did not inhibit development of COPD which was induced by *E.coli* extracellular vesicles.

9.1.1.2 Pharmacokinetics

After oral administration of YPL-001 at 12.5, 25, and 50 mg/kg doses (5.225, 10.45, and 20.9 mg/kg as verproside) in rats, verproside was rapidly absorbed; verproside was detected at the first blood sampling time (5 min) and absorbed rapidly, with the t_{max} achieved at 0.46-0.61 hour for all three doses. The post-absorption phase of the mean plasma verproside concentration-time profiles showed a poly-exponential decay.

The area under the plasma concentration-time curve (AUC) and the maximum plasma concentration (C_{max}) of verproside were linearly increased as the oral dose of YPL-001 increased. Alternately, the dose normalized (based on 12.5 mg/kg) AUCs and C_{max} of verproside were comparable among different doses studied. The elimination half-lives ($t_{1/2}$), 2.14 – 3.91 hours, and other PK parameters of verproside for all three doses were also comparable. These findings indicate that the PK parameters of verproside were independent of doses.

The fraction of dose of verproside excreted unchanged in urine at 24 hours was less than 0.10%. Verproside was not detected in the 24 hours feces sample for all three doses studied. These results indicate that verproside is almost completely eliminated by the first pass metabolism due to O-methylation, glucuronidation, sulfation, and intestinal microflora-mediated metabolism. Verproside is metabolized to verproside glucuronides (M1 and M2), verproside sulfates (M3 and M4), O-methylverproside such as picroside II (M5) and isovanilloylcatalpol (M6), 3,4-dihydroxybenzoic acid (M11), 3-methyoxy-4-hydroxybenzoic acid (M15) and 3-hydroxy-4-methoxybenzoic acid (M16), which are further metabolized to their glucuronides and sulfates including M5 glucuronide (M7), M5 sulfate (M9), M6 glucuronide (M8), M6 sulfate (M10), M11 glucuronide (M12), M11 sulfates (M13 and M14), M15 glucuronides (M17 and M18), M15 sulfate (M20), M16 glucuronide (M19), and M16 sulfate (M21). The O-methylation of verproside to

picroside II (M5) and isovanilloylcatalpol (M6) followed by glucuronidation and sulfation were identified as the major metabolic pathway in bile and urine samples.

Picroside II, a major metabolite of verproside, was detected in plasma samples but most plasma concentrations in 12.5 and 25 mg/kg YPL-001 treated groups were below the lower limit of quantification (LLOQ, 2.5 ng/mL) compared to 50 mg/kg YPL-001 treated group. The picroside II-to-verproside AUC ratios in the 50 mg/kg YPL-001 treated group were 13.9-65.1%, suggesting that picroside II may be one of the major YPL-001 metabolites. Plasma concentrations of isovanilloylcatalpol, a metabolite of verproside and isomer of picroside II, were below LLOQ (2.5 ng/mL) after oral administration of all three YPL-001doses tested.

Verproside, catalposide, and picroside II were not considerably bound to human plasma proteins; the binding values were 36.3-55.0% at verproside concentrations of 0.1, 1.0, and 10.0 μg/mL, 31.2-49.5% at catalposide concentrations of 0.5, 1, and 10 μg/mL, and 34.0-41.2% at picroside II concentrations of 0.5, 1, and 10 μg/mL.

9.1.1.3 Toxicology

Two single dose toxicity studies with YPL-001 have been completed in rat and dog. In the rat study, polyuria was observed in the 5,000 mg/kg dosing group of each sex between 2-4 hours after YPL-001 administration. Discolored stool was observed dose-dependently in the all dosing groups of each sex at 1-3 days post administration. Soft stool, mucous stool and soiled perineal region were observed at 1 day after administration in the 2,500 and 5,000 mg/kg dosing group of each gender. There were no notable changes of body weight in any study group. There were no notable gross necropsy findings in any of the study groups. Based on the results above, when YLP-001 is administered orally to Sprague-Dawley rats, the approximate lethal dose (ALD) is higher than 5,000 mg/kg. In the dog study, There were no changes with respect to the toxicity of the test article in the clinical signs, body weight change and necropsy findings after a single dose. Vomiting and discoloration of stool was noted. The Maximum Tolerated Dose (MTD) was determined to be 2,000 mg/kg for males and 1,000 mg/kg for females.

Two dose range finding (DRF) studies with YPL-001 have been completed in rat and dog, followed by two pivotal, 4-week, GLP repeated-dose toxicology studies in the same species. In the rat DRF study, YPL-001 induced anemia and hemolysis at 667 mg/kg/d and at higher doses. In addition, enlargement of cecum was observed at 667 mg/kg/d and at higher doses. The NOEL for this study was 74 mg/kg/d in both genders. In the dog DRF study, decreases in red blood cell (RBC) values were present in males at the high dose level (1000 mg/kg/d). In females the TBIL values were elevated at the 1000 mg/kg/d dose levels. Females had enlarged spleens at 125, 250 and 1000 mg/kg dose levels without dose relationship (trend was toward significance). The MTD for this study was 1000 mg/kg/d.

Primary results from the pivotal, 4-week rat study included:

There were no abnormal clinical signs observed in any group during dosing or the recovery periods and no mortality was reported.

Hematology: Compared to controls, there were decreases in values of RBC, hematocrit,

and hemoglobin at all dose levels of both genders in a dose-dependent fashion. The values of hemoglobin distribution width, red cell distribution width (RDW) and reticulocyte at all dose levels of both genders were higher or significantly higher than those of vehicle control.

Clinical Biochemistry: There were significant increases in the values of TBIL at all dose levels of both genders when compared with that of vehicle control. After the recovery period, there were no noticeable changes related to the test article.

Organ Weights: Slight increase in absolute & relative weights of the spleen at 540 mg/kg/d in males and notable increase in absolute & relative weights of the spleen at all dose levels of females were observed. Weights of left and right kidneys in female at 540 mg/kg/d were significantly higher than that of vehicle control. After the recovery period, the absolute weights of the spleen and both kidneys in both genders at 540 mg/kg/d were significantly higher than that of vehicle control.

Necropsy Findings: At necropsy, 6 cases of dark reddish discoloration of spleen were observed at 540 mg/kg/d in both genders, and 1 case of enlargement of cecum was observed at 540 mg/kg/d in female. After the recovery period, one case of dark reddish discoloration of spleen was observed at 540 mg/kg/d in the female. The histopathology examination revealed increased hematopoiesis of spleen at the high dose in both genders.

No Observed Adverse Effect Levels (NOAEL): The NOAEL for this study was 180 mg/kg/d for both genders.

Primary results from the pivotal, 4-week dog study included:

YPL-001 colored stool with/without soft stool or diarrhea was persistently observed in both sexes at 1000 mg/kg/d during the dosing period. It was not observed during the recovery period. No mortality was reported.

Hematology: There were no treatment-related changes.

Clinical Biochemistry: The TBIL increased in a dose-dependent manner in both genders at 111, 333 and 1000 mg/kg/d, and it was not recovered completely after the 2-week recovery period.

Organ Weights: There were no treatment-related changes.

Necropsy Findings: Slight red discoloration of mucous membranes in the stomach or duodenum was observed in female treatment groups but not observed after the 2-week recovery period.

NOAEL: The NOAEL for this study was 1000 mg/kg/d for both genders.

9.1.2 Clinical Experience

To date, 2 studies have been conducted in healthy subjects, a randomized, double-blind, placebo-controlled, sequential single ascending dose (SAD) clinical study (AA98496) and a randomized, double-blind, placebo-controlled, sequential multiple ascending dose (MAD) clinical study (AA98495).

9.1.2.1 SAD study

All 5 cohorts of 8 subjects (6 active and 2 placebo), with one cohort crossing over to assess food effect, were dosed and completed. All dosed levels (i.e., 40, 80, 160, 240, and 320 mg) were well tolerated with no SAEs reported during the conduct of the study. All 9 AEs reported in 7 subjects were mild in severity and the most frequent AE reported, regardless of causality, was headache. Of the 7 AEs experienced by subjects receiving the active drug, the Investigator considered 2 of these to be possibly related (nausea, and vomiting), 2 unlikely related, and 3 unrelated. Of the 2 AEs experienced by subjects receiving placebo, the Investigator considered 1 of these to be possibly related (headache), and 1 unrelated.

Plasma samples were analyzed using a validated bioanalytical method. Verproside concentrations were lower than concentrations observed from the animal PK data. The limit of quantitation (LOQ) was approximately 20% of the C_{max} after a single 160 mg dose and approximately 10% of the C_{max} after a single 320 mg dose. Therefore, the half-life could not be well characterized since only a few PK concentrations were available for the estimation.

Verproside appeared to be rapidly absorbed following oral administration and independent on dose, as suggested by median t_{max} values of approximately 0.5 to 0.67 hours under fasting conditions. Verproside appeared to be cleared rapidly from plasma, with mean $t_{1/2}$ values under 1 hour; plasma verproside concentrations were below the lower limit of quantification (BLQ) for all subjects by 6 hours postdose. Table 1 below summaries the PK parameters of verproside following single-dose administrations of YPL-001 at each dose level:

Table 1 Summary of PK Parameters

Pharmacokinetic Parameters	Dose Level Mean ± SD					
	40 mg (N = 1)[a]	80 mg (N = 6)[b]	160 mg (fasting) (N = 6)[c]	160 mg (fed) (N = 6)[d]	240 mg (N = 6)[e]	320 mg (N = 6)[f]
C_{max} (ng/mL)	1.19	1.14 ± 0.328	2.90 ± 1.76	1.08 ± 0.287	4.78 ± 5.66	4.49 ± 1.44
t_{max} (hr)[g]	0.4969	0.6682 (0.5158, 1.0025)	0.5074 (0.3331, 0.6700)	1.2538 (0.9994, 2.0008)	0.5867 (0.3486, 1.5022)	0.5057 (0.3419, 1.5014)
AUC_{0-t} (ng·hr/mL)	0.7422	0.7520 ± 0.3818	2.5616 ± 1.7947	1.2822 ± 0.3599	5.4567 ± 5.0158	5.3612 ± 0.8664
AUC_{0-inf} (ng·hr/mL)	·	·	3.8048 ± 1.8238	·	8.2199 ± 5.3327	6.2162 ± 0.7776
$t_{1/2}$ (hr)	·	·	0.677 ± 0.263	·	0.919 ± 0.176	0.713 ± 0.100

[a] Individual values are presented for the 40 mg dose level
[b] N=5 for AUC_{0-t}
[c] N=3 for AUC_{0-inf} and $t_{1/2}$,
[d] N=4 for AUC_{0-t}
[e] N=3 for AUC_{0-inf}, and $t_{1/2}$,
[f] N=5 for AUC_{0-inf}, and $t_{1/2}$,
[g] t_{max} is presented as Median (Minimum, Maximum)
· = Value missing or not reportable

9.1.2.2 MAD Study

In total, 2 cohorts of 8 subjects and 1 cohort of 10 subjects received multiple YPL-001 doses of 80, 160, or 240 mg BID. Each cohort was constituted of 2 subjects receiving placebo and the remaining subjects receiving the active drug. All dose levels were well tolerated. There were no deaths or SAEs in this study. One (1) subject was discontinued due to the AE of chest pain. Overall, TEAEs were experienced by 38% of subjects in this study. The Investigator considered 1 AE (chest pain) to be possibly related to study drug and the remaining AEs unlikely or unrelated. There were no treatment-related trends in physical examination, laboratory, vital sign, or ECG assessments in this study.

Verproside appeared to be rapidly absorbed following multiple-dose oral administration, as suggested by median t_{max} values of approximately 0.5 - 0.9 hours and independent of dose. Following a multiple oral doses of YPL-001, verproside appeared to be cleared rapidly from plasma, with mean $t_{½}$ values under 1.6 hours, and plasma verproside concentrations were BLQ for most subjects by 12 hours postdose.

Picroside II appeared to be also rapidly absorbed following single- and multiple-dose oral administration, as suggested by median t_{max} values of approximately 0.6 to 0.9 hours and independent of dose. Following a single oral dose of YPL-001, picroside II appeared to be cleared rapidly from plasma, with mean $t_{½}$ values under 1 hour, CL/F values of 14000 – 18500 L/hour, and plasma picroside II concentrations BLQ by 10 - 12 hours postdose. Following multiple oral doses, mean $t_{½}$ values were under 2.5 hours, and plasma picroside II concentrations were BLQ for most subjects by 12 hours postdose.

For all 3 dose levels, minimal to modest accumulation of verproside and picroside II was observed following BID administration of YPL-001 for 2 weeks. The mean peak and total exposure of verproside and picroside II in plasma appeared to increase in a dose-dependent manner between 80 and 160 mg of YPL-001, but no increase in plasma bioavailability was observed between 160 and 240 mg dose levels. Table 2 and Table 3 below summaries the PK parameters of verproside and picroside II, respectively, following multiple-dose administrations of YPL-001 at each dose level:

Table 2 Summary of Verproside PK Parameters

Pharmacokinetic Parameters	YPL-001 Dose Level Mean ± SD		
	80 mg	**160 mg**	**240 mg**
AUC_t (pg*hr/mL)	4709 ± 4080 (N=6)	10860 ± 11424 (N=6)	9658 ± 9246 (N=5)
AUC_{0-t}(pg*hr/mL)	4596 ± 4127 (N=6)	10770 ± 11489 (N=6)	9566 ± 9298 (N=5)
$C_{max\ ss}$ (pg/mL)	2414 ± 1281 (N=6)	6737 ± 7342 (N=6)	5458 ± 4387 (N=5)
$t_{max\ ss}$ (hr)*	0.756 (0.252, 2.00) (N=6)	0.759 (0.329, 1.50) (N=6)	0.528 (0.272, 0.751) (N=5)
$t_{½}$ (hr)	1.47 ± 0.425 (N=6)	1.30 ± 0.406 (N=6)	1.57 ± 0.236 (N=5)

* = t_{max_ss} is presented as median (minimum, maximum)

Table 3 Summary of Picroside II PK Parameters

Pharmacokinetic Parameters	YPL-001 Dose Level Mean ± SD		
	80 mg	160 mg	240 mg
AUC_t (pg*hr/mL)	2556 ± 599 (N=2)†	4287 ± 4369 (N=4)†	1985 ± 1024 (N=5)
AUC_{0t} (pg*hr/mL)	1124 ± 1044 (N=6)	3024 ± 3877 (N=6)	1804 ± 949 (N=5)
$C_{max\ ss}$ (pg/mL)	419 ± 240 (N=6)	1116 ± 1391 (N=6)	751 ± 490 (N=5)
$t_{max\ ss}$ (hr)*	0.756 (0.252, 2.00) (N=6)	0.759 (0.329, 1.50) (N=6)	0.748 (0.524, 0.751) (N=5)
$t_{½}$ (hr)	2.23 ± 0.254 (N=6)	1.84 ± 0.395 (N=6)	2.08 ± 0.793 (N=5)

* = t_{max_ss} is presented as median (minimum, maximum)
. = Value missing or not reportable

10. RATIONALE

10.1 Purpose of the Study

This study will be the initial exploration of multiple-dose administration of YPL-001 in COPD patients. The assessments of the safety, tolerability, COPD symptoms, PD, and PK of verproside and picroside II following administration of multiple doses of YPL-001 will guide decisions to further develop the drug and support the compound as a useful clinical candidate in the treatment of inflammatory diseases of the respiratory tract such as COPD and the data generated will support larger studies in patients with inflammatory diseases of the respiratory tract such COPD to demonstrate safety and evidence of efficacy and clinical benefit.

10.2 Dose Selection

This will be the first COPD patient study of YPL-001.

YPL-001 appeared well tolerated in a panel of standard animal toxicology studies. In the initial studies in humans, the initial dose of YPL-001 was justified conservatively according to the United States (US) Food and Drug Administration (FDA) guidance document “Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers”.[2]

Accordingly, the single and multiple dose escalation study (AA98496) initiated single doses at the 40 mg and 80 mg level, respectively. Dose escalations up to 320 mg and 240 mg in the SAD and MAD studies, respectively, were reached. All cohorts have been completed and all doses administered were well tolerated in human subjects and no clear pattern of toxicity is apparent.

Based on the review of safety, tolerability, and PK data from Cohorts 1 to 5 of the SAD study (AA98496) and Cohorts 1 to 3 of the MAD study, and the in vivo efficacy data in rat and mouse models, it is predicted that the therapeutic range should be between 1.2 mg/kg and 4.8 mg/kg which is equivalent to 84 mg to 336 mg daily in a 70 kg patient. Therefore, a low YPL-001 dose of 80 mg BID and the high YPL-001 dose of 160 mg BID were selected for this proof-of-concept study.

The total strength (23.75 mg) of identified compounds in YPL-001 as a whole in the 40 mg starting dose administered in the first-time-in-human dose escalation study (AA98496) corresponded to approximately 35% of the dosages that have been used in the traditional medicine setting in China (68.65 mg). In this present proof-of-concept study the total strength (47.50 mg) of identified compounds in the initial starting dose of 80 mg is still lower than the dosages that have been used in the traditional medicine setting in China, as shown in Table 4, corresponding to 70% of the traditional Chinese medicine.

Table 4: Traditional Chinese Medicine Use versus Proposed Clinical Starting Dose

Identified Compounds in YPL-001	1.40 g (Single Dose) Traditional Chinese Medicine[a] (mg)	2.80 g/day (Divided Dose) Traditional Chinese Medicine[a] (mg)	80 mg (Single Dose) for MAD Study[b] (mg)
Verproside	47.94	95.88	30.64
Veratric acid	2.10	4.20	1.08
Catalpolside	3.77	7.54	4.08
Picroside II	3.43	6.86	3.36
Isovanilloyl catalpol	3.53	7.06	4.72
6-*O*-veratroyl catalpol	7.88	15.76	3.62
Total	68.65	137.30	47.50

[a] Traditional medicine dosage from Chinese Medical Great Dictionary; Zhong Yao Da Ci Dian.
[b] Proposed dosage of YPL-001 in MAD study

11. RISK/BENEFIT

YPL-001 is being developed as a potential oral treatment for long term control of persistent asthma and COPD. YPL-001 belongs most closely with the leukotriene modifier class of drug and has the potential to inhibit the accumulation of neutrophils the increase of several proinflammatory cytokines and chemokines which play a major role in tissue remodeling. The development of a product to improve the treatment of asthma and COPD will be of benefit to the wider community/patients with respiratory disease.

The safety monitoring practices employed by this protocol (i.e., physical examination, vital signs, pulse oximetry, 12-lead ECG, hematology, serum chemistry, urinalysis, AE monitoring, and AE questioning) are deemed adequate to protect the patients' safety and should detect all expected TEAEs. The procedures employed in this study to assess efficacy are primarily non-invasive and present no undue risk to the patient.

The approximate volume of blood planned for collection from each patient over the course of the study (see Section 14.5), presents no undue risk to the patients nor does the possibility of collection (for wasting to ensure clean sample) of additional blood in the event an angiocatheter is utilized and the possibility of additional blood collection for recheck of safety labs if deemed necessary by the Investigator.

12. STUDY OBJECTIVES AND ENDPOINTS

12.1 Study Objectives

The primary objective of the study is to assess the safety and tolerability of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients.

The secondary objective of the study is to assess the number and magnitude of daily respiratory symptoms of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients.

The exploratory objectives of the study are to evaluate the following in moderate to severe COPD patients:

1. To assess BAL epithelial brushings for YPL-001 component levels.
2. To compare BAL samples for total cell count (cells/mL) macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; neutrophil, macrophage, lymphocyte, and eosinophil counts as absolute inflammatory cell numbers in YPL-001 groups versus placebo group.
3. To compare BAL samples for TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9 in YPL-001 groups versus placebo group.
4. To compare blood inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) and concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9 in YPL-001 groups versus placebo group.
5. To compare spirometric functions (FEV_1, FVC, FEV_1/FVC, and IC) in YPL-001 groups versus placebo group.
6. To compare patient reported outcomes (BDI/TDI, CAT) in YPL-001 groups versus placebo group.
7. To assess verproside and picroside II concentration in plasma and BAL and verproside and picroside II PK in plasma following multiple oral doses administration of two YPL-001 dose levels.

12.2 Study Endpoints

The primary endpoint is the number and severity of TEAEs following multiple oral doses of YPL-001 or placebo.

The secondary endpoint is the number of symptom free days and overall symptom burden following multiple oral doses of YPL-001 or placebo, assessed by measuring:

- daily PEF;
- major (e.g., estimated sputum quality [e.g., color, consistency] and quantity) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation;

- dyspnea (using the Modified Borg Dyspnea Scale); and
- activity (using the DASI).

The exploratory endpoints are:

1. YPL-001 component levels in epithelial brushings;
2. BAL biomarkers following multiple oral doses of YPL-001 or placebo, measuring:
   - total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells
   - total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers
   - concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9.
3. Blood biomarkers following multiple oral doses of YPL-001 or placebo, measuring:
   - inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils, and lymphocytes)
   - concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9.
4. Pulmonary function results (spirometry) following multiple oral doses of YPL-001 or placebo.
5. Quality of life scores using the BDI/TDI, CAT questionnaires.
6. Concentrations and PK of verproside and picroside II in plasma following multiple oral doses of YPL-001.
7. Concentrations of verproside and picroside II in BAL following multiple oral doses of YPL-001.

13. INVESTIGATIONAL PLAN

13.1 Overall Study Design and Plan

This is a Phase 2a, proof-of-concept, multicenter, randomized, double-blind, double-dummy, 3-treatment, parallel study, with low and high YPL-001 doses (80 mg and 160 mg BID) and a placebo control, in moderate to severe COPD patients.

At least 60 patients will be enrolled and randomized into 3 treatment groups (20 patients per group). Patients will participate only once. An approximately equal number of current and ex-smokers will be enrolled in the study.

Safety and tolerability will be assessed throughout the study. Assessment of respiratory symptoms and symptom burden in YPL-001 and placebo treatments will be performed daily through patient self-report of PEF, major and minor symptoms of COPD exacerbation, dyspnea, and activity in their e-diary. Spirometry measurement, BAL, and blood samples will be collected for the PD assessment of YPL-001 and placebo treatments. Serial blood samples will also be collected for PK assessment of verproside (the principal active ingredient of YPL-001) and picroside II. Other components of YPL-001 and its metabolites may also be analyzed in plasma.

Following screening, eligible patients will discontinue non permitted respiratory drugs if already receiving them and enter a 14 ± 2 days Run-in Period during which patients will be given albuterol taken on an as required basis and daily tiotropium 18 µg (one capsule inhaled daily in the morning) to be administered at home. On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their daily symptoms throughout the Run-in Period.

Patients will return to the CRU in the morning, –for Check-in of the Treatment Period to confirm their eligibility and assess their health conditions. If they still meet all of the inclusion criteria and none of the exclusion criteria, they will undergo Check-in scheduled study procedures. Patients will return to the CRU on the morning of Day 1 to be randomized and receive one of the 3 treatments and undergo all scheduled study procedures. Patients will return on the morning of Days 15 (± 2 days), 29 (± 2 days), 43 (± 2 days), 54 (± 1 day), and 56 of the Treatment Period for study drug administration and procedures. Prior to each release from the CRU, patients will receive a properly labeled kit and/or any unused wallets from previously provided kits (when applicable) with sufficient doses which will be self-administered by patients at home until the next morning visit at the CRU. Patients will continue recording their daily symptoms via the e-diary throughout the Treatment Period. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff.

The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

Patients will be instructed to call the Investigator if breathing worsens or if they need to take more than 8 puffs per day of albuterol for more than 2 consecutive days. If the Investigator determines that the patient is too unstable to continue in the study, he/she

will be discontinued. Rescue medication will be used for any patient with an exacerbation of COPD and will be administered in accordance with the study center standard of care.

Discontinued patients may be replaced at the discretion of the Sponsor.

13.2 Study Conduct

Please see the Study Events Flow Chart for a summary of the schedule of study participation and procedures in Section 6.

13.2.1 Screening

Screening will begin within 14 days of Day 1 (inclusive) of the Run-in Period. Informed consent will be obtained at screening (see Section 16.1.3) and prior to any study procedures being performed. Patients will have to meet all eligibility criteria before being enrolled in the study (see Section 13.3). Patients will be informed of the study restrictions (see Section 13.3.5).

The following will be recorded at screening: medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI, and history of tobacco use (including number of pack-year and cigarette smoked per day).

Screening procedures are listed in Section 6.

13.2.2 Patient Confinement

Patients will be admitted to the CRU on the morning of each scheduled visit at a time designated by the CRU as delineated in the Study Events Flow Chart (Section 6). Patients will remain in the clinic through completion of all scheduled study procedures.

13.2.3 Run-In Period (Days 1 to 14 [± 2 days])

Eligible patients will be admitted to the CRU on the morning of Day 1 of the Run-in Period at a time designated by the CRU. Patients will discontinue all restricted concomitant medications as indicated in Section 13.3.5.1 and undergo the Run-in procedures as listed in Section 6.

During the Run-in Period, patients will self-administer tiotropium (Spiriva® HandiHaler®) daily for 14 ± 2 days before Day 1 of the Treatment Period. Patients will be instructed to inhale 1 capsule of tiotropium (Spiriva® HandiHaler®) every morning. Patients will also receive albuterol for as needed use. Patient will keep this rescue albuterol throughout the Run-in Period.

Prior to release from the CRU, patients will receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. They must return the container (empty or not) at the next schedule visit, which is scheduled after 14 ± 2 days.

Each patient will also be issued and trained on the use of the e-diary to record their self-administered doses and their daily respiratory symptoms. Prior to each morning dose, patients will record at home their daily PEF, major (e.g., estimated sputum quality [e.g., color, consistency] and quantity) and minor (e.g., cough, wheeze, sore throat,

nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

13.2.4 Treatment Period (Days 1 to 56)

Patients who completed the Run-in Period and still meet all the inclusion criteria and none of the exclusion criteria will be randomized to receive one of the assigned treatments (80 mg or 160 mg YPL-001 BID, or placebo BID) on Day 1 through Day 55 (see Section 13.4.1 and Section 13.4.2).

Safety and tolerability will be monitored throughout the Treatment Period as listed in Section 6. Patients will continue to record their self-administered doses and their daily respiratory symptoms on their e-diary. Prior to each morning dose, patients will record at home their daily PEF, major (e.g., estimated sputum quality [e.g., color, consistency] and quantity) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

BAL samples for YPL-001 concentrations and PD assessments will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

Spirometry and quality of life questionnaires for PD assessments will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

Blood samples for PD and PK assessment will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

13.2.4.1 Meal Schedule

Patients will be required to fast overnight for at least 12 hours before the bronchoscopy and BAL collection at the Check-in of the Treatment Period and on Day 56. On Days 1 and 54 (± 1 day), patients will be required to fast overnight for at least 8 hours before and for at least 4 hours after the morning dose. On all other days, patients will be asked to fast for at least 2 hours before and 2 hours after each morning dose. Patients will also be asked to fast for at least 2 hours before and after each evening dose.

Patients will also be required to fast for at least 8 hours before the scheduled serum chemistry tests at the time points delineated in the Study Events Flow Chart (Section 6).

During in-clinic dosing, water (except that administered with dosing) will not be permitted from 1 hour before until 1 hour after each dosing. Water will be allowed as desired at all other times. On all other days, patients will be informed to follow the same restrictions.

On Days 1 and 54 (± 1 day), patients will fast from all food and drink except water between meals and snacks. Foods and beverages containing alcohol, xanthines, caffeine, vegetables from the mustard green family, mustard, tea (especially speedwell tea), or grapefruit/Seville oranges will not be served in the CRU. Across all CRUs, menus should be similar in content. The same menu and meal (except for snacks) schedule will be administered uniformly for all patients confined within the same CRU, across all treatment groups. Meals are not required to be completed by patients.

13.2.4.2 Early Termination

Early termination evaluations will be performed on patients prior to early termination. Patients who want to terminate from the study and are not currently on-site will be contacted and asked to return to the CRU to perform the early termination procedures.

The early termination procedures are listed in Section 6.

13.2.5 Follow-up Call (14 ± 2 days)

The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

13.2.6 Scheduled End of Study

The end of the study is scheduled after completion of the evaluations in the 3 treatment groups or after dose-limiting clinical safety endpoints have been reached to preclude continuation of the study. The clinical conduct of the study is intended to last approximately 12 to 24 months.

This time period may change in the event that the study is terminated early, additional time is required to review safety, or a decision is made to complete an unscheduled analysis for a group.

13.3 Selection of Study Population

13.3.1 Number of Patients

The study is planned to enroll at least 60 patients. An approximately equal number of current and ex-smokers will be enrolled. Patients will be divided in 3 treatment groups with 20 patients to receive one of the 3 treatments (i.e., low and high YPL-001 doses [80 mg and 160 mg BID] and a placebo control) as per the randomization schedule. Each treatment group will consist of an approximately equal number of current and ex-smokers.

13.3.2 Inclusion Criteria

Patient candidates must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Adult males and/or females, 30 to 85 years of age (inclusive).
2. History of COPD for at least 12 months prior to screening.
3. Diagnosed with COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines with symptoms compatible with COPD for at least 12 months prior to screening.

4. Classified as moderate to severe COPD based on the current severity classification GOLD Stage 2-3 disease in terms of post-bronchodilator spirometry at screening:
   - Post-bronchodilator FEV_1/FVC ratio of <70%
   - Post-bronchodilator FEV_1 ≥30 % and <80 % of predicted normal values
5. Weigh at least 52 kg for males and 45 kg for females and within the normal range according to accepted normal values of the Body Mass Index (BMI) chart 18.5-40.0 kg/m^2 inclusive.
6. In the judgment of the Investigator, the patient is medically stable with no change in symptoms, medication, or with clinical laboratory results that in the Investigator's opinion are compatible with the diagnosis of either COPD or a complication thereof and are judged acceptable for inclusion with predominantly bronchitic symptoms at screening.
7. Must be on a stable medical regimen for COPD ≥ 30 days prior to screening.
8. In the Investigator's opinion patients should be able to withhold tiotropium 24 hours prior to Day 1 of the Run-in Period, if already receiving it and prior to each scheduled CRU visit.
9. Must have oxygen saturation on room air > 93%.
10. Hemoglobin must be equal to or above the lower limit of normal at screening and check-in.
11. Current or ex-smoker with a history of >10 pack years. Ten pack years are defined as: 20 cigarettes a day for 10 years; 10 cigarettes a day for 20 years; or 40 cigarettes a day for 5 years (i.e., [number of cigarettes smoked per day × number of years smoked]/20). Patients, who undergo smoking cessation therapy, must be completed 3 months prior to screening visit and smoking status should not change between the patient's screening visit and patient's last study visit.
12. For a female of childbearing potential: either be sexually inactive (abstinent) for 14 days prior to the first dose and throughout the study or be using one of the following acceptable birth control methods:
    a. non-hormone releasing intrauterine device in place for at least 3 months prior to the first dose.
    b. surgical sterilization of the partner (vasectomy for 4 months minimum).
    c. physical barrier method (e.g., condom, diaphragm) with spermicide for at least 14 days prior to the first dose and throughout the study.
13. A female patient who claims to be sexually inactive, but becomes sexually active during the course of the study must agree to use a physical barrier method (e.g., condom, diaphragm) with spermicide from the time of the start of sexual activity through to the completion of the study.

14. For a female of non-childbearing potential: must have undergone one of the following sterilization procedures at least 6 months prior to the first dose:

    a. hysteroscopic sterilization;

    b. bilateral tubal ligation or bilateral salpingectomy;

    c. hysterectomy;

    d. bilateral oophorectomy;

    or be postmenopausal with amenorrhea for at least 1 year prior to the first dose and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status as per Investigator judgment.

15. Non-vasectomized males must agree to be sexually abstinent or to use a condom with spermicide when engaging in sexual activity from the first dose through completion of the last scheduled study procedures on Day 56 or upon early termination. Patients will be advised to use a condom with spermicide for 90 days following the last administration of the study drug, and to not donate sperm during this same period of time. In the event that the sexual partner is surgically sterile, use of a condom with spermicide is not necessary. No restrictions are required for vasectomized males provided their vasectomy has been performed 120 days or more prior to study start. Males who have been vasectomized less than 120 days prior to study start must follow the same restrictions as non-vasectomized males.

16. Understands study procedures and provides written informed consent for the trial.

17. Be able to comply with the protocol, such as all the study restrictions, and the assessments therein.

13.3.3 Exclusion Criteria

Patients will be excluded from the study if there is evidence of any of the following criteria at screening or check-in, as appropriate.

1. History of life-threatening COPD including respiratory arrest, intensive care unit admission and/or requiring intubation.
2. History of more than 2 hospitalizations for COPD within 12 months prior to screening.
3. Presentation of an acute exacerbation of COPD that will be associated with increase sputum volume or change in sputum color within 4 weeks before Day 1 of the Run-in Period.
4. Evidence of cor pulmonale, or clinically significant pulmonary hypertension.
5. Continuous use of more than 2L/day of oxygen.
6. History or presence of other respiratory disorders, such as asthma, α-1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis or other chronic pulmonary diseases.
7. A chest X-ray at screening (or within 3 months prior to screening) showing abnormalities, which in the opinion of the Investigator are clinically significant and unrelated to COPD.

8. A history of chronic disease including, but not limited to, unstable or uncontrolled hypertension (or been diagnosed with hypertension in the 6 months before screening), severe sleep apnea (assessed using the Berlin Questionnaire [refer to Section 14.1.8]), cardiovascular, endocrine, neurological, hepatic, gastrointestinal, renal, hematological, urological, immunological or ophthalmic diseases that the Investigator believes are clinically significant e.g., unstable and could impact patient safety by participation in the study.
9. History or presence of clinically significant cardiac arrhythmia, prostatic hyperplasia, bladder-neck obstruction, urinary retention, or narrow-angle glaucoma that, in the opinion of the PI, would contraindicate the administration of tiotropium.
10. Evidence of clinically relevant abnormal baseline hematology, serum chemistry, or urinalysis. Patients with an AST > 2 x ULN, ALT > 2 x ULN, bilirubin > 2 x ULN or creatinine > 2 x ULN (confirmation of results may be done once).
11. Diagnosed with hepatic impairment with a Child-Pugh class A score or higher.
12. Lung resection or lung reduction surgery within 12 months.
13. Positive alcohol (using urine dipstick or breathalyzer) test results at screening or at each CRU visit. If alcohol test is positive or subject reports consumption of alcohol within 48 hours prior to testing, alcohol test maybe rescheduled or repeated, at the discretion of the PI and if study visit time window allows.
14. Urine drug testing at screening or at each CRU visit, unless the positive drug screen is due to prescription drug use and is approved by the PI and the medical monitor.
15. Positive testing for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C infection with clinically significant liver impairement and/or a viral ribonucleic acid (RNA) titer of > 6.9 ± 0.8log molecules/mL.[3]
16. History or presence of alcoholism or drug abuse within the 2 years prior to Day 1 of the Treatment Period.
17. Hypersensitivity or idiosyncratic reaction to compounds related to YPL-001, including Speedwell tea and herbal remedies.
18. Requires one (or more) routine therapies for COPD during the indicated restricted time period as listed in Section 13.3.5.1.1.
19. Use of any drugs or substances known to be significant inhibitors (strong or moderate) of UDP-glucuronosyltransferase (UGT) (such as 17-beta-estradiol glucuronide, flavonoids [citrus fruit], silybin [herb supplement milk thistle]) and/or sulfotransferases (SULT) (refer to Appendix 1), within 12 hours prior to Day 1 of the Run-in Period. The use of low dose of acetylsalicylic acid (e.g., aspirin) will be allowed during the study, but prohibited 7 days prior to the bronchoscopy performed prior to dosing of Day 1 until the last PK blood sample collected on Day 1, and 7 days prior to Day 54 (± 1 day) dosing until completion of the bronchoscopy procedures on Day 56. Additional sources may be consulted by the PI or medical monitor to confirm lack of PK/PD interaction with study drug.
20. Blood donation or significant blood loss within 56 days prior to Day 1 of the Treatment Period.

21. Plasma donation within 7 days prior to Day 1 of the Treatment Period.
22. Participation in another clinical trial within 30 days prior to Day 1 of the Run-in Period.
23. Females who are pregnant or lactating.
24. Surgery within the past 3 months prior to Day 1 of the Treatment Period determined by the Investigator to be clinically relevant.
25. Active or history of any disease or condition that would, in the opinion of the Investigator and/or medical monitor, place the patient at an unacceptable risk to participate in this study.

13.3.4 Removal of Patients from the Study

Patient participation in this trial may be discontinued for any of the following reasons:

1. Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol.
2. Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient.
3. The patient interrupts trial study drug administration for more than 7 consecutive days of dosing or missed a total of 17 doses (15%) throughout the Treatment Period.
4. Patient's decision to withdraw.
5. Requirement for prohibited concomitant medication.
6. Patient failure to comply with protocol requirements or study related procedures.
7. Termination of the study by the Investigator, Sponsor, FDA, Celerion, or other regulatory authorities.

The clinical report will include reason(s) for patient withdrawals as well as details relevant to the patient withdrawal. If a patient is withdrawn from the trial prior to study completion, the patient will undergo all procedures scheduled for study completion (early termination evaluations) as the situation allows (see Section 13.2.4.2). Any patient withdrawn due to an AE (whether serious or non-serious) or clinically significant abnormal laboratory test values will be evaluated by the Investigator and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

Patients withdrawn may be replaced at the Sponsor’s discretion.

13.3.5 Study Restrictions

13.3.5.1 Concomitant Therapy

All medications taken during the 30 days prior to the first dose will be recorded and reviewed by the Investigator.

Any medication taken by patients during the course of the study will be recorded. Concomitant medication will be coded using the most current WHO drug dictionary available at Celerion (e.g., 01-MAR-2014 or later). If drug therapy other than that specified by the protocol is taken, a joint decision will be made by the Investigator and Sponsor to continue or discontinue the patient.

13.3.5.1.1 Prohibited Therapy

The following medications are not permitted within the time delineated below and during the study (from Day 1 of the Run-in Period to the completion of the last scheduled study procedures on Day 56 or upon early termination). Intake of these medications during the Run-in Period constitutes a non-eligibility criterion and the patients will not be randomized into the study. If any of these medications are taken during the Treatment Period, the need for this patient to be withdrawn from the study will be carefully evaluated by the Investigator and the Sponsor on the basis of the potential impact on efficacy or safety evaluation and in the patient's best interest:

1. Any medications administered for the treatment of worsening of COPD within 4 weeks prior to Day 1 of the Run-in Period:
   - nebulized, inhaled, oral, IV, IM corticosteroids;
   - oral or parenteral β2 agonists;
   - Antibiotics.
2. Inhaled corticosteroids (ICS), LABA, and/or inhaled ICS/LABA fixed combinations within 12 hours prior to Day 1 of the Run-in Period;
3. Inhaled long acting anticholinergic agents other than tiotropium within 2 weeks prior to Day 1 of the Run-in Period;
4. Inhaled short-acting β2-agonists (SABA) other than albuterol (e.g., terbutaline, fenoterol) within 12 hours prior to Day 1 of the Run-in Period;
5. Inhaled short-acting anticholinergic agents (SAMA) (e.g., ipratropium) within 12 hours prior to Day 1 of the Run-in Period;
6. PDE inhibitors (including roflumilast) within 2 weeks prior to Day 1 of the Run-in Period.
7. Leukotriene modifiers and xanthines derivatives within 2 weeks prior to Day 1 of the Run-in Period.
8. Drugs or substances known to be significant inhibitors (strong or moderate) of UGT and/or SULT, within 12 hours prior to Day 1 of the Run-in Period and through collection of the final PK sample. The use of low dose of acetylsalicylic acid (e.g., aspirin) will be allowed during the study, but prohibited 7 days prior to the bronchoscopy performed prior to dosing of Day 1 until the last PK blood sample

collected on Day 1, and 7 days prior to Day 54 (± 1 day) dosing until completion of the bronchoscopy procedures on Day 56.

9. Acetaminophen will be prohibited 24 hours prior to Day 1 of the Treatment Period and through collection of the final PK sample.
10. Vitamin supplements (except for prescribed vitamin supplement) and herbal products (especially Speedwell) will be prohibited 7 days prior Day 1 of the Treatment Period and through collection of the final PK sample.

13.3.5.1.2 Permitted Therapy

Throughout the study period (from Day 1 of the Run-in Period to the completion of the last scheduled study procedures on Day 56 or upon early termination) patients will be permitted to take the following medications in addition to the study drugs:

1. Albuterol, as required (except approximately 4 hours before schedule pulmonary function test);
2. Tiotropium (Spiriva® HandiHaler®) 18 µg once a day (except approximately 24 hours before schedule pulmonary function test);
3. Ibuprofen, as required, up to 1200 mg per day for intercurrent illness or AEs. Ibuprofen should not be taken for 2 hours before or after each dosing.
4. Prescribed vitamin supplement (except for Vitamin C).
5. In the case of a concomitant disease, appropriate treatment will be permitted if it does not interfere with the study evaluation parameters and does not qualify under the section "Prohibited Therapy" (see Section 13.3.5.1.1)

13.3.5.2 Prohibitions

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/caffeine (other than coffee and tea): 24 hours prior to each CRU visit and prior to dosing on Days 1 and 54 (± 1 day) of the Treatment Period through collection of Days 1 and 54 (± 1 day) last PK sample.
- Alcohol (other than red wine and beer): 48 hours prior to each CRU visit and 48 hours prior to dosing on Days 1 and 54 (± 1 day) of the Treatment Period through collection of Days 1 and 54 (± 1 day) last PK sample.
- Vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts), and mustard: 14 days prior to Day 1 of the Treatment Period through collection of Day 54 (± 1 day) last PK sample.
- Fruit Juice: 24 hours prior to each CRU visit and prior to dosing on Days 1 and 54 (± 1 day) of the Treatment Period through collection of Days 1 and 54 (± 1 day) last PK sample.
- Tea (especially Speedwell tea), coffee, and red wine: 7 days prior to Days 1 and 54 (± 1 day) of the Treatment Period through collection of Days 1 and 54 (± 1 day) last PK sample.

- Grapefruit/Seville orange and beer: 14 days prior to Day 1 of the Treatment Period through collection of Day 54 (± 1 day) last PK sample.

13.3.5.3 Activity

Patients will remain ambulatory or seated upright for 1 hour following each study medication administration.

Patients will be advised to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

13.4 Treatments

13.4.1 Treatments administered

13.4.1.1 Drug Administration During Run-in Period

Tiotropium (Spiriva® HandiHaler®) will be supplied as 18 µg capsules for inhalation.

Albuterol will be supplied as 100 µg albuterol base (1 actuation = 100 µg albuterol base) for oral inhalation. Albuterol may be administered via a nebulizer or a metered-dose inhaler.

Multiple oral inhalation of tiotropium (Spiriva® HandiHaler®) 18 µg capsule will be administered QD every morning for 14 ± 2 days during the Run-in Period. Albuterol will be administered on an as needed basis.

13.4.1.2 Drug Administration During Treatment Period

YPL-001 will be supplied as 80 mg tablets for oral administration.

Placebo will be supplied as YPL-001 80 mg matching placebo tablets for oral administration.

Treatments A, B, and C are described as follows:

Treatment A: Multiple oral YPL-001 80 mg doses (1 x 80 mg tablet + 1 x 1 YPL-001 80 mg matching placebo tablet) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days.

Treatment B: Multiple oral YPL-001 160 mg doses (2 x 80 mg tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days.

Treatment C: Multiple oral matching placebo (2 x 1 YPL-001 80 mg matching placebo tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days.

Each dose of Treatments A, B and C will be administered with approximately 240 mL of water.

In all treatments, one tiotropium (Spiriva® HandiHaler®) 18 µg capsule will also be administered QD every morning prior to study drugs administration. Albuterol will be administered on an as needed basis.

YPL-001 or placebo will be dispensed in accordance with the Randomization and Drug Dispensing Instructions provided in a separate document.

Prior to release from the CRU on Days 1, 15 (± 2 days), and 29 (± 2 days), of the Treatment Period, patients will receive a properly labeled new kit, which contains 4 wallets of 2 blister cards, with the appropriate doses which will be self-administered by patients at home. Any unused wallets from previously provided kits will also be dispensed to patients on Days 15 (± 2 days) and 29 (± 2 days). Prior to release from the CRU on Days 43 (± 2 days), and 54 (± 1 day), patients will received unused wallets from previously provided kits with the appropriate doses which will be self-administered by patients at home. Patients will also receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. Patients will record their self-administered doses in their e-diary, and whether the dose was administered with food, and must return the YPL-001 used and unused wallets and the tiotropium and albuterol container (empty or not) at the next schedule visit at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.

Patients will be instructed not to crush, split or chew the study drug.

The exact clock time of dosing will be recorded on on-site dosing days. Patients will be given instructions on how to record their drug administration in their e-diary on home-dosing days.

Each dose will be administered under fasting conditions as described in Section 13.2.4.1.

13.4.1.3 Stopping Rules

A decision to stop or suspend the study will be made jointly by the Sponsor and the Investigator following the review of all pertinent safety and tolerability. Together they will make one of the following determinations:

1. To continue with the study as planned.
2. To continue with the study and add additional safety evaluations.
3. To continue with the study by adjusting to a lower dose if 2 patients at any dose level meets any of the following criteria and the patient was determined to have received YPL-001 after unblinding:
   a. Has a drug–related, unexpected SAE.
   b. Experiences drug-related grade ≥ 3 toxicity.
4. The study will be terminated if ≥ 3 patients at any dose level meet any of the following criteria and the patients were determined to have received YPL-001 after unblinding:

a. Has a drug–related, unexpected SAE.
b. Experience drug related grade ≥ 3 toxicity.

PK data will not be required for the dose-escalation decision.

When applicable, a written statement fully documenting the reasons for study termination will be provided to the Institutional Review Board (IRB).

13.4.2 Method of Assigning Patients to Treatment Groups

Each patient will be assigned a unique screening identification number upon screening. Patients who complete the study screening assessments, complete the Run-in Period, and meet all the eligibility criteria will be assigned a unique randomization identification number, different from the screening number, and receive the corresponding product, according to a randomization scheme generated at Celerion. Each treatment group will consist of an approximately equal number of current and ex-smokers.

Patients will receive one of the 3 treatments (Treatments A, B, or C) on one occasion.

If replacement patients are used, the replacement patient number will be 100 more than the original (e.g., Patient No. 0101 will replace Patient No. 0001).

13.4.3 Blinding

This is a double-blind, double-dummy, randomized study.

13.4.3.1 Maintenance of Randomization

A computerized randomization scheme will be created by a Celerion unblinded statistician (who is not otherwise involved in the study) and shall be considered blinded (per the following).

The randomization will not be made available to the Sponsor, patients, or members of the staff responsible for the monitoring and evaluation of safety assessments.

The bioanalytical department will also be blinded to the randomization scheme.

13.4.3.2 Procedures for Breaking the Blind Prior to Study Completion

The site Pharmacist/Study Coordinator will receive two sets of randomization code envelopes, one set for “Current Smokers” and another for “Ex-Smokers”. Each individual envelope is marked on the outside with one of the randomization numbers and contains the treatment for that patient. These envelopes must be kept in a secure locked location.

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the patient.

In the event of a medical emergency, it is requested that the Investigator make every effort to contact the medical monitor or designee prior to breaking the blind. If breaking the blind is required because of a medical emergency, the treatment identity would be revealed by the qualified designee, for that patient only. In the event that the emergency is one, in which it appears that the other patients may be at imminent risk, the blind may be broken for all patients dosed at that dose level. The unblinding should be noted in the patient’s electronic case report form (eCRF).

In all cases where the code is broken, the Investigator should record the date, reason for code breaking and his/her name for signature on the envelope.

At the end of the study, the envelopes will be reviewed by the Sponsor.

13.4.3.3 Revealing of Randomization

In the absence of a medical emergency, the blinded randomization for this entire trial will not be revealed until the following conditions are fulfilled:

1. All data are entered in the database, edits checks are performed, queries closed, CRFs signed by the Investigator, and the database is officially locked.
2. All PK/PD samples have been analyzed and quality checked by the responsible analytical associate.

13.4.4 Treatment Compliance

During in-clinic dosing, a qualified designate will be responsible for monitoring the administration of timed oral doses. When appropriate, a mouth check will be performed by the qualified designate to ensure that the patients have swallowed the study medication. Once a patient has finished the water, the qualified designate will use a flashlight and a tongue depressor to check the side of the mouth, the sides of the upper and lower gums and the area under the tongue. Patients' hands will also be verified to ensure that the medication was ingested.

Self-administration by patients at home will be monitored via the e-diary and attempted phone calls will be performed to remind patients to take their medication, if they did not record their self-administration on the e-diary.

14. STUDY PROCEDURES

14.1 Safety Assessments

This study primarily assesses the safety and tolerability of YPL-001. Safety will be determined by evaluating physical examinations, vital signs, pulse oximetry, ECGs, clinical laboratory parameters, and AEs.

If deemed necessary, additional safety measurements will be performed at the discretion of the Investigator.

Study procedures should be completed as close to the prescribed/scheduled time as possible. The Quality of Life questionnaire should be performed prior to any other procedures. When the following procedures are scheduled at the same time, they will be performed in the following order:

1. Vital signs and pulse oximetry
2. ECG
3. Pulmonary function measurement
4. Bronchoscopy and BAL collection

All other procedures can be performed without specific order.

14.1.1 Body Height and Weight

Body height (centimeters) and body weight (kilograms) will be measured as outlined in the Study Events Flow Chart (Section 6).

14.1.2 Physical Examination

All full physical examinations will include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose and throat, respiratory system, cardiovascular system, gastrointestinal system, neurological condition, blood and lymphatic systems, and the musculoskeletal system.

A licensed physician will examine each patient as outlined in the Study Events Flow Chart (Section 6).

Medical history will be recorded at screening.

Physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator.

14.1.3 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate will be measured as outlined in the Study Events Flow Chart (Section 6).

Vital signs may be taken at any other times, if deemed necessary. Blood pressure and heart rate measurements will be performed with patients in a seated position for at least 1 minute, except when they are supine or semi-reclined because of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the Investigator.

When performed prior to the morning dose, blood pressure and heart rate will be measured within 2 hours prior to dosing. When performed prior to the bronchoscopy, blood pressure and heart rate will be measured within 4 hours prior to the bronchoscopy. When scheduled postdose, vital signs readings will be performed within approximately 10 minutes of the scheduled time point. When performing the bronchoscopy, vital signs (body temperature, respiratory rate, blood pressure, and heart rate) will be monitored continuously until the end of the procedure.

14.1.4 Pulse Oximetry

Oxygen saturation (%), and heart rate will be assessed using a pulse oximeter. All readings will be performed with a pulse oximeter (oxygen saturation [%], and heart rate) as outlined in the Study Events Flow Chart in Section 6.

When performed prior to the morning dose, pulse oximetry monitoring will be measured within 2 hours prior to dosing. When performed prior to the bronchoscopy, pulse oximetry monitoring will be measured within 4 hours prior to the bronchoscopy. Readings may be taken at other times, if deemed necessary by the Investigator. When performing the bronchoscopy, oxygen saturation will be monitored continuously until the end of the procedure.

Any clinically relevant oxygen saturation reading below 93% will be documented as an AE, as per Investigator discretion.

14.1.5 Electrocardiogram Monitoring

When performed prior to the morning dose, ECG will be measured within 2 hours prior to dosing. When performed prior to the bronchoscopy, ECG will be measured within 4 hours prior to the bronchoscopy. When performing the bronchoscopy, ECG will be monitored continuously until the end of the procedure.

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6). Patients will be required to lie quietly in a supine position for at least 5 minute prior to ECG measurements. Single 12-lead ECGs may be performed at various unscheduled time points, if deemed necessary by the Investigator.

Single 12-lead ECGs will be interpreted and signed and dated by the Investigator. The ECGs will be classified as normal, having a non-clinically significant abnormality (NCS), or having a clinically significant abnormality (CS). In addition, ECG parameters of ventricular rate, PQ or PR interval, QRS duration, and QT interval (corrected according to Bazett's formula [QTcB] and uncorrected) will be noted on the CRF.

14.1.6 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 6). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator. The clinical laboratory tests include the following:

14.1.6.1 Hematology

- Hemoglobin
- Hematocrit
- RBC count (including a reticulocytes count)
- Platelet count
- Mean Corpuscular Hemoglobin (MCH)
- Mean Corpuscular Volume (MCV)
- Mean Corpuscular Hemoglobin Concentration (MCHC)
- RDW
- White blood cell (WBC) count with differential (including eosinophil, neutrophil, basophil, lymphocytes, and monocytes)

14.1.6.2 Serum Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.

- BUN
- Creatinine*
- Bilirubin (total and direct)
- Uric acid
- Albumin
- Alkaline phosphatase (ALP)
- Creatine kinase (CK)
- Lactate dehydrogenase (LDH)
- Estimated glomerular filtration rate
- Alpha-1 Antitrypsin**
- AST
- ALT
- Amylase
- Lipase
- Glucose (fasting)
- Carbon dioxide (CO_2)/Bicarbonate (HCO_3)
- Sodium
- Potassium
- Chloride

* Creatinine clearance will be calculated using Cockcroft-Gault formula at screening.

** To be performed at screening only.

14.1.6.3 Serology

- HIV
- HBsAg
- HCV
- HCV viral RNA titer

14.1.6.4 Human Chorionic Gonadotropin (Serum Pregnancy Test)

The test will be performed for females only.

14.1.6.5 Follicle-Stimulating Hormone

The test will be performed in postmenopausal females only.

14.1.6.6 Urinalysis

- pH
- Specific gravity
- Protein
- Glucose
- Ketones
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Leukocyte Esterase

If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination will be performed.

14.1.6.7 Urine/Breathalyzer Alcohol Screen

Alcohol levels will be tested using urine dipsticks or breathalyzers.

14.1.6.8 Urine Drug Screen

- Cannabinoids
- Cocaine
- Amphetamines
- Barbiturates
- Benzodiazepines
- Opiates

14.1.6.9 Additional Tests

- Prothrombin time/international normalized ratio (PT/INR)

14.1.7 Chest X-Ray

A baseline chest x-ray will be performed at the screening visit. If the patient has had an x-ray within the last 3 months prior to the screening visit, and the CRU has access to the report and images, this can be used as the baseline chest x-ray and does not need to be repeated.

14.1.8 Berlin Questionnaire

The Berlin Questionnaire is a validated screening questionnaire used to quickly identify the risk (low to high) of sleep disordered breathing. The questionnaire consists of three categories and risk is based on the responses to individual items and overall scores in the symptom categories. Assessments will be performed according to the Study Events Flow Chart (Section 6). The questionnaire will be provided as a separate document and a copy of the questionnaire to be used will be kept in the study binder.

14.1.9 Adverse Events

14.1.9.1 Adverse Event Definition

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.[4]

14.1.9.2 Monitoring

The patients will be instructed to inform the Investigator or clinic staff of any AEs and intercurrent illnesses experienced during the trial. Additionally, a specific inquiry regarding AEs will be conducted prior to each dosing at the CRU, after the last scheduled study procedures on Day 56 (or upon early withdrawal), and at the follow-up phone call. The inquiry will be made in a non-specific manner using open-ended questions so as not to bias the response (e.g., How have you been feeling since your last visit?).

All symptoms will be evaluated by the Investigator.

Any patient who has a clinically significant AE (whether serious or non-serious) or clinically significant abnormal laboratory test value will be evaluated by the Investigator, or other monitoring physician, and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

Treatment of SAEs will be performed by a physician, either at the CRU or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal or unknown (lost to follow-up).

14.1.9.3 Reporting

AEs will be coded using the most current MedDRA® available at Celerion (e.g., 17.0 or higher). The Sponsor will inform the Celerion Global Project Manager which version is to be used prior to initiation of the study.

The Investigator will review each event and assess its relationship to drug treatment (unrelated, unlikely, possible, probable, definite). The severity of each sign or symptom reported will be graded based on the NIH NCI CTCAE toxicity grading scale 5-point severity scale (Grade 1, 2, 3, 4 and 5) [5] and the date and time of onset, time relationship to drug dosing, duration, and outcome (resolved, improved, unchanged, worse, fatal, or unknown/lost to follow-up) of each event will be noted.

The relationship of each AE will be assessed using the following definitions:

Unrelated	▪ Event occurring before dosing. ▪ Event or intercurrent illness due wholly to factors other than drug treatment.
Unlikely	▪ Poor temporal relationship with drug treatment. ▪ Event easily explained by patient's clinical state or other factors.
Possible	▪ Reasonable temporal relationship with drug treatment. ▪ Event could be explained by patient's clinical state or other factors.
Probable	▪ Reasonable temporal relationship with drug treatment. ▪ Likely to be known reaction to agent or chemical group, or predicted by known pharmacology. ▪ Event cannot easily be explained by patient's clinical state or other factors.
Definite	▪ Distinct temporal relationship with drug treatment. ▪ Known reaction to agent or chemical group, or predicted by known pharmacology. ▪ Event cannot be explained by patient's clinical state or other factors.

The following definitions for rating severity will be used:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**. Note**:** An experience may be severe but may not be serious, e.g., severe headache).
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A semi-colon indicates 'or' within the description of the grade; ADL = Activities of Daily Living

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

14.1.9.4 Serious Adverse Events

If any AEs are serious, as defined by the Food and Drug Administration (FDA) Code of Federal Regulations (CFR), Chapter 21, special procedures will be followed. All SAEs will be reported to the Medical Monitor via fax or e-mail within one working day of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012[4]. The institutional review board (IRB) will be notified of the Alert Reports as per FDA regulations.

If an SAE occurs to a patient on this study, the Medical Monitor is to be contacted (see Section 4).

A SAE is any AE or suspected adverse reaction that in the view of either the Investigator or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

14.2 Symptom Assessments

14.2.1 Electronic Diary

On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their self-administered doses, whether the dose was administered with food, and daily respiratory symptoms throughout the Run-in and Treatment Periods. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff.

Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality [e.g., color, consistency] and quantity) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

14.2.2 Peak Expiratory Flow

PEF assessments will be made daily prior to each dose from Day 1 of the Run-in Period to Day 56 of the Treatment Period. Three measurements will be made at each time point using a hand held PEF meter. Readings not performed in the CRU will be recorded in the patient e-diary. All PEF assessments should be performed before administration of a bronchodilator where possible.

14.2.3 Symptoms of Chronic Obstructive Pulmonary Disease Exacerbation

Patient will be asked to record the major (e.g., estimated sputum quality [e.g., color, consistency] and quantity) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation via the e-diary before each dosing.

14.2.4 Dyspnea (Modified Borg Dyspnea Scale)

Severity level of patient's dyspnea will be assessed via the modified Borg dyspnea scale programmed within the e-diary. The modified Borg dyspnea scale is a self-administered categorical scale with a score from 0 to 10, where 0 (as a measure of dyspnea) corresponds to the sensation of normal breathing (absence of dyspnea) and 10 corresponds to the patient's maximum possible sensation of dyspnea.

14.2.5 Activity (Duke Activity Status Index)

Patient's functional capacity and activity status will be assessed via the DASI programmed within the e-diary. DASI is a self-administered 12-item questionnaire that assesses daily activities such as personal care, ambulation, household tasks, sexual function and recreation with respective metabolic costs. Each item has a specific weight based on the metabolic cost. The final score ranges between 0 and 58.2 points. The higher the score, the better the functional capacity.

14.3 Pharmacodynamic Assessments

14.3.1 Pulmonary Function (Spirometry)

Spirometry measures will be taken at the time points delineated in the Study Events Flow Chart (Section 6) using a standard calibrated spirometer to determine the parameters detailed below.

- FEV_1;
- FVC (forced vital capacity);
- FEV_1/FVC;
- IC.

Short acting β2-agonist and anticholinergic bronchodilators (e.g., albuterol, ipratropium bromide) and long acting β2-agonist and anticholinergic bronchodilators (e.g., salmeterol, tiotropium) agents will be withheld approximately 4 and 24 hours, respectively, before each pre-bronchodilator spirometry.

Every effort will be made to perform all assessments for a given patient on the same instrument throughout the study.

At screening, baseline pre-bronchodilator spirometry will be performed (prior to albuterol administration) for a minimum of 3 times and a maximum of 8 times in order to obtain 3 manoeuvers with FEV_1 values within 150 mL of each other, using the manoeuver with the highest value of FEV_1 and FVC as the basis for comparison.

Patients shall receive 4 inhalations of albuterol (100 µg/inhalation) for a total dose of 400 µg via metered-dose inhaler using a spacer. Within approximately 20 to 30 minutes after albuterol administration, the baseline post-bronchodilator spirometry will be performed.

Assessment of FEV_1 stability will take place:

1. Prior to Day 1 dosing of the Treatment Period (Check-in measurement): Predose FEV_1 is defined as the time point prior to Day 1 dosing in the Treatment Period and will be performed pre- and post-bronchodilatator administration. Predose FEV_1 will be compared to the corresponding baseline measurement. If the best FEV_1 measurement at predose at Check-in of the Treatment Period has declined by greater than 20% from the best FEV_1 at screening, the visit may be rescheduled up to 3 times, at the discretion of the Investigator.

2. Following Day 1 dosing: At all other spirometry time point, measurements will be performed once. If the value shows a difference of greater than 150 mL decline than the best FEV_1 value collected predose at Check-in, up to 3 measures will be performed.

   Consideration should be given, if a patient experiences any change in post Day 1 dose FEV_1 from the Day 1 predose FEV_1 value (measured following dosing with albuterol) equal to or greater than 20 % and should alert the Investigator to consider whether individual patients should continue to dose. The pulmonary function manoeuver(s) used to make this assessment must be valid and meet acceptable quality spirometry standards.

The Investigator may also use his or her discretion as to the completion of dosing for any period in which an FEV_1 decline and/or respiratory symptoms occur(s).

14.3.2 Bronchoscopy and Bronchoalveolar Lavage (BAL) Biomarkers

Patients will be fasted for 12 hours before the bronchoscopy procedures. If required, blood pressure medications can be taken with small sip of water based on preapproval of local Investigator.

14.3.2.1 Bronchoscopy

The bronchoscopy with bronchial brushings will be performed at the time points delineated in the Study Events Flow Chart (Section 6) by a licensed physician experienced in conducting the procedure according to guidelines published on the use of bronchoscopy for research on airway diseases such as COPD.[6,7]

Albuterol will be administered 20 minutes prior to the beginning of the bronchoscopy. An intravenous line will also be established to administer conscious sedation, and to administer emergency medications if the need were to arise. During the procedure, oxygen saturation (S_PO_2), blood pressure, and heart rate and rhythm (continuous electrocardiogram) will be monitored. Oxygen 2-4 L via nasal cannula will be administered during bronchoscopy and oxygen saturation will be maintained at ≥95%. Conscious sedation will be achieved with incremental doses of 1–4 mg midazolam and 50-100 µg fentanyl. Local upper and lower airway topical anesthesia will be achieved with 1% or 2% lidocaine. The dose of lidocaine administered during the procedure will not exceed a total of 450 mg. The bronchoscope will usually be inserted preferably through the nares into trachea. The bronchoscope will be wedged into 2 subsegments of the right middle or lower lobe, as deemed appropriate by the Investigator. Emergency treatments for cardiopulmonary arrest and pneumothorax will be immediately available in the bronchoscopy room. The patient will remain in the recovery suite for observation for a minimum of 2 hours after the procedure.

14.3.2.2 Bronchial Brushings

Prior to BAL, a cytology brush is inserted into the bronchoscope channel and brushings are collected twice from each of 4 quadrants of visible subsegments of the right middle or lower lobe, as deemed appropriate by the Investigator, under direct visualization. The cellular material is washed off in saline following each brushing. The brushing is performed a total of 8 times. The liquid is centrifuged and the cell pellet is stored at -70°C.

Samples must be protected from UV light during collection, processing, and storage.

14.3.2.3 Bronchoalveolar Lavage (BAL)

BAL in the right middle or lower lobe, as deemed appropriate by the Investigator, will be performed at the time points delineated in the Study Events Flow Chart (Section 6) by a licensed physician experienced in conducting the procedure. A total of 180 mL BAL, using 6 x 30 mL aliquots of normal saline warmed to room temperature, will be performed using each subsegment of the right middle or lower lobe, as deemed appropriate by the Investigator. BAL fluid will be aspirated following each 30 mL instillation. The lavage material, which averages 25% return in COPD patients, typically yields 1-10 x 10^6 macrophages. The centrifuged cell pellet and supernatant will be kept cooled until processed or stored as indicated in the laboratory manual to be provided as a separate document.

Samples must be protected from UV light during collection, processing, and storage.

14.3.2.4 Biomarkers

BAL samples will be analyzed for:

- YPL-001 component levels in epithelial brushings;
- total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells
- total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils

as absolute inflammatory cell numbers

- concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9.

14.3.3 Blood Biomarkers

Blood samples will be collected via direct venipuncture or an angiocatheter at the time points delineated in the Study Events Flow Chart (Section 6) for PD assessments of biomarkers. Biomarker assessments include:

- inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils, and lymphocytes)
- concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9.

Blood will be drawn into 3 tubes. A manual for blood sampling, collection, processing, and sample shipment will be provided in a separate document.

14.3.4 Quality of Life Questionnaires

14.3.4.1 Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI)

Dyspnea at baseline (Check-in of the Treatment Period) will be assessed with the BDI. This instrument has 3 domains (functional impairment, magnitude of task, and magnitude of effort) with the values added for a combined focal score. Functional impairment determines the impact of breathlessness on the ability to carry out activities; magnitude of task determines the type of task that causes breathlessness, magnitude of effort establishes the level of effort that results in breathlessness. The BDI scores range from 0 (very severe impairment) to 4 (no impairment) for each domain with the baseline focal score consisting of the sum of each domain (0 to 12).

Dyspnea throughout the study will be performed at the time points delineated in the Study Events Flow Chart (Section 6). The change from baseline is measured by the TDI score which ranges from -3 (major deterioration) to +3 (major improvement) for each domain with the TDI focal score consisting in the sum of each domain (-9 to +9).

The same Investigator or designee will interview specifically the patients during the study.

A copy of the questionnaire to be used will be kept in the study binder.

14.3.4.2 COPD Assessment Test (CAT)

CAT is a short and simple questionnaire of 8 items completed by patients to be performed at the time points delineated in the Study Events Flow Chart (Section 6). Scores for each of the 8 items are summed to give a single, final score ranging from 0 (no impact on daily activities) to 40 (very high impact on daily activity). This is a measure of the overall impact of a patient's condition on their life. Scores for the individual items within the questionnaire will provide insight into the relative influence that the different components of COPD have on its overall impact on a patient's life.[8,9]

A copy of the questionnaire to be used will be kept in the study binder.

14.4 Pharmacokinetic Assessments

The sampling schedule and/or collection intervals delineated in the Study Events Flow Chart (Section 6) may be modified based on the results from previously dosed patients.

14.4.1 Blood Sampling and Processing

Samples must be protected from UV light during collection, processing, and storage.

Samples will be collected via direct venipuncture or an angiocatheter at the time points delineated in the Study Events Flow Chart (Section 6).

Blood will be drawn into 4 mL pre-chilled evacuated tubes containing K_2EDTA. A manual for blood sampling, collection, processing, and sample shipment will be provided in a separate document.

14.5 Blood Volume for Study Assessments

Table 5: Blood Volume during Study

Sample Type	Number of Time Points	Volume per Time Point*	Sample Volume Over Course of Study
Screening laboratory safety tests (including hematology, serum chemistry, serology, PT/INR), FSH (for postmenopausal female patients only), and serum pregnancy (for female patients only).	1	~ 17 mL** or 21 mL***	~ 17 mL** or 21 mL***
On-study serum chemistry and serum pregnancy (for female patients only) when scheduled at the same time	3	~ 8.5 mL	~ 25.5 mL
Additional on-study serum pregnancy (for female patients only)	2	~ 3.5 mL	~ 7 mL
On-study hematology	3	~ 4 mL	~ 12 mL
Blood samples for PD biomarkers (except CRP and fibrinogen)	8	~ 6 mL	~ 48 mL
Blood samples for PD biomarker - CRP	8	~ 4 mL	~ 32 mL
Blood samples for PD biomarker - Fibrinogen	8	~ 3.5 mL	~ 28 mL
Blood samples for PK of verproside and picroside II	37	~ 4 mL	~ 148 mL
Total Blood Volume for males† →			~ 310.5 mL** or 314.5 mL***
Total Blood Volume for females† →			~ 317.5 mL **or 321.5 mL***

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

** For patients enrolled at UAB Lung Health Center, Florida Pulmonary Research Institute, LLC, or Temple University School of Medicine.

***For patients enrolled at Aventiv Research Inc. only.

† If an angiocatheter is used, up to 5 mL of blood will be used to flush the catheter prior to each collection of PK and/or PD blood samples. Hence the total blood volume collected may increase by approximately 205 mL.

15. DATA ANALYSIS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCPs.

15.1 Statistical Analysis

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a SAP. The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP.

15.1.1 Sample Size Calculation

According to the exploratory nature of this study no formal statistical hypotheses will be tested. However, a sample size of 60 evaluable patients is deemed to be sufficient to assess the safety and tolerability and to provide an indication of the potential effect of YPL-001 on COPD exacerbation symptoms, selected biomarkers and pulmonary function parameters.

15.1.2 Patients to Analyze

Safety population: the safety population data set will include all available data for patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo. Safety data for all discontinued patients will be included in this set for the time points for which their data are available.

Symptom monitoring population: the symptom monitoring population data set will include all available data for patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo. Symptom monitoring data for all discontinued patients will be included in this set for the time points for which their data are available.

PK population:

- The PK full data set will include all patients receiving at least one dose of YPL-001 and having at least one measurable plasma concentration of verproside and picroside II.
- The PK per-protocol data set will include all patients receiving all scheduled doses of YPL-001 and having sufficient samples collected to determine PK parameters from plasma concentrations of verproside and picroside II on Day 1 and/or Day 54 (± 1 day).

PD population:

- The PD full data set will include all patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo and provide at least 1 post-baseline PD measurement.

- The PD per-protocol data set will include all patients receiving all scheduled doses of the investigational product (i.e., YPL-001) or placebo and having measurable PD data.

PK/PD population: All patients who receive at least one dose of YPL-001 and having any measurable concentration of verproside and picroside II and measurable PD data will be included in the PK/PD relationship assessment, as applicable.

15.1.3 Safety Analysis

The following analyses will be performed. Safety analyses will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data, when appropriate.

Medical History:

Medical history will be listed by patient.

Adverse Events:

AEs will be coded using the most current MedDRA® available at Celerion (e.g., 17.0 or higher) and data will be summarized by SOC and preferred term. The number of TEAEs will be reported. In addition, the number and percent of patients reporting each TEAE will be summarized separately for each treatment.

A by-patient AE data listing, including verbatim term, preferred term, treatment, severity, outcome, and relationship to treatment, will be provided.

Physical Examination:

Changes in physical examinations will be described in the text of the final report and significant findings will be reported as AEs.

Clinical Laboratory Tests, Electrocardiograms, Vital Signs and Pulse Oximetry:

All clinical laboratory tests, 12-lead ECGs, vital signs, and pulse oximetry measurements and their change from baseline, if applicable, will be summarized by treatment and time point of collection.

A shift table describing out-of-normal range shifts will be provided for clinical laboratory results.

A normal-abnormal shift table will be presented for ECGs.

Peak Expiratory Flow:

PEF measurements and its change from baseline, will be summarized by treatment and time point of collection.

Concomitant Medications:

Concomitant medications will be listed by patient and coded using the most current WHO drug dictionary available at Celerion (e.g., 01-MAR-2014 or later).

15.1.4 Symptom Monitoring Analysis

Symptom free days and overall symptom burden will be evaluated and compared across treatment groups. Secondary outcome analysis will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative data and frequency counts will be compiled for classification of qualitative data, when appropriate.

Peak Expiratory Flow and Symptoms of COPD Exacerbation:

PEF measurements and symptoms of COPD exacerbation and their change from baseline will be summarized by treatment and time point of collection.

Dyspnea and Activity:

The Modified Borg Dyspnea Scale and DASI scores will be listed and presented descriptively.

Additional analysis may be performed if deemed appropriate.

15.1.5 Pharmacodynamic Analysis

15.1.5.1 Biomarkers

When applicable, the following PD biomarkers will be summarized by treatment group using descriptive statistics (arithmetic means, SD, CV, N, minimum, maximum, and median). Figures will be created to display mean and individual level or activity as a function of time, as appropriate:

- Pulmonary biomarker (i.e., Pulmonary Function measurements [Spirometry]): pre- and post-bronchodilator change in activity by time point will be calculated relative to the pre- and post-bronchodilator baseline activity;
- BAL biomarkers (i.e., total cell count [cells/mL] of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; total cell count [cells/mL] of neutrophils, macrophages, lymphocytes and eosinophils as absolute inflammatory cell numbers; and concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9): raw and % change from baseline levels; and
- Blood biomarkers (i.e., inflammatory markers [total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes] and concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9): raw and % change from baseline levels.

PK/PD relationship may be explored graphically using scatter plots and an appropriate regression model.

15.1.5.2 Quality of Life

The quality of life parameters reported from the BDI/TDI and CAT questionnaires will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.

15.1.6 Pharmacokinetic Analysis

15.1.6.1 Pharmacokinetic Parameters

15.1.6.1.1 Plasma

PK parameters will be computed from the individual plasma verproside and picroside II concentrations using a noncompartmental approach. Appropriate validated PK software (e.g., WinNonlin Professional) will be used. PK parameters for other components of YPL-001 and its metabolites may also be computed, as appropriate.

The following PK parameters will be computed following Day 1 morning dose:

AUC_{0-12}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to 12 hours.
AUC_{0-t}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (C_t). This parameter will be reported only if plasma concentrations fall below the lower limit of quantitation before the last time point prior to the evening drug administration on Day 1 for at least one patient. Otherwise, only AUC_{0-12} will be reported.
AUC_{0-inf}	Area under the drug concentration-time curve from time zero to infinity, $AUC_{0-inf} = AUC_{0-t} + C_t/k_{el}$, where k_{el} is the terminal elimination rate constant. †
C_{max}	Maximum observed drug concentration.
t_{max}	Time of the maximum drug concentration (obtained without interpolation).
k_{el}	Apparent terminal elimination rate constant, calculated by linear regression of the terminal linear portion of the log concentration vs. time curve. †
$t_{1/2}$	Apparent elimination half-life, calculated as $\ln(2)/k_{el}$. †
CL/F	Oral clearance [$Dose/AUC_{0-inf}$]. †
V_Z/F	Apparent volume of distribution at the terminal phase, calculated as $Dose/(k_{el} * AUC_{0-inf})$.†

† All k_{el} and related PK parameters ($AUC_{0\text{-}inf}$, $t_{1/2}$, CL/F, and V_z/F) will be reported only if the half-life of verproside or picroside II can be appropriately estimated from a 12-hour sampling period following dosing.

The following PK parameters will be computed following Day 54 (± 1 day) morning dose:

AUC_{τ}	The area under the plasma concentration versus time curve over the final dosing interval, as calculated by the log-linear trapezoidal method (e.g., 0-12 hours).
$AUC_{0\text{-}t}$	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (C_t).
C_{max_ss}	Maximum observed drug concentration at steady-state.
$C_{min,ss}$	Minimum observed/measured non-zero concentration at steady-state.
C_{trough}	Concentration at the end of a dosing interval.
C_{avg}	Ratio of AUC_{τ} to the dosing interval, τ.
%Fluc	Percent fluctuation will be calculated as follows: $\frac{C_{\max\_ss} - C_{\min\_ss}}{C_{avg}} \; x \; 100$
Swing	Percent swing will be calculated as follows: $\frac{C_{\max\_ss} - C_{\min\_ss}}{C_{\min\_ss}} \; x \; 100$
t_{max_ss}	Time to reach the maximum drug concentration (obtained without interpolation) at steady-state.
CL_{ss}/F	Total body clearance estimated at steady-state after oral administration, calculated as Dose/AUC_{τ}.
V_{z_ss}/F	Apparent volume of distribution at steady-state, calculated as (CL_{ss}/F)/k_{el}.*

* All k_{el} and related PK parameters ($t_{1/2}$ or V_{z_ss}/F) will not be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

If metabolite data are available, metabolite to parent ratios may be calculated for $AUC_{0\text{-}t}$, AUC_{τ}, and C_{max_ss}.

15.1.6.1.2 Bronchoalveolar Lavage

Levels of YPL-001 components in epithelial brushing will be listed.

15.1.6.2 Statistical Methods for Pharmacokinetic Analyses

PK parameters will be summarized by treatment group using descriptive statistics (arithmetic means, SD, CV, N, minimum, maximum, and median). In addition, geometric means will be calculated for AUC_{τ} and C_{max_ss}, as appropriate. Figures will be created to display mean and individual verproside and picroside II concentration-time curves. Additional PK analyses may be performed if deemed appropriate.

No value for k_{el}, $t_{1/2}$, and V_{z_ss}/F, as appropriate, will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

An estimate of the relative systemic exposure of AUC_{τ} and C_{max_ss} will be performed by dose normalized ratio analysis expressing the geometric mean ratio and 90% CI of the geometric mean ratio.

Steady-state will be assessed by visual inspection of predose plasma C_{trough} values on Days 15 (± 2 days), 29 (± 2 days), 43 (± 2 days), and 54 (± 1 day) following multiple oral dose administration of YPL-001.

Additional analyses will be performed as deemed necessary upon review of the data.

15.1.7 Assessment of Efficacy

Efficacy will not be assessed in this study.

16. STUDY ADMINISTRATION

16.1 Ethics

16.1.1 Institutional Review Board

This protocol will be reviewed by an IRB and the study will not start until the Board has approved the protocol or a modification thereof. The Board is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The board is ICH compliant.

16.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, GCP, 21 CFR Parts 50, 56, and 312, the ethical princliples set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

16.1.3 Patient Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the patients in non-technical terms. Patients will be required to read, sign and date an informed consent form summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Patients will be given a copy of their informed consent form.

16.2 Termination of the Study

The Sponsor reserves the right to discontinue this study and the Investigator reserves the right to terminate their participation at any time.

16.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion relevant to the quality of this study. Designated personnel of Celerion will be responsible for maintaining quality assurance (QA) and quality control (QC) to ensure that the trial is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and Good Laboratory Practice requirements as well as applicable regulatory requirements.

The Clinical Study Report will be audited by the QA department and the quality assurance audit certificate will be included in the study report.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to statistical database lock.

Patient compliance will be monitored throughout the study via procedures such as questioning at check-in to review inclusion and exclusion criteria, urine drug screen at

check-in, mouth check following dosing, and confinement for all conduct procedures with clinical research staff on site at all times.

16.4 Direct Access to Source Data/Documents

The Investigator must maintain, at all times, the primary records (i.e., source documents) of each patient's data. Examples of source documents are laboratory reports, drug inventory, study drug label records, and eCRFs that are used as the source.

Celerion will ensure that the sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6] 5.1.2 & 6.10). In the event that other trial-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

16.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of YPL-001 80 mg tablets, and matching placebo tablets to allow completion of this study. The lot numbers and expiration dates (where available) of the drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the drugs supplied. At the conclusion of the study, any unused drugs (including placebo) will either be retained by the CRU, or returned to the Sponsor, depending on the specific requirements of the regulatory bodies to whom the study report will be submitted. If no supplies remain, this fact will be indicated in the Drug Accountability section of the final report.

16.6 Data Handling and Record Keeping

Celerion standard eCRFs will be used. Each eCRF is reviewed and signed off by the Investigator.

All raw data generated in connection with this study, together with the original copy of the final report, will be retained at each CRU in a designated storage facility, until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

16.7 Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be discussed between Sponsor and the Investigator. All revisions and/or amendments to the protocol in writing must be approved by the Sponsor, the Investigator, and the IRB before implementation.

16.8 Finance and Insurance

Finance and insurance will be addressed in a separate document.

16.9 Publication Policy

All unpublished information given to Celerion by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor's written consent to publish the article.

17. REFERENCES

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[9] The COPD Assessment Test healthcare professional user guide: expert guidance on frequently asked questions (issue 3: February 2012). Jones PW, Jenkins C, Bauerle O (on behalf of the CAT Development Steering Group).

18. APPENDICES

18.1 Appendix 1 - SULT Drug Interaction Table

The following list provides medications that are substrates and inhibitors of sulfotransferase. Adapted from Zhang H, Cui D, Wang B, Han YH, et al. Pharmacokinetic drug interactions involving 17alpha-ethinylestradiol: a new look at an old drug. Clin Pharmacokinet. 2007;46(2):133-57; Coughtrie MW, Johnston LE. Interactions between dietary chemicals and human sulfotransferases-molecular mechanisms and clinical significance. Drug Metab Dispos. 2001;29(4 Pt 2):522-528; King RS, Ghosh AA, and Wu J Inhibition of human phenol and estrogen sulfotransferase by certain non-steroidal anti-inflammatory agents. Curr Drug Metab. 2006;7(7):745–753; Nagai M, et al. Inhibitory effects of herbal extracts on the activity of human sulfotransferase isoform sulfotransferase 1A3 (SULT1A3). Biol Pharm Bull. 2009;32(1):105-109; and Harris, R. M.; Waring, R. H. Sulfotransferase inhibition: potential impact of diet and environmental chemicals on steroid metabolism and drug. Current Drug Metabolism 2008;9(4):269-275.

Inhibitors
17-beta-estradiol glucuronide
Vitamin C
Brown rice
Beer
Meclofenamate
Nimesulide
Salicylic acid
Acetylsalicylic acid
Naproxen
Banaba extract
Rafuma extract
Grape seed extract
Peanut seed coat extract
Gingko extract
Biloba leaf extract
St. John’s wort
Gymnema
Milk thistle

Celerion Project No.: AA98497

Sponsor Project No.: YPL-001-YJP-130403

IND No.: 114903

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

1. PROTOCOL REVISION HISTORY

DATE/NAME	DESCRIPTION
28-Apr-2016 by Caroline Engel	Final Protocol, Amendment 6 This protocol amendment is generated to change the Sponsor representative, CEO and President, to Su-Jun Park. Therefore Section 2 Sponsor – Signatories was updated accordingly. And to add the following Investigator and clinical site: Faisal Fakih, MD Florida Pulmonary Research Institute, LLC 1788 W. Fairbanks Avenue,Suite B Winter Park, Florida, 32789 United States Tel.: +1 407 740-8078 Therefore, Section 3 Investigators Signatures was updated accordingly. Section 4 Additional Key Contacts for the Study was also updated to add the corresponding certified clinical laboratory. In addition, the following changes were made to facilitate the clinical conduct at each investigative site: 1. To allow patients to recover from the bronchoscopy procedure before going through a 12 hours' period of PK blood draws and collect quality samples, a recovery period was added between these procedures; Procedures scheduled on Day -1 will now be performed within 3 days prior to Day 1 (now defined as Check-in procedures). In addition, the PK sampling previously scheduled on Day 56 will be conducted on Day 54 (± 1 day) before the bronchoscopy now scheduled on Day 56, instead of Day 55. Therefore, the following sections were updated acccordingly: • Section 5 Synopsis - Summary of Study Design, Dosage, Dosage Form, Route, and Dose Regimen, and Exploratory Outcome Measures. • Section 6 Study Events Flow Chart • Section 13.1 Overall Study Design and Plan • Section 13.2.4 Treatment Period (Days 1 to 56) • Section 13.2.4.1 Meal Schedule • Section 13.3.5.2 Prohibitions • Section 13.4.1.2 Drug Administration During Treatment Period • Section 14.3.1 Pulmonary Function (Spirometry) • Section 14.3.4.1 Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) • Section 15.1.2 Patients to Analyze • Section 15.1.6.1.1 Plasma

DATE/NAME	DESCRIPTION
28-Apr-2016 by Caroline Engel	• Section 15.1.6.2 Statistical Methods for Pharmacokinetic Analyses 2. To provide flexibility in the schedule of events, electrocardiograms, vital sign and pulse oximetry will be measured within 4 hours of bronchoscopy procedures, instead of 2 hours. Therefore, Section 6 Study Events Flow Chart, Section 14.1.3 Vital Signs, Section 14.1.4 Pulse Oximetry, and Section 14.1.5 Electrocardiogram Monitoring were updated accordingly. 3. Exclusion criterion #9 was updated to clarify that patients withclinically significant cardiac arrhythmia; prostatic hyperplasia; bladder-neck obstruction; urinary retention; and narrow-angle glaucoma that, in the opinion of the PI, would contraindicate the administration of tiotropium, will be excluded. 4. To allow flexibility, subjects with a positive alcohol screen or subjects reporting consumption of alcohol within 48 hours prior to testing, an alcohol test may be rescheduled or repeated, at the discretion of the PI if there is sufficient time remaining to perform the visit procedures within the time window specified for this visit (e.g., ± 2 days of Day 15 visit). Therefore exclusion criterion # 13 was split into two exclusion criteria; criteria #13 (alcohol screen) and #14 (drug screen), which were updated accordingly. 5. Exclusion criterion #15 was updated to exclude subject with a positive results for hepatitis C antibodies only if they present with clinically significant liver impairment and/or a viral ribonucleic acid (RNA) titer of > 6.9 ± 0.8log molecules/mL. Section 14.1.6.3 Serology was updated accordingly. Section 17 Reference was updated to include reference #3 as a justification to the titer value selected. 6. The Child-Pugh scale should only be used to classify patients with a diagnosis of hepatic impairment. Thus, exclusion criteria #11 was clarified to exclude patients with diagnosed hepatic impairment and a Child-Pugh class A score or higher. Patients without hepatic impairment with normal laboratory results for bilirubin, albumin, prothrombin time/international normalized ratio (which automatically would fall in a Class A Score of 5) will not be assigned a Child-Pugh score and will thus be allowed to enrol. In addition, to assess the extent of hepatic impairment according to exclusion criterion # 11, a blood sample for prothrombin time/international normalized ratio will be collected at screening. Thus, a new section (14.1.6.9 Additional Tests) was added, and Section 6 Study Events Flow Chart, Section 8 Abbreviations, and Table 5: Blood Volume during Study were updated accordingly. 7. Prescribed vitamin supplement will be allowed, therefore the following sections were updated accordingly: • Section 13.3.5.1.1 Prohibited Therapy • Section 13.3.5.1.2 Permitted Therapy 8. Minor editorial and typographical corrections were made where applicable.

DATE/NAME	DESCRIPTION
05-Nov-2015 by Caroline Engel	Final Protocol, Amendment 5 This protocol amendment is generated to add the following Investigator and clinical site: Samir Arora, MD Aventiv Research Inc. 99 North Brice Road, Suite 260 Columbus, Ohio 43213 United States Tel: + 1 614 501-6164 Therefore, Section 3 Investigators Signature was updated accordingly. Section 4 Additional Key Contacts for the Study was also updated to add the correcponding certified clinical laboratory. All 3 sites clinical sites will be using the Western Institutional Review Board. Section 4 Additional Key Contacts for the Study was updated accordingly. Minor editorial corrections were made where applicable.
16-Sep-2015 by Caroline Engel	Final Protocol, Amendment 4 This protocol amendment is generated to clarify and adjust study procedures as listed below: 1. Brigham and Women's Hospital Investigator signature and contact information was removed throughout the protocol since the center will not be participating during this study. The following sections were updated accordingly: • Section 3 Investigators Signatures • Section 4 Additional Key Contacts for the Study 2. The age limits were changed from 40 - 80 years of age, inclusively, to 30 - 85 years of age, inclusively. The following sections were updated accordingly: • Section 5 Synopsis - Study Population • Section 13.3.2 Inclusion Criteria – Inclusion criterion #1 3. To provide scheduling flexibility to the patients, a ±2-day window was added to the return visits on Days 15, 29, and 43. The following sections were updated accordingly: • Section 5 Synopsis - Summary of Study Design and Exploratory Outcome Measures • Section 6 Study Events Flow Chart • Section 13.1 Overall Study Design and Plan • Section 13.4.1.2 Drug Administration During Treatment Period • Section 15.1.6.2 Statistical Methods for Pharmacokinetic Analyses

DATE/NAME	DESCRIPTION
16-Sep-2015 by Caroline Engel	4. Breathalyzer was added as an alternative method to the urine dipstick for the alcohol screen. The following sections were updated accordingly: • Section 6 Study Events Flow Chart • Section 13.3.3 Exclusion Criteria – Exclusion criterion #13 • Section 14.1.6.7 Urine/Breathalyzer Alcohol Screen was added • Section 14.1.6.8 (previously 14.1.6.7) was renamed Urine Drug Screen (previously Urine Drug/Alcohol Screen). 5. Only patients suffering from severe sleep apnea, as assessed by the Berlin Questionnaire, will be excluded from the study; The following sections were updated accordingly: • Section 6 Study Events Flow Chart • Section 13.3.3 Exclusion Criteria - exclusion criterion #8. • Section 14.1.8 Berlin Questionnaire was added. 6. The body mass index upper limit was increased from 32.0 kg/m^2 to 40.0 kg/m^2 inclusively. Therefore inclusion criterion #5 of Section 13.3.2 Inclusion Criteria was revised accordingly. 7. Drug screen false positive will be allowed if they are due to the use of prescription medication following approval from the PI and the medical monitor, the exclusion criterion #13 of Section 13.3.3 Exclusion Criteria was revised accordingly. 8. Smoking restriction prior to the bronchoscopy procedures was removed. Therefore, Section 14.3.2 Bronchoscopy and Bronchoalveolar Lavage (BAL) Biomarkers was updated accordingly. 9. Only strong and moderate inhibitors of UDP-glucuronosyltransferase and/or sulfotransferases are prohibited, therefore to prevent confusion with the list of substrats that was provided in Appendix 1, Appendix 1 was remove and the only 3 inhibitors listed in that table was enumarated in exclusion criterion #18. The list of substrate in appendix 2 (now rename Appendix 1) was also remove. This change will prevent possible confusion with the lists provided in the appendices. Exclusion criterion #18 of Section 13.3.3 Exclusion Criteria was revised accordingly. 10. To be consistent with Section 6 Study Events Flow Chart, pulse oximetry was added to the order of procecedures listed in Section 14.1 Safety Assessments. 11. Typographic and editorial corrections were made where applicable.

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	Final Protocol, Amendment 3 This protocol amendment is generated to clarify and adjust study procedures as listed below. The changes to the protocol are presented with new text in **bold** font and deleted text in ~~strikethrough~~ font. **Serious Adverse Event Contact Information** Drug Safety Solution's Medical Monitor will be contacted in case of serious adverse events. Hence the information under Sponsor Contact for Serious Adverse Events (Medical Monitor) in Section 4 Additional Key Contacts for the Study was corrected as follows: ~~Primary Contact:~~ ~~Yongnam Lee, Ph.D.~~ ~~Principal Scientist,~~ ~~Yungjin Pharm. CO., LTD.~~ ~~#451-20 Cheonho-3 dong, Gangdong-gu, Seoul, 134-721, Republic of Korea~~ ~~Tel.: +82-(31) 546-6980 ext. 220~~ ~~Fax: +82-(31) 546-6983~~ ~~E-mail: nami0209@yungjin.co.kr~~ ~~Mobile: +82-(10) 6311-4228~~ ~~Secondary Contact:~~ ~~Kangrae Ha, B.Sc.~~ ~~E-mail: hakr@yungjin.co.kr~~ **Dr. Kathy Smith** **Drug Safety Solution** **Tel.: +1 919 264-5626** **E-mail: ksmith@drugsafety.biz** Section 14.1.8.4 Serious Adverse Events and Section 13.4.3.2 Procedures for Breaking the Blind Prior to Study Completion was also corrected accordingly. **Certified Clinical Laboratory:** Brigham and Women's Hospital and UAB Lung Health Center clinical laboratories contact information were added to Section 4 Additional Key Contacts for the Study. **Clinical Indication:** As indicated in the objectives of the study, the study will examine the pharmacodynamic (PD) effect of YPL-001 in patients with chronic obstructive pulmonary disease (COPD) only. Therefore, to prevent potential confusion and to capture the intended indication of the study specifically "asthma" was removed from the Clinical Indication in Section 5 synopsis and Section 10.1 Purpose of the Study.

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	**Study Population:** As indicated throughout the protocol, patients will be will be adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3). Hence to be consistent with the GOLD Stage standards, the first sentence under Study Population from Section 5, Synopsis was corrected as follow: "Patients will be adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3) with a predominant bronchitic component ~~and a history of frequent (>2/year) COPD exacerbations,~~ between 40 and 80 years of age (inclusive)." **Randomization and Drug Dispensing** Instruction for randomization and drug dispensing are provided in a separate document. To be consistent with this document, which states that two sets of randomization code envelopes will be provided to site pharmacist/study coordinators and patients will received appropriately labeled kits and/or any unused wallets from previously provided kits (when applicable) for YPL-001 home dosing in addition to the containers for tiotropium/albuterol home dosing, the following section were modified accordingly: • Section 5 Synopsis under Summary of Study Design and Study Products • Section 6 Study Event Flow Chart, Day 1 Study Drug Administration at CRU - Footnotes "k" and "p" • Section 6 Study Event Flow Chart, Days 2 to 55 Study Drug Administration at Home – Footnotes "j" and "o" • Section 13.1 Overall Study Design and Plan • Section 13.4.1.2 Drug Administration During Treatment Period • Section 13.4.3.1 Maintenance of Randomization • Section 13.4.3.2 Procedures for Breaking the Blind Prior to Study Completion In addition, and "X" was also added in the "Randomization" row under Day 1 predose in Section 6 Study Events Flow Chart. **Fasting Conditions** As indicated throughout the protocol, subjects will be required to fast for at least 8 hours before and 4 hours after YPL-001/placebo morning administration on Days 1 and 56. For clarity, footnote "q" was added to Day 1 Study Drug Administration at CRU and footnote "k" was added to Day 56 Study Drug Administration at CRU in Section 6 Study Events Flow Chart. **Analytes to be Measured** As indicated throughout the protocol, blood samples will be collected for

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	the analyses of verproside and picroside II in plasma. Hence, the row identified as "Blood for Verproside Phamacokinetics" on Day 56 of Section 6 Study Events Flow Chart, was corrected to read: "Blood for Verproside **& Picroside II PK**". **End-of-Treatment – Early Termination Procedures** All procedures listed under End-of-Treatment/Early Termination column in Section 6 Study Events Flow Chart are also scheduled to be performed on Day 55 before the bronchoscopy procedures. Therefore, as it is not required to repeat these procedures for two consecutive days, End-of-Treatment procedures were removed on Day 56, however early termination (ET) procedures were listed under the new ET column. Hence, the following sections were corrected accordingly. • Section 6 Study Events Flow Chart • Section 13.2.4.2 End-of-Treatment or Early Termination (Day 56), (renamed Section 13.2.4.2 Early Termination). • Section 13.3.2 Inclusion Criteria – Criterion #16 • Section 13.3.4 Removal of Patients from the Study • Section 13.3.5.1.1 Prohibited Therapy • Section 13.3.5.1.2 Permitted Therapy • Section 14.1.8.2 Monitoring • Section 14.5 Blood Volume for Study Assessments (Table 5: Blood Volume during Study) In addition, the following sentence was added to Section 13.2.4.2 End-of-Treatment or Early Termination (Day 56), (renamed Section 13.2.4.2 Early Termination): "Patients who want to terminate from the study and are not currently on-site will be contacted and asked to return to the CRU to perform the early termination procedures" **Investigator's Brochure Version** In Section 9.1 YPL-001, the Investigator's Brochure version was updated to reflect the reference section and the most recent version of the Investigator's Brochure. **Method of Blood Collection** Throughout the protocol, the option of using an angiocatheter was added. Hence, the following sections were corrected accordingly: • Section 11 Risk/Benefit • Section 14.3.3 Blood Biomarkers • Section 14.4.1 Blood Sampling and Processing • Section 14.5 Blood Volume for Study Assessments **Recording of Meal** To be consistent with clinical sites standard procedures, the last sentence

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	of Section 13.2.4.1 Meal Schedule was corrected as follow: "Meals are not required to be completed by patients ~~and all meals and snacks eaten by patients will be recorded on the CRFs~~.' **Coffee, Tea and Alcohol Prohibition** As indicated in Section 13.3.5.2 Prohibitions, coffee tea, and red wine will be restricted for 7 days prior to Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample. Beer will be restricted for 14 days prior to Day 1 of the Treatment Period through collection of Day 56 last PK sample. Any other product containing xanthines or caffeine will be restricted 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample. Any other alcohol product will be restricted 48 hours prior to each CRU visit, 48 hours prior to dosing on Days 1 and 56 last PK sample. Hence, the xanthines/caffeine prohibition and the alcohol prohibition were corrected as follows for clarification: "Xanthines/caffeine **(other than coffee and tea)**: 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample." "Alcohol **(other than red wine and beer)**: 48 hours prior to each CRU visit, 48 hours prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample." **e-Diary** Home dosing will be recorded using a yes/no answer in the e-diary. Therefore the last sentence of the second to last paragraph of Section 13.4.1.2 Drug Administration During Treatment Period was corrected as follows: ***"***Patients will be given instructions on ~~recording of dosing times~~ **how to record their drug administration** in their e-diary on home-dosing days.' In addition, estimation of sputum quantity was added to the list of major symptoms of COPD exacerbation recorded daily by the patients on their e-diary, "color" and "consistency" was moved as example of sputum quality, and a statement indicating that the e-diary device will be return in case of early termination was also added. Hence, the following sections were corrected accordingly: • Section 5 Synopsis under Secondary Outcome Measures • Section 5 Synopsis under Summary of Study Design • Section 6 Study Events Flow Chart – Day 1, Footnote "j" • Section 6 Study Events Flow Chart – Days 2-55, Footnote "i" • Section 6 Study Events Flow Chart – Day 56, Footnotes "g" and "h" • Section 12.2 Study Endpoints • Section 13.1 Overall Study Design and Plan • Section 13.2.3 Run-In Period (Days 1 to 14 [± 2 days]) • Section 13.2.4 Treatment Period (Days 1 to 56)

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	• Section 14.2.1 Electronic Diary • Section 14.2.3 Symptoms of Chronic Obstructive Pulmonary Disease Exacerbation **Treatment Compliance** Drug administration at home will be monitored by HGE Technologies Inc. via the e-diary. Therefore, the last sentence of Section 13.4.4. Treatment Compliance was corrected as follow: "Self-administration by patients at home will be monitored ~~by the CRU~~ via the e-diary and attempted phone calls will be performed to remind patients to take their medication, if they did not record their self-administration on the e-diary." **Oxygen Saturation** For consistency throughout the protocol, "oxygen levels, saturation (%)" was replaced with "oxygen saturation (%)." **Tiotropium Treatment** As indicated in Section 13.3.2 Inclusion Criteria and Section 13.3.5.1.2 Permitted Therapy, tiotropium will be withheld 24 hours prior to pulmonary function (spirometry) measurements. Hence, the 2nd paragraph of Section 14.3.1 Pulmonary Function (Spirometry), was corrected to read: "Short acting β2-agonist and anticholinergic bronchodilators (e.g., albuterol, ipratropium bromide) and long acting β2-agonist and anticholinergic bronchodilators (e.g., salmeterol, tiotropium) agents will be withheld approximately 4 and ~~12~~ **24** hours, respectively, before each pre-bronchodilator spirometry." **Spirometer Across Clinical Site** The 3rd paragraph of Section 14.3.1 Pulmonary Function (Spirometry) was corrected as follow: "Every effort will be made to perform all assessments for a given patient on the same instrument throughout the study~~ and all sites should be using the same brand and model of spirometer for this study~~." **Bronchoalveolar Lavage (BAL) Collection** It is planned that a maximum of 180 mL BAL will be performed during each planned bronchoscopy procedures. Therefore, to prevent confusion, the second sentence of Section 14.3.2.3, Bronchoalveolar Lavage (BAL) was corrected to read: "A **total of** 180 mL BAL**, using 6 x 30 mL aliquots of normal saline warmed to room temperature,** will be performed ~~in~~ **using** each subsegment of the right middle or lower lobe, as deemed appropriate by the Investigator~~, using 6 x 30 mL aliquots of normal saline warmed to room temperature~~." **Blood Volume for Clinical Safety Laboratory Tests, Pharmacodynamic (PD) Markers and Pharmacokinetic (PK) Samples:**

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	Blood collection volume for PD markers, as indicated in Section 14.3.3 Blood Biomarkers and Section 14.5 Blood Volume for Study Assessments, only accounts for 1 tube. However, 3 tubes will be required to assess CRP (4 mL tube), fibrinogen (3.5 mL tube) and the rest of the PD biomarkers (6 mL tube). The blood volume per time point will be approximately 13.5 mL instead of 4.5 mL. As indicated above, End-of-Treatment listed on Day 56 were removed as the same tests are scheduled on Day 55 before the bronchoscopy procedures. Hence one sample was removed for a total of 3 on-study hematology and serum chemistry tests to be performed throughout the study. In addition, 4 mL of blood will be sufficient for the determination of verproside and picroside II concentration in plasma at each time point. Therefore the total blood volume was corrected to 310.5 mL for males and 317.5 mL for females. Section 14.3.3 Blood Biomarkers, Section 14.4.1 Blood Sampling and Processing, and Section 14.5 Blood Volume for Study Assessments were corrected accordingly. Minor typographic and editorial corrections were made where applicable.
16-Feb-2015 by Caroline Engel	Final Protocol, Amendment 2 This protocol amendment is generated to clarify and adjust study procedures as listed below. **Number of Subjects:** The sample size was revised to 60 subjects as it is sufficient to meet the objectives of the study. In case of dropouts, discontinued patients may be replaced at the discretion of the Sponsor as indicated throughout the protocol. Therefore the following sections were corrected accordingly to indicate that at least 60 subjects are planned to be enrolled and randomized with 20 patients to receive one of the 3 treatments: • Section 5 Synopsis (the 1st sentence of the 2nd paragraph under Summary of Study Design and the 1st and 2nd sentences under Number of Patients). • The 1st sentence of the 2nd paragraph of Section 13.1 Overall Study Design and Plan. • The 1st and 3rd sentences of Section 13.3.1 Number of Patients. • The last sentence of Section 15.1.1 Sample Size Calculation. **Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) and COPD Assessment Test (CAT):** BDI/TDI and CAT questionnaires will not be used as a diagnostic tool to assess the patient's potential to meet all inclusion criteria and none of the exclusion criteria. Therefore these questionnaires are not required at screening. In addition, it is not required to perform them for 2 consecutive days to meet the study objectives and therefore, Day 55 assessments were removed.

DATE/NAME	DESCRIPTION
16-Feb-2015 by Caroline Engel	Section 6 Study Events Flow Chart was corrected accordingly. The first sentence in Section 14.3.4.1 Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) was also corrected to be consistent with Section 6. **Early Termination Procedures:** Weight, and oxygen levels, saturation (%), and heart rate assessed using a pulse oximeter were added to the procedures performed at the end of the Treatment Period on Day 56 or prior to early termination from the study to monitor subject's safety appropriately. A pulmonary function (spirometry) test was also added prior to early termination for safety monitoring. Section 6 Study Events Flow Chart was corrected accordingly. **Recording Concomitant Medication:** Concomitant medication will be recorded at each study visit by the clinical staff in to the electronic data capture system. Therefore, concomitant medications was removed from the list of events that will be recorded by the patients via their e-diary throughout the protocol. The following sections were corrected accordingly: • Footnotes in Section 6 Study Events Flow Chart. • The first sentence of the 4th paragraph of Section 13.2.3 Run-In Period (Days 1 to 14 [± 2 days]). • The 2nd sentence of the 2nd paragraph of Section 13.2.4 Treatment Period (Days 1 to 56). • The 2nd sentence of the first paragraph of Section 14.2.1 Electronic Diary. **Subject Numbering:** The first paragraph of Section 13.4.2 Method of Assigning Patients to Treatment Groups was modified to clarify that the screening number and randomization number are two separate identification number given to each subject at different stages of the study. **Adverse Events Reporting** Footnotes were added to clarify the rating severity definitions in Section 14.1.8.3 Reporting. Minor editorial and typographical corrections were made where applicable.
20-Nov-2014 by Ziv Machnes	Final Protocol, Amendment 1 This protocol amendment is generated to update the study population with regards to smoking frequency, to update the handling procedures for BAL samples, and to clarify other study procedures as listed below. **Study Population:** Section 13.3.2 - Inclusion Criteria, bullet 11 was updated to indicate that the study population will consist only of current and ex-smokers with a

DATE/NAME	DESCRIPTION
20-Nov-2014 by Ziv Machnes	history of >10 pack years. As such, the indications for 'packs/year' were replaced with 'pack years' and the allowance for current smokers with <10 pack/years was removed. Wording was added to indicate an approximately equal number of current and ex-smokers will be enrolled, and that each treatment group will consist of an approximately equal number of smokers and ex-smokers. In addition, the stratification criteria for the randomization was updated to consist of either current or ex-smokers. The following sections were affected: • Section 5 – Synopsis (under Study Population and Number of Patients) • Section 13.1 - Overall Study Design and Plan (second paragraph) • Section 13.3.1 – Number of Patients. • Section 13.4.2 - Method of Assigning Patients to Treatment Groups. **BAL Sample Handling:** Section 14.3.2.3 - Bronchoalveolar Lavage (BAL) was updated to indicate that sample handling, processing and storage procedures will be provided in a separate document. **Follow-up Procedures:** The wording in regards to follow-up procedures to be conducted on 14 days (± 2 day), after the last study drug administration, was updated to indicated a phone-call and not a visit, as indicated correctly in Section 6 – Study Event Flow Chart. Study event were updated accordingly. The following sections were affected: • Section 5 – Synopsis (under Duration of Participation for Patients, and Exploratory Outcome Measures [under Blood Assessments, Pulmonary Assessment, and Quality of Life Assessments]) • Section 13.3.5.2 – Prohibitions (under Alcohol) • Section 14.1.8.2 – Monitoring (first paragraph). **Study Duration:** The total duration of the study indicated in Section 5 – Synopsis (under Duration of Participation for Patients) was corrected to 12 weeks to correspond with the actual study duration as indicated throughout the protocol. **Inflammatory Markers in Blood Samples:** The list of cell types to be evaluated as part of the inflammatory markers in the blood was updated to include monocytes instead of macrophages, as macrophages are not expected to be present in blood. The following sections were affected: • Section 5 – Synopsis (under Study Objectives, fourth exploratory

DATE/NAME	DESCRIPTION
20-Nov-2014 by Ziv Machnes	objective, and under Exploratory Outcome Measures [under Pharmacodynamic Assesments, Blood Assessments, first bullet]) • Section 12.1 - Study Objectives (fourth exploratory objective) • Section 12.2 - Study Endpoints (third exploratory endpoint) • Section 14.3.3 - Blood Biomarkers (first bullet) • Section 15.1.5.1 - Biomarkers (third bullet) **Neutrophil Evaluation in BAL Samples** Neutrophils were added to the list of cell types to be evaluated as a percentage of the total cell count in BAL samples. The following sections were affected: • Section 5 – Synopsis (under Study Objectives, second exploratory objective and under Exploratory Outcome Measures [under Pharmacodynamic Assessments, Bronchoalveolar Lavage Assessments, second bullet]) • Section 12.1 - Study Objectives (second exploratory objective) • Section 12.2 - Study Endpoints (second exploratory endpoint) • Section 14.3.2.4 - Biomarkers (second bullet) • Section 15.1.5.1 – Biomarkers (second bullet) **Location of Study Drug Administration**: Wording was added in Section 6 – Study Events Flow Chart for Day 56, to clarify that the study drug will be administered at the CRU. **Meal Schedule**: The indication for fasting requirement in Section 13.2.4.1 – Meal Schedule, was corrected to indicate patients will fast overnight for at least 12 hours before bronchoscopy and BAL collection on Days -1 and 55 instead of Days -1 and 56, as correctly indicated in Section 6 – Study Events Flow Chart. **ECG Monitoring:** Following an update in Celerion's standard operating procedure, Section 14.1.5 – Electrocardiogram Monitoring was updated to include at least 5 minutes of rest prior to each ECG measurement (instead of at least 1 minute as previously indicated). **Hematology:** The tests included in the hematology panel Section 14.1.6.1 – Hematology were updated to indicate that the red blood cell (RBC) count will include a reticulocytes count, and that the white blood cell (WBC) count with differential will include monocytes but will not include reticulocytes. **Bronchoscopy and BAL:** Due to the sensitivity of YPL-001 components to UV light, a warning was

DATE/NAME	DESCRIPTION
20-Nov-2014 by Ziv Machnes	added to protect all samples from exposure to UV light, as indicated for the PK blood samples. The following sections were affected: • Section 14.3.2.2 - Bronchial Brushings • Section 14.3.2.3 - Bronchoalveolar Lavage (BAL) **PK Population:** The indication for measurable concentration of verproside and picroside II in urine was removed from the definition of PK population in Section 15.1.2 - Patients to Analyze, as there is no urine PK sampling planned for this study. Minor typographic and editorial corrections were made where applicable.
18-Sep-2014 by Caroline Engel	Final Protocol

2. SPONSOR – SIGNATORIES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

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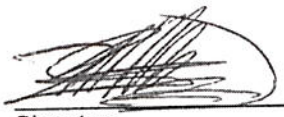

Signature

May 20, 2016
Date

5/26/2016

2. SPONSOR – SIGNATORIES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

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May 20, 2016

Date

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3. INVESTIGATORS SIGNATURES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

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INVESTIGATORS SIGNATURES (*CONTINUED*)

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

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4. ADDITIONAL KEY CONTACTS FOR THE STUDY

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Institutional Review Board Main Office Location	Western Institutional Review Board 1019 39th Avenue SE, Suite 120 Puyallup, Washington, 98374-2115 United States Tel.: +1 360 252-2500

5. SYNOPSIS

Compound:	YPL-001
Clinical Indication:	Treatment of inflammatory diseases of the respiratory tract such chronic obstructive pulmonary disease (COPD)
Study Type:	Phase 2a, proof of concept
Study Objectives:	The **primary objective** of the study is to assess the safety and tolerability of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients. The **secondary objective** of the study is to assess the number and magnitude of daily respiratory symptoms of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients. The **exploratory objectives** of the study are to evaluate the following in moderate to severe COPD patients: 1. To assess bronchoalveolar lavage (BAL) epithelial brushings for YPL-001 component levels. 2. To compare BAL samples for total cell count (cells/mL) macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; neutrophil, macrophage, lymphocyte and eosinophil counts as absolute inflammatory cell numbers in YPL-001 groups versus placebo group. 3. To compare BAL samples for tumor necrosis factors alpha (TNF-α), interleukin (IL)-1β, IL-4, IL-5, IL-6, IL-8, IL-13, myeloperoxidase (MPO), neutrophil elastase, monocyte chemotactic protein (MCP)-1, and matrix metalloproteinase (MMP)-9 in YPL-001 groups versus placebo group. 4. To compare blood inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) and concentrations of C-reactive protein (CRP), fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9 in YPL-001 groups versus placebo group. 5. To compare spirometric functions (forced expiratory volume in one second [FEV_1], forced vital capacity [FVC], FEV_1/FVC, and inspiratory capacity [IC]) in YPL-001 groups versus placebo group. 6. To compare patient reported outcomes (Baseline Dyspnea Index [BDI]/Transition Dyspnea Index [TDI], COPD Assessment Test [CAT]) in YPL-001 groups versus placebo group. 7. To assess verproside and picroside II concentration in plasma and BAL and verproside and picroside II pharmacokinetics (PK) in plasma following multiple oral doses administration of two YPL-001 dose levels.

Summary of Study Design:	This is a Phase 2a, proof-of-concept, multicenter, randomized, double-blind, double-dummy, 3-treatment, parallel study, with low and high YPL-001 doses (80 mg and 160 mg twice daily [BID]) and a placebo control in moderate to severe COPD patients. At least 60 patients will be enrolled and randomized into 3 treatment groups (20 patients per group). Patients will participate only once. Safety and tolerability will be assessed throughout the study. Assessment of respiratory symptoms and symptom burden in YPL-001 and placebo treatments will be performed daily through patient self-report of peak expiratory flow (PEF), major and minor symptoms of COPD exacerbation, dyspnea, and activity in their electronic diary (e-diary). Spirometry measurement, bronchoalveolar lavage (BAL), and blood samples will be collected for the pharmacodynamic (PD) assessment of YPL-001 and placebo treatments. Serial blood samples will also be collected for PK assessment of verproside (the principal active ingredient of YPL-001) and picroside II. Other components of YPL-001 and its metabolites may also be analyzed in plasma. Following screening, eligible patients will discontinue non permitted respiratory drugs if already receiving them and enter a 14 ± 2 days Run-in Period during which patients will be given albuterol taken on an as required basis and daily tiotropium 18 µg (one capsule inhaled daily in the morning) to be administered at home. On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their daily symptoms throughout the Run-in Period. Patients will return to the clinical research unit (CRU) in the morning within 3 days prior to Day 1 (define hereafter as Check-in) of the Treatment Period to confirm their eligibility and assess their health conditions. If they still meet all of the inclusion criteria and none of the exclusion criteria, they will undergo Check-in scheduled study procedures. Patients will return to the CRU on the morning of Day 1 to be randomized and receive one of the 3 treatments and undergo all scheduled study procedures. Patients will return on the morning of Days 15 (± 2 days), 29 (± 2 days), 43 (± 2 days), 54 (± 1 day), and 56 of the Treatment Period for study drug administration and procedures. Prior to each release from the CRU, patients will receive a properly labeled YPL-001 kit (and/or any unused wallets from previously provided kits [when applicable]) and tiotropium/albuterol container with sufficient doses which will be self-administered by patients at home until the next morning visit at the CRU. Patients will continue recording their daily symptoms via the e-diary throughout the Treatment Period. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff. The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any adverse event (AE) has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary. Patients will be instructed to call the Investigator if breathing worsens or if they need to take more than 8 puffs per day of albuterol for more than 2 consecutive days. If the Investigator determines that the patient is too unstable to continue in the study, he/she will be discontinued. Rescue medication will be used for any patient with an exacerbation of COPD and

	will be administered in accordance with the study center standard of care.
Study Population:	Patients will be adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3) with a predominant bronchitic component, between 30 and 85 years of age (inclusive). An approximately equal number of current and ex-smokers will be enrolled.
Number of Patients:	The study is planned to enroll at least 60 patients. Patients will be divided in 3 treatment groups with 20 patients to receive one of the 3 treatments (i.e., low and high YPL-001 doses [80 mg and 160 mg BID] and a placebo control) as per the randomization schedule. Each treatment group will consist of an approximately equal number of current and ex-smokers.
Duration of Participation for Patients:	The planned length of participation in the study for each patient is approximately 12 weeks (from Day 1 of the Run-in Period through completion of the follow-up procedures on Day 70 [± 2 days]).
Duration of Study Conduct:	The study is planned to take place over approximately 12 to 24 months (from screening of the first patient through completion of all study procedures for the last patient). This time period may change in the event that the study is terminated early, additional time is required to review safety, or a decision is made to complete an unscheduled analysis for a group.
Study Products:	YPL-001 will be supplied as 80 mg tablets for oral administration. Placebo will be supplied as YPL-001 80 mg matching placebo tablets for oral administration. YPL-001 or placebo will be dispensed in accordance with the Randomization and Drug Dispensing Instructions provided in a separate document.
Dosage, Dosage Form, Route, and Dose Regimen:	Treatments are described as follows: Treatment A: Multiple oral YPL-001 80 mg doses (1 x 80 mg tablet + 1 x 1 YPL-001 80 mg matching placebo tablet) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days.. Treatment B: Multiple oral YPL-001 160 mg doses (2 x 80 mg tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Treatment C: Multiple oral matching placebo (2 x 1 YPL-001 80 mg matching placebo tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. In all treatments, one tiotropium (Spiriva® HandiHaler®) 18 µg capsule will also be administered QD every morning prior to study drugs administration. Albuterol will be administered on an as needed basis. Each dose of Treatments A, B, and C will be administered orally with approximately 240 mL of water.

Stopping Rules:	A decision to stop or suspend the study will be made jointly by the Sponsor and the Investigator following the review of all pertinent safety and tolerability. Together they will make one of the following determinations: 1. To continue with the study as planned. 2. To continue with the study and add additional safety evaluations. 3. To continue with the study by adjusting to a lower dose if 2 patients at any dose level meets any of the following criteria and the patient was determined to have received YPL-001 after unblinding: a. Has a drug–related, unexpected serious adverse event (SAE). b. Experiences drug-related grade ≥ 3 toxicity. 4. The study will be terminated if ≥ 3 patients at any dose level meet any of the following criteria and the patients were determined to have received YPL-001 after unblinding: a. Has a drug–related, unexpected SAE. b. Experience drug related grade ≥ 3 toxicity.
Primary Outcome Measures	Safety and tolerability will be monitored through physical examinations, vital signs, pulse oximetry, ECGs, clinical laboratory tests, and AEs.
Safety and Tolerability Analysis	The following analyses will be performed. Safety analyses will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data, when appropriate. **Medical History:** Medical history will be listed by patient. **Adverse Events:** AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion (e.g., 17.0 or higher) and data will be summarized by System organ class (SOC) and preferred term. The number of treatment-emergent AEs (TEAEs) will be reported. In addition, the number and percent of patients reporting each TEAE will be summarized separately for each treatment. A by-patient AE data listing, including verbatim term, preferred term, treatment, severity, outcome, and relationship to treatment, will be provided. **Physical Examination:** Changes in physical examinations will be described in the text of the final report and significant findings will be reported as AEs. **Clinical Laboratory Tests, Electrocardiograms, Vital Signs, and Pulse Oximetry Measurements:** All clinical laboratory tests, 12-lead ECGs, vital signs, and pulse oximetry measurements and their change from baseline, if applicable, will be summarized by treatment and time point of collection. A shift table describing out-of-normal range shifts will be provided for clinical laboratory results. A normal-abnormal shift table will be presented for ECGs.

Safety and Tolerability Analysis (continued):	**Concomitant Medications:** Concomitant medications will be listed by patient and coded using the most current World Health Organization (WHO) drug dictionary available at Celerion (e.g., 01-MAR-2014 or later).
Secondary Outcome Measures:	PEF, major (e.g., estimated sputum quality [e.g., color, consistency], and quantity) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (Duke Activity Status Index [DASI]) self-reported daily by the patients using an e-diary.
Symptom Monitoring Analysis:	Symptom free days and overall symptom burden will be evaluated and compared across treatment groups. Secondary outcome analysis will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative data and frequency counts will be compiled for classification of qualitative data, when appropriate. **Peak Expiratory Flow and Symptoms of COPD Exacerbation:** PEF measurements and symptoms of COPD exacerbation and their change from baseline will be summarized by treatment and time point of collection. **Dyspnea and Activity:** The Modified Borg Dyspnea Scale and DASI scores will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.
Exploratory Outcome Measures:	**Pharmacodynamic Assessments:** <u>Bronchoalveolar Lavage Assessments:</u> BAL samples will be collected at baseline and again at the completion of the study for PD assessments of biomarkers. Biomarker assessments include: 1. epithelial brushings for YPL-001 component levels; 2. total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells 3. total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers 4. concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9. <u>Blood Assessments:</u> Blood samples will be collected at screening, and throughout the study for PD assessments of biomarkers. Biomarker assessments include: 1. inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) 2. concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9. <u>Pulmonary Assessment:</u> Pulmonary function measurements (spirometry [FEV_1, FVC, FEV_1/FVC, and

Exploratory Outcome Measures (continued):	IC] will be performed at screening, and throughout the study. Quality of Life Assessments: Patient reported outcomes (e-diary, BDI/TDI, CAT) will be performed at baseline, and throughout the study. **Pharmacokinetic Assessments:** Bronchoalveolar Lavage Assessments: BAL samples will be collected at baseline and again at the completion of the study to determine verproside and picroside II concentrations in BAL. Other components of YPL-001 and its metabolites may also be analyzed. Plasma Assessments: Serial blood samples will be collected prior to the initial dosing and through 12 hours following dosing on Days 1 and 54 (± 1 day) to determine verproside and picroside II concentrations in plasma. Predose samples will also be collected in the morning of Days 15 (± 2 days), 29 (± 2 days), 43 (± 2 days) and 54 (± 1 day) for C_{trough} determination. Other components of YPL-001 and its metabolites may also be analyzed. The sampling schedule and/or collection intervals may be modified based on the results as the study progress.
Pharmacodynamic Analysis:	**Blood, Plasma, and Pulmonary biomarkers:** When applicable, the raw data and % change from baseline or placebo, as appropriate, for PD markers (BAL biomarkers, blood biomarkers, and pulmonary biomarker) will be summarized by time point and treatment using descriptive statistics (arithmetic means, standard deviations [SD], coefficients of variation [CV], sample size [N], minimum, maximum, and median). Figures will be created to display mean and individual level or activity as a function of time. **Quality of Life:** The quality of life parameters will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.
Pharmacokinetic Parameters and Analysis:	Noncompartmental PK parameters, including AUC_{0-t}, AUC_{0-inf}, AUC_{τ}, k_{el}, C_{max}, C_{max_ss}, C_{min_ss}, C_{trough}, t_{max}, t_{max_ss}, CL/F, CL_{ss}/F, V_z/F, V_{z_ss}/F, and $t_{1/2}$, as appropriate, will be calculated from plasma concentrations of verproside and picroside II from patients who received YPL-001 only. Additional PK parameters may be calculated if deemed appropriate. Plasma PK parameters may also be calculated for other components of YPL-001 and its metabolites. PK parameters will be summarized by treatment using descriptive statistics. Relative exposure of verproside and picroside II will be assessed between the two YPL-001 dose levels, and steady-state will be assessed by visual inspection in the active treatment groups. Verproside and picroside II concentration in BAL samples from patients who received YPL-001 only will be listed.

6. STUDY EVENTS FLOW CHART

Study Procedures[a]	Screen[b]	Run-in Period		Treatment Period																			
Days →		1	2-14 (±2)	Up to -3 [c]	1																		
Hours →				C-I	Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12
Administrative Procedures																							
Informed Consent	X																						
Inclusion/Exclusion Criteria	X	X																					
Medical History	X																						
Randomization					X																		
Safety Evaluations																							
Physical Examination[d]	X			X[e]																			
Height	X																						
Weight	X			X[e]																			
Chest X-ray[f]	X																						
Berlin Questionnaire	X																						
12-Lead Electrocardiogram	X			X[g]																			
Vital Signs[h]	X			X[g]	X						X		X						X				
Pulse Oximetry	X			X[g]																			
Hem, Chem, and UA[i]	X			X[e]																			
PT/INR	X																						
Serum Pregnancy Test (♀ only)	X			X[e]																			
Serum FSH (postmenopausal ♀ only)	X																						
Urine Drug Screen	X				X																		
Urine or Breathalyzer Alcohol Screen	X				X																		
HIV/Hepatitis Screen	X																						
AE Inquiries																							
AE Monitoring										X													
ConMeds Monitoring	X									X													
Symptoms Monitoring																							
Diary Training		X																					
Diary Use[j]										X													
PEF, COPD exacerbation, dyspnea and activity[k]										X													
Study Drug Administration																							
Tiotropium Administration[l]		X	X	X	X																		

Study Procedures[a]	**Screen**[b]	**Run-in Period**		**Treatment Period**																		
Days →		1	2-14 (±2)	Up to -3 [c]	1																	
Hours →				C-I	Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12
Study Drug Administration at CRU[m,n]						X																X
Pharmacodynamic																						
Pulmonary Function (Spirometry)[o]	X			X[e]																		
Pharmacodynamic																						
Bronchoscopy and BAL Biomarkers[p]				X																		
Blood Biomarkers	X				X						X											
BDI/TDI & CAT				X[e]																		
Pharmacokinetic																						
Blood for Verproside & Picroside II PK					X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[q]
Other Procedures																						
Visit & Return Visits[r]	X	X		X	X																	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.
b. Within 14 days of Day 1 (inclusive) of the Run-in Period.
c. Scheduled procedures may be performed within 3 days prior to Day 1 dosing.
d. A full physical examination will be performed at screening. Symptom-driven physical examinations will be performed at other scheduled times, and may be performed at other times at the Investigator's discretion.
e. To be performed prior to the bronchoscopy procedures.
f. To be performed at screening or within 3 months (inclusive) of screening.
g. ECGs, vital sign and pulse oximetry will be measured within 4 hours of bronchoscopy procedures. During the bronchoscopy procedures and BAL sample collection, patients will be continuously monitored for ECGs, vital signs (blood pressure, heart rate, respiration rate, and body temperature), and oxygen saturation.
h. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
i. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.
j. Patients will be provided with an e-diary device to record their self-administered doses, whether the dose was administered with food, and daily respiratory symptoms.
k. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality [e.g., color, consistency] and quantity) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).
l. Patients will receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. They must return the container (empty or not) at the next schedule visit.
m. Prior to release from the CRU, patients will receive a properly labeled kit with sufficient study drug for their assigned treatment which will be self-administered by patients at home until the next morning visit at the CRU. Patients must return the used and unused wallets at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.
n. On Day 1, patients will be required to fast overnight for at least 8 hours before and 4 hours after YPL-001/placebo morning administration.
o. Pulmonary function will be performed prior to and 20 to 30 minutes after inhalation of approximately 400 µg albuterol.
p. Bronchoscopy and BAL sample collection will be performed following a 12-hour fast.
q. To be performed prior to dosing.
r. Patients will be admitted to the CRU at the time indicated by the CRU.

STUDY EVENTS FLOW CHART *(CONTINUED)*

Study Procedures[a]	Treatment Period									
Days →	2-14	15 (± 2)		16-28	29 (± 2)		30-42	43 (± 2)		44-53
Hours →		AM	PM		AM	PM		AM	PM	
Safety Evaluations										
Physical Examination[b]					X[c]					
Weight					X[c]					
12-Lead Electrocardiogram					X[c]					
Vital Signs[d]		X[c]			X[c]			X[c]		
Hem, Chem, and UA[e]					X[c]					
Serum Pregnancy Test (♀ only)		X[c]			X[c]			X[c]		
Urine Drug Screen		X[c]			X[c]			X[c]		
Urine or Breathalyzer Alcohol Screen		X[c]			X[c]			X[c]		
AE Inquiries		X[c]			X[c]			X[c]		
AE Monitoring	X									
ConMeds Monitoring	X									
Symptoms Monitoring										
Diary Use[f]	X									
PEF, COPD exacerbation, dyspnea and activity[g]	X									
Study Drug Administration										
Tiotropium Administration[h]	X									
Study Drug Administration at CRU		X			X			X		
Study Drug Administration at Home[i]	X		X	X		X	X		X	X
Pharmacodynamic										
Pulmonary Function (Spirometry)[j]		X[c]			X[c]			X[c]		
Blood Biomarkers		X[c]			X[c]			X[c]		
BDI/TDI & CAT		X[c]			X[c]			X[c]		
Pharmacokinetic										
Blood for Verproside & Picroside II PK		X[c]			X[c]			X[c]		
Other Procedures										
Return Visits[k]		X			X			X		

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.
b. Symptom-driven physical examinations will be performed at scheduled times, and may be performed at other times at the Investigator's discretion.
c. To be performed or completed prior to dosing.
d. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
e. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.
f. Patients will be provided with an e-diary device to record their self-administered doses, whether the dose was administered with food, and daily respiratory symptoms.
g. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality [e.g., color, consistency] and quantity) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).
h. Patients will receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. They must return the container (empty or not) at the next schedule visit.
i. Prior to release from the CRU on Days 15 (± 2 days), 29 (± 2 days), and 43 (± 2 days) patients will receive a properly labeled kit and/or any unused wallets from previously provided kits (when applicable) with sufficient study drug for their assigned treatment which will be self-administered by patients at home until the next morning visit at the CRU. Patients must return the used and unused wallets at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.
j. Pulmonary function will be performed prior to and 20 to 30 minutes after inhalation of approximately 400 µg albuterol.
k. Patients will be admitted to the CRU at the time indicated by the CRU.

STUDY EVENTS FLOW CHART *(CONTINUED)*

Study Procedures[a]	Treatment Period																				ET[b]	FU[c]
Days →	54 (± 1 day)																		55	56		
Hours →	Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12				
Safety Evaluations																						
Physical Examination[d]																				X[e]	X	
Weight																				X[e]	X	
12-Lead Electrocardiogram																				X[f]	X	
Vital Signs[g]	X						X		X						X			X		X[f]	X	
Pulse Oximetry																				X[f]	X	
Hem, Chem, and UA[h]																				X[e]	X	
Serum Pregnancy Test (females only)																				X[e]		
Urine Drug Screen	X																			X[e]		
Urine or Breathalyzer Alcohol Screen	X																			X[e]		
AE Inquiries	X																			X[e]	X	
AE Monitoring	X																					X
Concomitant Medication Monitoring	X																					
Symptoms Monitoring																						
Diary Use[i]	X																			X[e]	X	
PEF, COPD exacerbation, dyspnea and activity[j]	X																					
Study Drug Administration																						
Tiotropium Administration	X																		X	X		
Study Drug Administration at CRU[k]		X																X				
Study Drug Administration at Home[l]																			X			
Pharmacodynamic																						
Pulmonary Function (Spirometry)[m]																				X[n]	X	
Bronchoscopy and BAL Biomarkers[o]																				X		
Blood Biomarkers	X[p]						X															
BDI/TDI & CAT	X[p]																					
Pharmacokinetic																						
Blood for Verproside & Picroside II PK	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Other Procedures																						
Return Visits[q]	X																			X	X	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.

b. To be performed prior to early termination from the study.

c. The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

d. Symptom-driven physical examinations will be performed at scheduled times, and may be performed at other times at the Investigator's discretion.

e. To be performed or completed prior to bronchoscopy procedures.

f. ECGs, vital sign and pulse oximetry will be measured within 4 hours of bronchoscopy procedures. During the bronchoscopy procedures and BAL sample collection, patients will be continuously monitored for ECGs, vital signs (blood pressure, heart rate, respiration rate, and body temperature), and oxygen saturation.

g. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.

h. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.

i. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff.

j. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality [e.g., color, consistency] and quantity) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

k. On Day 54 (± 1 day), patients will be required to fast overnight for at least 8 hours before and 4 hours after YPL-001/placebo morning administration.

l. Prior to release from the CRU on Day 54 (± 1 day) patients will receive a properly labeled kit and/or any unused wallets from previously provided kits (when applicable) with sufficient study drug for their assigned treatment which will be self-administered by patients at home until the next morning visit at the CRU. Patients must return the used and unused wallets at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.

m. Pulmonary function will be performed prior to and 20 to 30 minutes after inhalation of approximately 400 µg albuterol.

n. To be completed prior to bronchoscopy procedures.

o. Bronchoscopy and BAL sample collection will be performed following a 12-hour fast.

p. To be performed at predose on Day 54 (± 1 day) or upon early termination.

q. Patients will be admitted to the CRU at the time indicated by the CRU.

Abbreviations: ♀ = Female, AE = Adverse events, AM = Morning, BAL = bronchoalveolar lavage, BDI/TDI = Baseline Dyspnea Index/Transition Dyspnea Index Test, CAT = COPD Assessment Test, Chem = Serum chemistry, C-I = Check-in, COPD = chronic obstructive pulmonary disease, CRU = Clinical research unit, ConMeds = Concomitant medication, DASI = Duke Activity Status Index, ECG = Electrocardiogram, e-diary = electronic diary, ET = Early termination, FSH = Follicle-stimulating hormone, Hem = Hematology, HIV = Human immunodeficiency virus, IL= interleukin, PEF = Peak expiratory flow, PK = Pharmacokinetics, PM = Evening, Preg = Serum pregnancy, PT/INR = Prothrombin time/international normalized ratio, Screen = Screening, UA = Urinalysis.

7. TABLE OF CONTENTS

8. ABBREVIATIONS

Only those uncommon abbreviations specific to this study are listed. Pharmacokinetic (PK) parameter abbreviations and definitions may be found in Section 15.1.6.1.

AE	Adverse event
AHR	Airway hyper-responsiveness
ALD	Approximate lethal dose
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
BALF	Bronchoalveolar lavage fluid
BDI	Baseline Dyspnea Index
BID	Twice daily
BLQ	Below the lower limit of quantification
BMI	Body mass index
bpm	Beat per minute
BUN	Blood urea nitrogen
°C	Degrees Celsius
CAT	COPD Assessment Test
Chem	Chemistry
CFR	Code of Federal Regulations
CK	Creatine kinase
CNS	Central nervous system
CO_2	Carbon dioxide
COPD	Chronic obstructive pulmonary disease
CRO	Contract Research Organization
CRP	C-reactive protein
CRU	Clinical research unit
CS	Clinically significant abnormality
CSC	Cigarette smoking condensate

CXCL	Chemokine (C-X-C motif) ligand
CV	Coefficient of variation
DASI	Duke Activity Status Index
dL	Deciliter
DRF	Dose range finding
e-diary	Electronic diary
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
ERS	European Respiratory Society
F	Female
°F	Degrees Fahrenheit
FDA	Unites States Foods and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FU	Follow-up
FVC	Forced vital capacity
g	gram
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HBsAg	hepatitis B surface antigen
HCO_3	Bicarbonate
HCV	hepatitis C antibodies
HED	Human equivalent dose
Hem	Hematology
HIV	Human immunodeficiency virus
hr	Hour
IC	Inspiratory capacity
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroid
IgE	Immunoglobulin E
IL	Interleukin
IND	Investigational New Drug

INR	International normalized ratio
IRB	Institutional Review Board
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
kg	Kilogram
kg/m^2	Kilogram per meter squared
LABA	long acting beta agonist
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
LOQ	Limit of quantitation
LPS	Lipopolysaccharide
LSM	Least-squares means
µg	Microgram
m^2	Square meter
M	Male
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCO	Myeloperoxidase
MCP	Monocyte chemotactic protein
MCV	Mean Corpuscular Volume
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
MIP	Monocyte inhibitory protein
mL	Milliliter
mmHg	Millimeter of mercury
MMP	Matrix metalloproteinase
msec	Millisecond
MTD	Maximum Tolerated Dose
N	Sample size
NCS	Not clinically significant
ng	Nanogram
No.	Number
NOAEL	No observed adverse effect levels

OTC	Over-the-counter
OVA	Ovalbumin
PD	Pharmacodynamic(s)
PEF	Peak expiratory flow
PK	Pharmacokinetic(s)
PT	Prothrombin time
QA	Quality Assurance
QC	Quality Control
QT	Interval between the Q and T waves on the electrocardiogram tracing
QTcF	Corrected QT interval with Fridericia's formula
RBC	Red blood cell
RDW	Red cell distribution width
Resp	Respiration
RNA	Ribonucleic acid
ROS	Reactive oxygen species
SABA	Short-acting β2-agonist
SAD	Single ascending dose
SAE	Serious adverse event
SAMA	Short-acting anticholinergic agent
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SULT	Sulfotranferase
TBIL	Total bilirubin
TDI	Transition Dyspnea Index
TEAE	Treatment-emergent adverse event
Th	T helper
TNF-α	Tumor necrosis factors alpha
UA	Urinalysis
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

9. INTRODUCTION AND BACKGROUND

This study is being conducted as the third in a series of studies for the clinical development of YPL-001. The trial will be conducted in compliance with the protocol, GCP, and applicable regulatory requirements. The patient population will be comprised of moderate to severe (GOLD Stage 2-3) COPD patients.

9.1 YPL-001

YPL-001 drug product is an oral dosage form of an herbal extract from the aerial parts of the plant Speedwell (*Pseudolysimachion rotundum* subsp. *Subintegrum*). *Pseudolysimachion* (*Veronica*) is a perennial herb which has been used as a traditional medicine in Korea and China for the treatment of inflammatory diseases of the respiratory tract such as asthma and COPD.

As a botanical drug product, the drug substance is a mixture of chemical species (iridoids [including verproside] and other related compounds) and biological activity is considered to be from the mixture and not from an individual component. It is unknown if the total activity from individual components is additive or synergistic. Five active constituents, classified as iridoids, have been identified in the herbal extract: verproside, picroside II, catalpolside, isovanilloyl catalpol, and 6-*O*-veratroylcatalpol. Recent experimentation has revealed that the principal active ingredient in *Pseudolysimachion* is verproside, a dihydroxylated catalpol derivative.

YPL-001, containing verproside and other active ingredients, is being developed as a potential oral treatment for long term inflammatory diseases of the respiratory tract such as asthma or bronchitic COPD. Current long term control medications include corticosteroids, cromolyn sodium, immunomodulators, long acting beta agonists, (LABAs), methylxanthines, and leukotriene modifiers. YPL-001 belongs most closely with the leukotriene modifier class of drug.

A brief overview of available information regarding YPL-001 follows below. Details can be found in the YPL-001 Investigator's Brochure of June 3, 2014. [1]

9.1.1 Preclinical Trials

9.1.1.1 Pharmacology

Five *in vivo* primary pharmacology studies have been completed.

In ovalbumin-sensitized mice, an animal model for asthma, YPL-001 reduced elevated immunoglobulin E (IgE), IL-4, IL-5, IL-13, airway hyper-responsiveness, and mucus hyper-secretion.

In the lipopolysaccharide (LPS)- and cigarette smoking condensate (CSC)-induced COPD mice model, verproside and roflumilast treatment inhibited the accumulation of neutrophils in Bronchoalveolar lavage fluid (BALF) as well as the increase of several proinflammatory cytokines and chemokines. Neutrophil infiltration induced by LPS and CSC treatments was associated with a significant increase in BALF levels of the chemoattractants, TNF-α, chemokine (C-X-C motif) ligand (CXCL)-1, and monocyte inhibitory protein (MIP)-2. These data also demonstrated that the effect of YPL-001 and

verproside involves down-regulation of the influx of neutrophils and production of TNF-α, CXCL-1, and MIP-2 molecules which play a major role in tissue remodeling.

YPL-001 significantly suppressed the increase of inflammatory cell counts, particularly neutrophils in BALF and also effectively suppressed elevated levels of TNF-α, CXCL-1 and MIP-2 with the reduction in airway inflammatory responses in CSC- and LPS-induced COPD mice.

YPL-001 also effectively suppressed the increased inflammatory cell count, particularly neutrophils in BALF and also significantly inhibited elevated levels of TNF-α, IL-1β and IL-6 with the reduction in reactive oxygen species (ROS) production and elastase activity in cigarette smoke- and LPS-induced COPD mice.

In the LPS- and cigarette smoke-induced COPD rats model, YPL-001 significantly inhibited the increase of inflammatory cell count, particularly neutrophils in BALF and also effectively suppressed elevated levels of TNF-α, IL-1β, IL-6, MIP-2 and CRP.

YPL-001 effectively inhibited development of both T helper (Th)2 and Th1/Th17 type asthma in these murine models. These effects resulted from inhibition of cytokine and chemokine production by infiltrated inflammatory cells and antigen specific T cells in lymph nodes. YPL-001 did not inhibit development of COPD which was induced by *E.coli* extracellular vesicles.

9.1.1.2 Pharmacokinetics

After oral administration of YPL-001 at 12.5, 25, and 50 mg/kg doses (5.225, 10.45, and 20.9 mg/kg as verproside) in rats, verproside was rapidly absorbed; verproside was detected at the first blood sampling time (5 min) and absorbed rapidly, with the t_{max} achieved at 0.46-0.61 hour for all three doses. The post-absorption phase of the mean plasma verproside concentration-time profiles showed a poly-exponential decay.

The area under the plasma concentration-time curve (AUC) and the maximum plasma concentration (C_{max}) of verproside were linearly increased as the oral dose of YPL-001 increased. Alternately, the dose normalized (based on 12.5 mg/kg) AUCs and C_{max} of verproside were comparable among different doses studied. The elimination half-lives ($t_{1/2}$), 2.14 – 3.91 hours, and other PK parameters of verproside for all three doses were also comparable. These findings indicate that the PK parameters of verproside were independent of doses.

The fraction of dose of verproside excreted unchanged in urine at 24 hours was less than 0.10%. Verproside was not detected in the 24 hours feces sample for all three doses studied. These results indicate that verproside is almost completely eliminated by the first pass metabolism due to O-methylation, glucuronidation, sulfation, and intestinal microflora-mediated metabolism. Verproside is metabolized to verproside glucuronides (M1 and M2), verproside sulfates (M3 and M4), O-methylverproside such as picroside II (M5) and isovanilloylcatalpol (M6), 3,4-dihydroxybenzoic acid (M11), 3-methyoxy-4-hydroxybenzoic acid (M15) and 3-hydroxy-4-methoxybenzoic acid (M16), which are further metabolized to their glucuronides and sulfates including M5 glucuronide (M7), M5 sulfate (M9), M6 glucuronide (M8), M6 sulfate (M10), M11 glucuronide (M12), M11 sulfates (M13 and M14), M15 glucuronides (M17 and M18), M15 sulfate (M20), M16 glucuronide (M19), and M16 sulfate (M21). The O-methylation of verproside to

picroside II (M5) and isovanilloylcatalpol (M6) followed by glucuronidation and sulfation were identified as the major metabolic pathway in bile and urine samples.

Picroside II, a major metabolite of verproside, was detected in plasma samples but most plasma concentrations in 12.5 and 25 mg/kg YPL-001 treated groups were below the lower limit of quantification (LLOQ, 2.5 ng/mL) compared to 50 mg/kg YPL-001 treated group. The picroside II-to-verproside AUC ratios in the 50 mg/kg YPL-001 treated group were 13.9-65.1%, suggesting that picroside II may be one of the major YPL-001 metabolites. Plasma concentrations of isovanilloylcatalpol, a metabolite of verproside and isomer of picroside II, were below LLOQ (2.5 ng/mL) after oral administration of all three YPL-001doses tested.

Verproside, catalposide, and picroside II were not considerably bound to human plasma proteins; the binding values were 36.3-55.0% at verproside concentrations of 0.1, 1.0, and 10.0 μg/mL, 31.2-49.5% at catalposide concentrations of 0.5, 1, and 10 μg/mL, and 34.0-41.2% at picroside II concentrations of 0.5, 1, and 10 μg/mL.

9.1.1.3 Toxicology

Two single dose toxicity studies with YPL-001 have been completed in rat and dog. In the rat study, polyuria was observed in the 5,000 mg/kg dosing group of each sex between 2-4 hours after YPL-001 administration. Discolored stool was observed dose-dependently in the all dosing groups of each sex at 1-3 days post administration. Soft stool, mucous stool and soiled perineal region were observed at 1 day after administration in the 2,500 and 5,000 mg/kg dosing group of each gender. There were no notable changes of body weight in any study group. There were no notable gross necropsy findings in any of the study groups. Based on the results above, when YLP-001 is administered orally to Sprague-Dawley rats, the approximate lethal dose (ALD) is higher than 5,000 mg/kg. In the dog study, There were no changes with respect to the toxicity of the test article in the clinical signs, body weight change and necropsy findings after a single dose. Vomiting and discoloration of stool was noted. The Maximum Tolerated Dose (MTD) was determined to be 2,000 mg/kg for males and 1,000 mg/kg for females.

Two dose range finding (DRF) studies with YPL-001 have been completed in rat and dog, followed by two pivotal, 4-week, GLP repeated-dose toxicology studies in the same species. In the rat DRF study, YPL-001 induced anemia and hemolysis at 667 mg/kg/d and at higher doses. In addition, enlargement of cecum was observed at 667 mg/kg/d and at higher doses. The NOEL for this study was 74 mg/kg/d in both genders. In the dog DRF study, decreases in red blood cell (RBC) values were present in males at the high dose level (1000 mg/kg/d). In females the TBIL values were elevated at the 1000 mg/kg/d dose levels. Females had enlarged spleens at 125, 250 and 1000 mg/kg dose levels without dose relationship (trend was toward significance). The MTD for this study was 1000 mg/kg/d.

Primary results from the pivotal, 4-week rat study included:

There were no abnormal clinical signs observed in any group during dosing or the recovery periods and no mortality was reported.

Hematology: Compared to controls, there were decreases in values of RBC, hematocrit,

and hemoglobin at all dose levels of both genders in a dose-dependent fashion. The values of hemoglobin distribution width, red cell distribution width (RDW) and reticulocyte at all dose levels of both genders were higher or significantly higher than those of vehicle control.

Clinical Biochemistry: There were significant increases in the values of TBIL at all dose levels of both genders when compared with that of vehicle control. After the recovery period, there were no noticeable changes related to the test article.

Organ Weights: Slight increase in absolute & relative weights of the spleen at 540 mg/kg/d in males and notable increase in absolute & relative weights of the spleen at all dose levels of females were observed. Weights of left and right kidneys in female at 540 mg/kg/d were significantly higher than that of vehicle control. After the recovery period, the absolute weights of the spleen and both kidneys in both genders at 540 mg/kg/d were significantly higher than that of vehicle control.

Necropsy Findings: At necropsy, 6 cases of dark reddish discoloration of spleen were observed at 540 mg/kg/d in both genders, and 1 case of enlargement of cecum was observed at 540 mg/kg/d in female. After the recovery period, one case of dark reddish discoloration of spleen was observed at 540 mg/kg/d in the female. The histopathology examination revealed increased hematopoiesis of spleen at the high dose in both genders.

No Observed Adverse Effect Levels (NOAEL): The NOAEL for this study was 180 mg/kg/d for both genders.

Primary results from the pivotal, 4-week dog study included:

YPL-001 colored stool with/without soft stool or diarrhea was persistently observed in both sexes at 1000 mg/kg/d during the dosing period. It was not observed during the recovery period. No mortality was reported.

Hematology: There were no treatment-related changes.

Clinical Biochemistry: The TBIL increased in a dose-dependent manner in both genders at 111, 333 and 1000 mg/kg/d, and it was not recovered completely after the 2-week recovery period.

Organ Weights: There were no treatment-related changes.

Necropsy Findings: Slight red discoloration of mucous membranes in the stomach or duodenum was observed in female treatment groups but not observed after the 2-week recovery period.

NOAEL: The NOAEL for this study was 1000 mg/kg/d for both genders.

9.1.2 Clinical Experience

To date, 2 studies have been conducted in healthy subjects, a randomized, double-blind, placebo-controlled, sequential single ascending dose (SAD) clinical study (AA98496) and a randomized, double-blind, placebo-controlled, sequential multiple ascending dose (MAD) clinical study (AA98495).

9.1.2.1 SAD study

All 5 cohorts of 8 subjects (6 active and 2 placebo), with one cohort crossing over to assess food effect, were dosed and completed. All dosed levels (i.e., 40, 80, 160, 240, and 320 mg) were well tolerated with no SAEs reported during the conduct of the study. All 9 AEs reported in 7 subjects were mild in severity and the most frequent AE reported, regardless of causality, was headache. Of the 7 AEs experienced by subjects receiving the active drug, the Investigator considered 2 of these to be possibly related (nausea, and vomiting), 2 unlikely related, and 3 unrelated. Of the 2 AEs experienced by subjects receiving placebo, the Investigator considered 1 of these to be possibly related (headache), and 1 unrelated.

Plasma samples were analyzed using a validated bioanalytical method. Verproside concentrations were lower than concentrations observed from the animal PK data. The limit of quantitation (LOQ) was approximately 20% of the C_{max} after a single 160 mg dose and approximately 10% of the C_{max} after a single 320 mg dose. Therefore, the half-life could not be well characterized since only a few PK concentrations were available for the estimation.

Verproside appeared to be rapidly absorbed following oral administration and independent on dose, as suggested by median t_{max} values of approximately 0.5 to 0.67 hours under fasting conditions. Verproside appeared to be cleared rapidly from plasma, with mean $t_{1/2}$ values under 1 hour; plasma verproside concentrations were below the lower limit of quantification (BLQ) for all subjects by 6 hours postdose. Table 1 below summaries the PK parameters of verproside following single-dose administrations of YPL-001 at each dose level:

Table 1 Summary of PK Parameters

Pharmacokinetic Parameters	Dose Level Mean ± SD					
	40 mg (N = 1)[a]	80 mg (N = 6)[b]	160 mg (fasting) (N = 6)[c]	160 mg (fed) (N = 6)[d]	240 mg (N = 6)[e]	320 mg (N = 6)[f]
C_{max} (ng/mL)	1.19	1.14 ± 0.328	2.90 ± 1.76	1.08 ± 0.287	4.78 ± 5.66	4.49 ± 1.44
t_{max} (hr)[g]	0.4969	0.6682 (0.5158, 1.0025)	0.5074 (0.3331, 0.6700)	1.2538 (0.9994, 2.0008)	0.5867 (0.3486, 1.5022)	0.5057 (0.3419, 1.5014)
AUC_{0-t} (ng·hr/mL)	0.7422	0.7520 ± 0.3818	2.5616 ± 1.7947	1.2822 ± 0.3599	5.4567 ± 5.0158	5.3612 ± 0.8664
AUC_{0-inf} (ng·hr/mL)	·	·	3.8048 ± 1.8238	·	8.2199 ± 5.3327	6.2162 ± 0.7776
$t_{1/2}$ (hr)	·	·	0.677 ± 0.263	·	0.919 ± 0.176	0.713 ± 0.100

[a] Individual values are presented for the 40 mg dose level
[b] N=5 for AUC_{0-t}
[c] N=3 for AUC_{0-inf} and $t_{1/2}$,
[d] N=4 for AUC_{0-t}
[e] N=3 for AUC_{0-inf}, and $t_{1/2}$,
[f] N=5 for AUC_{0-inf}, and $t_{1/2}$,
[g] t_{max} is presented as Median (Minimum, Maximum)
· = Value missing or not reportable

9.1.2.2 MAD Study

In total, 2 cohorts of 8 subjects and 1 cohort of 10 subjects received multiple YPL-001 doses of 80, 160, or 240 mg BID. Each cohort was constituted of 2 subjects receiving placebo and the remaining subjects receiving the active drug. All dose levels were well tolerated. There were no deaths or SAEs in this study. One (1) subject was discontinued due to the AE of chest pain. Overall, TEAEs were experienced by 38% of subjects in this study. The Investigator considered 1 AE (chest pain) to be possibly related to study drug and the remaining AEs unlikely or unrelated. There were no treatment-related trends in physical examination, laboratory, vital sign, or ECG assessments in this study.

Verproside appeared to be rapidly absorbed following multiple-dose oral administration, as suggested by median t_{max} values of approximately 0.5 - 0.9 hours and independent of dose. Following a multiple oral doses of YPL-001, verproside appeared to be cleared rapidly from plasma, with mean $t_{½}$ values under 1.6 hours, and plasma verproside concentrations were BLQ for most subjects by 12 hours postdose.

Picroside II appeared to be also rapidly absorbed following single- and multiple-dose oral administration, as suggested by median t_{max} values of approximately 0.6 to 0.9 hours and independent of dose. Following a single oral dose of YPL-001, picroside II appeared to be cleared rapidly from plasma, with mean $t_{½}$ values under 1 hour, CL/F values of 14000 – 18500 L/hour, and plasma picroside II concentrations BLQ by 10 - 12 hours postdose. Following multiple oral doses, mean $t_{½}$ values were under 2.5 hours, and plasma picroside II concentrations were BLQ for most subjects by 12 hours postdose.

For all 3 dose levels, minimal to modest accumulation of verproside and picroside II was observed following BID administration of YPL-001 for 2 weeks. The mean peak and total exposure of verproside and picroside II in plasma appeared to increase in a dose-dependent manner between 80 and 160 mg of YPL-001, but no increase in plasma bioavailability was observed between 160 and 240 mg dose levels. Table 2 and Table 3 below summaries the PK parameters of verproside and picroside II, respectively, following multiple-dose administrations of YPL-001 at each dose level:

Table 2 Summary of Verproside PK Parameters

Pharmacokinetic Parameters	YPL-001 Dose Level Mean ± SD		
	80 mg	**160 mg**	**240 mg**
AUC_t (pg*hr/mL)	4709 ± 4080 (N=6)	10860 ± 11424 (N=6)	9658 ± 9246 (N=5)
AUC_{0-t}(pg*hr/mL)	4596 ± 4127 (N=6)	10770 ± 11489 (N=6)	9566 ± 9298 (N=5)
$C_{max\ ss}$ (pg/mL)	2414 ± 1281 (N=6)	6737 ± 7342 (N=6)	5458 ± 4387 (N=5)
$t_{max\ ss}$ (hr)*	0.756 (0.252, 2.00) (N=6)	0.759 (0.329, 1.50) (N=6)	0.528 (0.272, 0.751) (N=5)
$t_{½}$ (hr)	1.47 ± 0.425 (N=6)	1.30 ± 0.406 (N=6)	1.57 ± 0.236 (N=5)

* = t_{max_ss} is presented as median (minimum, maximum)

Table 3 Summary of Picroside II PK Parameters

Pharmacokinetic Parameters	YPL-001 Dose Level Mean ± SD		
	80 mg	160 mg	240 mg
AUC_t (pg*hr/mL)	2556 ± 599 (N=2)†	4287 ± 4369 (N=4)†	1985 ± 1024 (N=5)
AUC_{0t} (pg*hr/mL)	1124 ± 1044 (N=6)	3024 ± 3877 (N=6)	1804 ± 949 (N=5)
$C_{max\ ss}$ (pg/mL)	419 ± 240 (N=6)	1116 ± 1391 (N=6)	751 ± 490 (N=5)
$t_{max\ ss}$ (hr)*	0.756 (0.252, 2.00) (N=6)	0.759 (0.329, 1.50) (N=6)	0.748 (0.524, 0.751) (N=5)
$t_{½}$ (hr)	2.23 ± 0.254 (N=6)	1.84 ± 0.395 (N=6)	2.08 ± 0.793 (N=5)

* = t_{max_ss} is presented as median (minimum, maximum)
. = Value missing or not reportable

10. RATIONALE

10.1 Purpose of the Study

This study will be the initial exploration of multiple-dose administration of YPL-001 in COPD patients. The assessments of the safety, tolerability, COPD symptoms, PD, and PK of verproside and picroside II following administration of multiple doses of YPL-001 will guide decisions to further develop the drug and support the compound as a useful clinical candidate in the treatment of inflammatory diseases of the respiratory tract such as COPD and the data generated will support larger studies in patients with inflammatory diseases of the respiratory tract such COPD to demonstrate safety and evidence of efficacy and clinical benefit.

10.2 Dose Selection

This will be the first COPD patient study of YPL-001.

YPL-001 appeared well tolerated in a panel of standard animal toxicology studies. In the initial studies in humans, the initial dose of YPL-001 was justified conservatively according to the United States (US) Food and Drug Administration (FDA) guidance document “Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers”.[2]

Accordingly, the single and multiple dose escalation study (AA98496) initiated single doses at the 40 mg and 80 mg level, respectively. Dose escalations up to 320 mg and 240 mg in the SAD and MAD studies, respectively, were reached. All cohorts have been completed and all doses administered were well tolerated in human subjects and no clear pattern of toxicity is apparent.

Based on the review of safety, tolerability, and PK data from Cohorts 1 to 5 of the SAD study (AA98496) and Cohorts 1 to 3 of the MAD study, and the in vivo efficacy data in rat and mouse models, it is predicted that the therapeutic range should be between 1.2 mg/kg and 4.8 mg/kg which is equivalent to 84 mg to 336 mg daily in a 70 kg patient. Therefore, a low YPL-001 dose of 80 mg BID and the high YPL-001 dose of 160 mg BID were selected for this proof-of-concept study.

The total strength (23.75 mg) of identified compounds in YPL-001 as a whole in the 40 mg starting dose administered in the first-time-in-human dose escalation study (AA98496) corresponded to approximately 35% of the dosages that have been used in the traditional medicine setting in China (68.65 mg). In this present proof-of-concept study the total strength (47.50 mg) of identified compounds in the initial starting dose of 80 mg is still lower than the dosages that have been used in the traditional medicine setting in China, as shown in Table 4, corresponding to 70% of the traditional Chinese medicine.

Table 4: Traditional Chinese Medicine Use versus Proposed Clinical Starting Dose

Identified Compounds in YPL-001	1.40 g (Single Dose) Traditional Chinese Medicine[a] (mg)	2.80 g/day (Divided Dose) Traditional Chinese Medicine[a] (mg)	80 mg (Single Dose) for MAD Study[b] (mg)
Verproside	47.94	95.88	30.64
Veratric acid	2.10	4.20	1.08
Catalpolside	3.77	7.54	4.08
Picroside II	3.43	6.86	3.36
Isovanilloyl catalpol	3.53	7.06	4.72
6-*O*-veratroyl catalpol	7.88	15.76	3.62
Total	68.65	137.30	47.50

[a] Traditional medicine dosage from Chinese Medical Great Dictionary; Zhong Yao Da Ci Dian.
[b] Proposed dosage of YPL-001 in MAD study

11. RISK/BENEFIT

YPL-001 is being developed as a potential oral treatment for long term control of persistent asthma and COPD. YPL-001 belongs most closely with the leukotriene modifier class of drug and has the potential to inhibit the accumulation of neutrophils the increase of several proinflammatory cytokines and chemokines which play a major role in tissue remodeling. The development of a product to improve the treatment of asthma and COPD will be of benefit to the wider community/patients with respiratory disease.

The safety monitoring practices employed by this protocol (i.e., physical examination, vital signs, pulse oximetry, 12-lead ECG, hematology, serum chemistry, urinalysis, AE monitoring, and AE questioning) are deemed adequate to protect the patients' safety and should detect all expected TEAEs. The procedures employed in this study to assess efficacy are primarily non-invasive and present no undue risk to the patient.

The approximate volume of blood planned for collection from each patient over the course of the study (see Section 14.5), presents no undue risk to the patients nor does the possibility of collection (for wasting to ensure clean sample) of additional blood in the event an angiocatheter is utilized and the possibility of additional blood collection for recheck of safety labs if deemed necessary by the Investigator.

12. STUDY OBJECTIVES AND ENDPOINTS

12.1 Study Objectives

The primary objective of the study is to assess the safety and tolerability of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients.

The secondary objective of the study is to assess the number and magnitude of daily respiratory symptoms of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients.

The exploratory objectives of the study are to evaluate the following in moderate to severe COPD patients:

1. To assess BAL epithelial brushings for YPL-001 component levels.
2. To compare BAL samples for total cell count (cells/mL) macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; neutrophil, macrophage, lymphocyte, and eosinophil counts as absolute inflammatory cell numbers in YPL-001 groups versus placebo group.
3. To compare BAL samples for TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9 in YPL-001 groups versus placebo group.
4. To compare blood inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) and concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9 in YPL-001 groups versus placebo group.
5. To compare spirometric functions (FEV_1, FVC, FEV_1/FVC, and IC) in YPL-001 groups versus placebo group.
6. To compare patient reported outcomes (BDI/TDI, CAT) in YPL-001 groups versus placebo group.
7. To assess verproside and picroside II concentration in plasma and BAL and verproside and picroside II PK in plasma following multiple oral doses administration of two YPL-001 dose levels.

12.2 Study Endpoints

The primary endpoint is the number and severity of TEAEs following multiple oral doses of YPL-001 or placebo.

The secondary endpoint is the number of symptom free days and overall symptom burden following multiple oral doses of YPL-001 or placebo, assessed by measuring:

- daily PEF;
- major (e.g., estimated sputum quality [e.g., color, consistency] and quantity) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation;

- dyspnea (using the Modified Borg Dyspnea Scale); and
- activity (using the DASI).

The exploratory endpoints are:

1. YPL-001 component levels in epithelial brushings;
2. BAL biomarkers following multiple oral doses of YPL-001 or placebo, measuring:
   - total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells
   - total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers
   - concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9.
3. Blood biomarkers following multiple oral doses of YPL-001 or placebo, measuring:
   - inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils, and lymphocytes)
   - concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9.
4. Pulmonary function results (spirometry) following multiple oral doses of YPL-001 or placebo.
5. Quality of life scores using the BDI/TDI, CAT questionnaires.
6. Concentrations and PK of verproside and picroside II in plasma following multiple oral doses of YPL-001.
7. Concentrations of verproside and picroside II in BAL following multiple oral doses of YPL-001.

13. INVESTIGATIONAL PLAN

13.1 Overall Study Design and Plan

This is a Phase 2a, proof-of-concept, multicenter, randomized, double-blind, double-dummy, 3-treatment, parallel study, with low and high YPL-001 doses (80 mg and 160 mg BID) and a placebo control, in moderate to severe COPD patients.

At least 60 patients will be enrolled and randomized into 3 treatment groups (20 patients per group). Patients will participate only once. An approximately equal number of current and ex-smokers will be enrolled in the study.

Safety and tolerability will be assessed throughout the study. Assessment of respiratory symptoms and symptom burden in YPL-001 and placebo treatments will be performed daily through patient self-report of PEF, major and minor symptoms of COPD exacerbation, dyspnea, and activity in their e-diary. Spirometry measurement, BAL, and blood samples will be collected for the PD assessment of YPL-001 and placebo treatments. Serial blood samples will also be collected for PK assessment of verproside (the principal active ingredient of YPL-001) and picroside II. Other components of YPL-001 and its metabolites may also be analyzed in plasma.

Following screening, eligible patients will discontinue non permitted respiratory drugs if already receiving them and enter a 14 ± 2 days Run-in Period during which patients will be given albuterol taken on an as required basis and daily tiotropium 18 µg (one capsule inhaled daily in the morning) to be administered at home. On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their daily symptoms throughout the Run-in Period.

Patients will return to the CRU in the morning, –for Check-in of the Treatment Period to confirm their eligibility and assess their health conditions. If they still meet all of the inclusion criteria and none of the exclusion criteria, they will undergo Check-in scheduled study procedures. Patients will return to the CRU on the morning of Day 1 to be randomized and receive one of the 3 treatments and undergo all scheduled study procedures. Patients will return on the morning of Days 15 (± 2 days), 29 (± 2 days), 43 (± 2 days), 54 (± 1 day), and 56 of the Treatment Period for study drug administration and procedures. Prior to each release from the CRU, patients will receive a properly labeled kit and/or any unused wallets from previously provided kits (when applicable) with sufficient doses which will be self-administered by patients at home until the next morning visit at the CRU. Patients will continue recording their daily symptoms via the e-diary throughout the Treatment Period. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff.

The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

Patients will be instructed to call the Investigator if breathing worsens or if they need to take more than 8 puffs per day of albuterol for more than 2 consecutive days. If the Investigator determines that the patient is too unstable to continue in the study, he/she

will be discontinued. Rescue medication will be used for any patient with an exacerbation of COPD and will be administered in accordance with the study center standard of care.

Discontinued patients may be replaced at the discretion of the Sponsor.

13.2 Study Conduct

Please see the Study Events Flow Chart for a summary of the schedule of study participation and procedures in Section 6.

13.2.1 Screening

Screening will begin within 14 days of Day 1 (inclusive) of the Run-in Period. Informed consent will be obtained at screening (see Section 16.1.3) and prior to any study procedures being performed. Patients will have to meet all eligibility criteria before being enrolled in the study (see Section 13.3). Patients will be informed of the study restrictions (see Section 13.3.5).

The following will be recorded at screening: medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI, and history of tobacco use (including number of pack-year and cigarette smoked per day).

Screening procedures are listed in Section 6.

13.2.2 Patient Confinement

Patients will be admitted to the CRU on the morning of each scheduled visit at a time designated by the CRU as delineated in the Study Events Flow Chart (Section 6). Patients will remain in the clinic through completion of all scheduled study procedures.

13.2.3 Run-In Period (Days 1 to 14 [± 2 days])

Eligible patients will be admitted to the CRU on the morning of Day 1 of the Run-in Period at a time designated by the CRU. Patients will discontinue all restricted concomitant medications as indicated in Section 13.3.5.1 and undergo the Run-in procedures as listed in Section 6.

During the Run-in Period, patients will self-administer tiotropium (Spiriva® HandiHaler®) daily for 14 ± 2 days before Day 1 of the Treatment Period. Patients will be instructed to inhale 1 capsule of tiotropium (Spiriva® HandiHaler®) every morning. Patients will also receive albuterol for as needed use. Patient will keep this rescue albuterol throughout the Run-in Period.

Prior to release from the CRU, patients will receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. They must return the container (empty or not) at the next schedule visit, which is scheduled after 14 ± 2 days.

Each patient will also be issued and trained on the use of the e-diary to record their self-administered doses and their daily respiratory symptoms. Prior to each morning dose, patients will record at home their daily PEF, major (e.g., estimated sputum quality [e.g., color, consistency] and quantity) and minor (e.g., cough, wheeze, sore throat,

nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

13.2.4 Treatment Period (Days 1 to 56)

Patients who completed the Run-in Period and still meet all the inclusion criteria and none of the exclusion criteria will be randomized to receive one of the assigned treatments (80 mg or 160 mg YPL-001 BID, or placebo BID) on Day 1 through Day 55 (see Section 13.4.1 and Section 13.4.2).

Safety and tolerability will be monitored throughout the Treatment Period as listed in Section 6. Patients will continue to record their self-administered doses and their daily respiratory symptoms on their e-diary. Prior to each morning dose, patients will record at home their daily PEF, major (e.g., estimated sputum quality [e.g., color, consistency] and quantity) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

BAL samples for YPL-001 concentrations and PD assessments will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

Spirometry and quality of life questionnaires for PD assessments will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

Blood samples for PD and PK assessment will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

13.2.4.1 Meal Schedule

Patients will be required to fast overnight for at least 12 hours before the bronchoscopy and BAL collection at the Check-in of the Treatment Period and on Day 56. On Days 1 and 54 (± 1 day), patients will be required to fast overnight for at least 8 hours before and for at least 4 hours after the morning dose. On all other days, patients will be asked to fast for at least 2 hours before and 2 hours after each morning dose. Patients will also be asked to fast for at least 2 hours before and after each evening dose.

Patients will also be required to fast for at least 8 hours before the scheduled serum chemistry tests at the time points delineated in the Study Events Flow Chart (Section 6).

During in-clinic dosing, water (except that administered with dosing) will not be permitted from 1 hour before until 1 hour after each dosing. Water will be allowed as desired at all other times. On all other days, patients will be informed to follow the same restrictions.

On Days 1 and 54 (± 1 day), patients will fast from all food and drink except water between meals and snacks. Foods and beverages containing alcohol, xanthines, caffeine, vegetables from the mustard green family, mustard, tea (especially speedwell tea), or grapefruit/Seville oranges will not be served in the CRU. Across all CRUs, menus should be similar in content. The same menu and meal (except for snacks) schedule will be administered uniformly for all patients confined within the same CRU, across all treatment groups. Meals are not required to be completed by patients.

13.2.4.2 Early Termination

Early termination evaluations will be performed on patients prior to early termination. Patients who want to terminate from the study and are not currently on-site will be contacted and asked to return to the CRU to perform the early termination procedures.

The early termination procedures are listed in Section 6.

13.2.5 Follow-up Call (14 ± 2 days)

The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

13.2.6 Scheduled End of Study

The end of the study is scheduled after completion of the evaluations in the 3 treatment groups or after dose-limiting clinical safety endpoints have been reached to preclude continuation of the study. The clinical conduct of the study is intended to last approximately 12 to 24 months.

This time period may change in the event that the study is terminated early, additional time is required to review safety, or a decision is made to complete an unscheduled analysis for a group.

13.3 Selection of Study Population

13.3.1 Number of Patients

The study is planned to enroll at least 60 patients. An approximately equal number of current and ex-smokers will be enrolled. Patients will be divided in 3 treatment groups with 20 patients to receive one of the 3 treatments (i.e., low and high YPL-001 doses [80 mg and 160 mg BID] and a placebo control) as per the randomization schedule. Each treatment group will consist of an approximately equal number of current and ex-smokers.

13.3.2 Inclusion Criteria

Patient candidates must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Adult males and/or females, 30 to 85 years of age (inclusive).
2. History of COPD for at least 12 months prior to screening.
3. Diagnosed with COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines with symptoms compatible with COPD for at least 12 months prior to screening.

4. Classified as moderate to severe COPD based on the current severity classification GOLD Stage 2-3 disease in terms of post-bronchodilator spirometry at screening:
   - Post-bronchodilator FEV_1/FVC ratio of <70%
   - Post-bronchodilator FEV_1 ≥30 % and <80 % of predicted normal values
5. Weigh at least 52 kg for males and 45 kg for females and within the normal range according to accepted normal values of the Body Mass Index (BMI) chart 18.5-40.0 kg/m^2 inclusive.
6. In the judgment of the Investigator, the patient is medically stable with no change in symptoms, medication, or with clinical laboratory results that in the Investigator's opinion are compatible with the diagnosis of either COPD or a complication thereof and are judged acceptable for inclusion with predominantly bronchitic symptoms at screening.
7. Must be on a stable medical regimen for COPD ≥ 30 days prior to screening.
8. In the Investigator's opinion patients should be able to withhold tiotropium 24 hours prior to Day 1 of the Run-in Period, if already receiving it and prior to each scheduled CRU visit.
9. Must have oxygen saturation on room air > 93%.
10. Hemoglobin must be equal to or above the lower limit of normal at screening and check-in.
11. Current or ex-smoker with a history of >10 pack years. Ten pack years are defined as: 20 cigarettes a day for 10 years; 10 cigarettes a day for 20 years; or 40 cigarettes a day for 5 years (i.e., [number of cigarettes smoked per day × number of years smoked]/20). Patients, who undergo smoking cessation therapy, must be completed 3 months prior to screening visit and smoking status should not change between the patient's screening visit and patient's last study visit.
12. For a female of childbearing potential: either be sexually inactive (abstinent) for 14 days prior to the first dose and throughout the study or be using one of the following acceptable birth control methods:
    a. non-hormone releasing intrauterine device in place for at least 3 months prior to the first dose.
    b. surgical sterilization of the partner (vasectomy for 4 months minimum).
    c. physical barrier method (e.g., condom, diaphragm) with spermicide for at least 14 days prior to the first dose and throughout the study.
13. A female patient who claims to be sexually inactive, but becomes sexually active during the course of the study must agree to use a physical barrier method (e.g., condom, diaphragm) with spermicide from the time of the start of sexual activity through to the completion of the study.

14. For a female of non-childbearing potential: must have undergone one of the following sterilization procedures at least 6 months prior to the first dose:

    a. hysteroscopic sterilization;

    b. bilateral tubal ligation or bilateral salpingectomy;

    c. hysterectomy;

    d. bilateral oophorectomy;

    or be postmenopausal with amenorrhea for at least 1 year prior to the first dose and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status as per Investigator judgment.

15. Non-vasectomized males must agree to be sexually abstinent or to use a condom with spermicide when engaging in sexual activity from the first dose through completion of the last scheduled study procedures on Day 56 or upon early termination. Patients will be advised to use a condom with spermicide for 90 days following the last administration of the study drug, and to not donate sperm during this same period of time. In the event that the sexual partner is surgically sterile, use of a condom with spermicide is not necessary. No restrictions are required for vasectomized males provided their vasectomy has been performed 120 days or more prior to study start. Males who have been vasectomized less than 120 days prior to study start must follow the same restrictions as non-vasectomized males.

16. Understands study procedures and provides written informed consent for the trial.

17. Be able to comply with the protocol, such as all the study restrictions, and the assessments therein.

13.3.3 Exclusion Criteria

Patients will be excluded from the study if there is evidence of any of the following criteria at screening or check-in, as appropriate.

1. History of life-threatening COPD including respiratory arrest, intensive care unit admission and/or requiring intubation.
2. History of more than 2 hospitalizations for COPD within 12 months prior to screening.
3. Presentation of an acute exacerbation of COPD that will be associated with increase sputum volume or change in sputum color within 4 weeks before Day 1 of the Run-in Period.
4. Evidence of cor pulmonale, or clinically significant pulmonary hypertension.
5. Continuous use of more than 2L/day of oxygen.
6. History or presence of other respiratory disorders, such as asthma, α-1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis or other chronic pulmonary diseases.
7. A chest X-ray at screening (or within 3 months prior to screening) showing abnormalities, which in the opinion of the Investigator are clinically significant and unrelated to COPD.

8. A history of chronic disease including, but not limited to, unstable or uncontrolled hypertension (or been diagnosed with hypertension in the 6 months before screening), severe sleep apnea (assessed using the Berlin Questionnaire [refer to Section 14.1.8]), cardiovascular, endocrine, neurological, hepatic, gastrointestinal, renal, hematological, urological, immunological or ophthalmic diseases that the Investigator believes are clinically significant e.g., unstable and could impact patient safety by participation in the study.
9. History or presence of clinically significant cardiac arrhythmia, prostatic hyperplasia, bladder-neck obstruction, urinary retention, or narrow-angle glaucoma that, in the opinion of the PI, would contraindicate the administration of tiotropium.
10. Evidence of clinically relevant abnormal baseline hematology, serum chemistry, or urinalysis. Patients with an AST > 2 x ULN, ALT > 2 x ULN, bilirubin > 2 x ULN or creatinine > 2 x ULN (confirmation of results may be done once).
11. Diagnosed with hepatic impairment with a Child-Pugh class A score or higher.
12. Lung resection or lung reduction surgery within 12 months.
13. Positive alcohol (using urine dipstick or breathalyzer) test results at screening or at each CRU visit. If alcohol test is positive or subject reports consumption of alcohol within 48 hours prior to testing, alcohol test maybe rescheduled or repeated, at the discretion of the PI and if study visit time window allows.
14. Urine drug testing at screening or at each CRU visit, unless the positive drug screen is due to prescription drug use and is approved by the PI and the medical monitor.
15. Positive testing for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C infection with clinically significant liver impairement and/or a viral ribonucleic acid (RNA) titer of > 6.9 ± 0.8log molecules/mL.[3]
16. History or presence of alcoholism or drug abuse within the 2 years prior to Day 1 of the Treatment Period.
17. Hypersensitivity or idiosyncratic reaction to compounds related to YPL-001, including Speedwell tea and herbal remedies.
18. Requires one (or more) routine therapies for COPD during the indicated restricted time period as listed in Section 13.3.5.1.1.
19. Use of any drugs or substances known to be significant inhibitors (strong or moderate) of UDP-glucuronosyltransferase (UGT) (such as 17-beta-estradiol glucuronide, flavonoids [citrus fruit], silybin [herb supplement milk thistle]) and/or sulfotransferases (SULT) (refer to Appendix 1), within 12 hours prior to Day 1 of the Run-in Period. Additional sources may be consulted by the PI or medical monitor to confirm lack of PK/PD interaction with study drug.
20. Blood donation or significant blood loss within 56 days prior to Day 1 of the Treatment Period.
21. Plasma donation within 7 days prior to Day 1 of the Treatment Period.

22. Participation in another clinical trial within 30 days prior to Day 1 of the Run-in Period.
23. Females who are pregnant or lactating.
24. Surgery within the past 3 months prior to Day 1 of the Treatment Period determined by the Investigator to be clinically relevant.
25. Active or history of any disease or condition that would, in the opinion of the Investigator and/or medical monitor, place the patient at an unacceptable risk to participate in this study.

13.3.4 Removal of Patients from the Study

Patient participation in this trial may be discontinued for any of the following reasons:

1. Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol.
2. Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient.
3. The patient interrupts trial study drug administration for more than 7 consecutive days of dosing or missed a total of 17 doses (15%) throughout the Treatment Period.
4. Patient's decision to withdraw.
5. Requirement for prohibited concomitant medication.
6. Patient failure to comply with protocol requirements or study related procedures.
7. Termination of the study by the Investigator, Sponsor, FDA, Celerion, or other regulatory authorities.

The clinical report will include reason(s) for patient withdrawals as well as details relevant to the patient withdrawal. If a patient is withdrawn from the trial prior to study completion, the patient will undergo all procedures scheduled for study completion (early termination evaluations) as the situation allows (see Section 13.2.4.2). Any patient withdrawn due to an AE (whether serious or non-serious) or clinically significant abnormal laboratory test values will be evaluated by the Investigator and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

Patients withdrawn may be replaced at the Sponsor’s discretion.

13.3.5 Study Restrictions

13.3.5.1 Concomitant Therapy

All medications taken during the 30 days prior to the first dose will be recorded and reviewed by the Investigator.

Any medication taken by patients during the course of the study will be recorded. Concomitant medication will be coded using the most current WHO drug dictionary available at Celerion (e.g., 01-MAR-2014 or later). If drug therapy other than that specified by the protocol is taken, a joint decision will be made by the Investigator and Sponsor to continue or discontinue the patient.

13.3.5.1.1 Prohibited Therapy

The following medications are not permitted within the time delineated below and during the study (from Day 1 of the Run-in Period to the completion of the last scheduled study procedures on Day 56 or upon early termination). Intake of these medications during the Run-in Period constitutes a non-eligibility criterion and the patients will not be randomized into the study. If any of these medications are taken during the Treatment Period, the need for this patient to be withdrawn from the study will be carefully evaluated by the Investigator and the Sponsor on the basis of the potential impact on efficacy or safety evaluation and in the patient's best interest:

1. Any medications administered for the treatment of worsening of COPD within 4 weeks prior to Day 1 of the Run-in Period:
   - nebulized, inhaled, oral, IV, IM corticosteroids;
   - oral or parenteral β2 agonists;
   - Antibiotics.
2. Inhaled corticosteroids (ICS), LABA, and/or inhaled ICS/LABA fixed combinations within 12 hours prior to Day 1 of the Run-in Period;
3. Inhaled long acting anticholinergic agents other than tiotropium within 2 weeks prior to Day 1 of the Run-in Period;
4. Inhaled short-acting β2-agonists (SABA) other than albuterol (e.g., terbutaline, fenoterol) within 12 hours prior to Day 1 of the Run-in Period;
5. Inhaled short-acting anticholinergic agents (SAMA) (e.g., ipratropium) within 12 hours prior to Day 1 of the Run-in Period;
6. PDE inhibitors (including roflumilast) within 2 weeks prior to Day 1 of the Run-in Period.
7. Leukotriene modifiers and xanthines derivatives within 2 weeks prior to Day 1 of the Run-in Period.
8. Drugs or substances known to be significant inhibitors (strong or moderate) of UGT and/or SULT, within 12 hours prior to Day 1 of the Run-in Period and through collection of the final PK sample.
9. Acetaminophen will be prohibited 24 hours prior to Day 1 of the Treatment Period and through collection of the final PK sample.
10. Vitamin supplements (except for prescribed vitamin supplement) and herbal products (especially Speedwell) will be prohibited 7 days prior Day 1 of the Treatment Period and through collection of the final PK sample.

13.3.5.1.2 Permitted Therapy

Throughout the study period (from Day 1 of the Run-in Period to the completion of the last scheduled study procedures on Day 56 or upon early termination) patients will be permitted to take the following medications in addition to the study drugs:

1. Albuterol, as required (except approximately 4 hours before schedule pulmonary function test);
2. Tiotropium (Spiriva® HandiHaler®) 18 µg once a day (except approximately 24 hours before schedule pulmonary function test);
3. Ibuprofen, as required, up to 1200 mg per day for intercurrent illness or AEs. Ibuprofen should not be taken for 2 hours before or after each dosing.
4. Prescribed vitamin supplement (except for Vitamin C).
5. In the case of a concomitant disease, appropriate treatment will be permitted if it does not interfere with the study evaluation parameters and does not qualify under the section "Prohibited Therapy" (see Section 13.3.5.1.1)

13.3.5.2 Prohibitions

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/caffeine (other than coffee and tea): 24 hours prior to each CRU visit and prior to dosing on Days 1 and 54 (± 1 day) of the Treatment Period through collection of Days 1 and 54 (± 1 day) last PK sample.
- Alcohol (other than red wine and beer): 48 hours prior to each CRU visit and 48 hours prior to dosing on Days 1 and 54 (± 1 day) of the Treatment Period through collection of Days 1 and 54 (± 1 day) last PK sample.
- Vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts), and mustard: 14 days prior to Day 1 of the Treatment Period through collection of Day 54 (± 1 day) last PK sample.
- Fruit Juice: 24 hours prior to each CRU visit and prior to dosing on Days 1 and 54 (± 1 day) of the Treatment Period through collection of Days 1 and 54 (± 1 day) last PK sample.
- Tea (especially Speedwell tea), coffee, and red wine: 7 days prior to Days 1 and 54 (± 1 day) of the Treatment Period through collection of Days 1 and 54 (± 1 day) last PK sample.
- Grapefruit/Seville orange and beer: 14 days prior to Day 1 of the Treatment Period through collection of Day 54 (± 1 day) last PK sample.

13.3.5.3 Activity

Patients will remain ambulatory or seated upright for 1 hour following each study medication administration.

Patients will be advised to refrain from strenuous physical activity which could cause

muscle aches or injury, including contact sports at any time from screening until completion of the study.

13.4 Treatments

13.4.1 Treatments administered

13.4.1.1 Drug Administration During Run-in Period

Tiotropium (Spiriva® HandiHaler®) will be supplied as 18 µg capsules for inhalation.

Albuterol will be supplied as 100 µg albuterol base (1 actuation = 100 µg albuterol base) for oral inhalation. Albuterol may be administered via a nebulizer or a metered-dose inhaler.

Multiple oral inhalation of tiotropium (Spiriva® HandiHaler®) 18 µg capsule will be administered QD every morning for 14 ± 2 days during the Run-in Period. Albuterol will be administered on an as needed basis.

13.4.1.2 Drug Administration During Treatment Period

YPL-001 will be supplied as 80 mg tablets for oral administration.

Placebo will be supplied as YPL-001 80 mg matching placebo tablets for oral administration.

Treatments A, B, and C are described as follows:

Treatment A: Multiple oral YPL-001 80 mg doses (1 x 80 mg tablet + 1 x 1 YPL-001 80 mg matching placebo tablet) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days.

Treatment B: Multiple oral YPL-001 160 mg doses (2 x 80 mg tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days.

Treatment C: Multiple oral matching placebo (2 x 1 YPL-001 80 mg matching placebo tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days.

Each dose of Treatments A, B and C will be administered with approximately 240 mL of water.

In all treatments, one tiotropium (Spiriva® HandiHaler®) 18 µg capsule will also be administered QD every morning prior to study drugs administration. Albuterol will be administered on an as needed basis.

YPL-001 or placebo will be dispensed in accordance with the Randomization and Drug Dispensing Instructions provided in a separate document.

Prior to release from the CRU on Days 1, 15 (± 2 days), and 29 (± 2 days), of the Treatment Period, patients will receive a properly labeled new kit, which contains 4 wallets of 2 blister cards, with the appropriate doses which will be self-administered by

patients at home. Any unused wallets from previously provided kits will also be dispensed to patients on Days 15 (± 2 days) and 29 (± 2 days). Prior to release from the CRU on Days 43 (± 2 days), and 54 (± 1 day), patients will received unused wallets from previously provided kits with the appropriate doses which will be self-administered by patients at home. Patients will also receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. Patients will record their self-administered doses in their e-diary, and whether the dose was administered with food, and must return the YPL-001 used and unused wallets and the tiotropium and albuterol container (empty or not) at the next schedule visit at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.

Patients will be instructed not to crush, split or chew the study drug.

The exact clock time of dosing will be recorded on on-site dosing days. Patients will be given instructions on how to record their drug administration in their e-diary on home-dosing days.

Each dose will be administered under fasting conditions as described in Section 13.2.4.1.

13.4.1.3 Stopping Rules

A decision to stop or suspend the study will be made jointly by the Sponsor and the Investigator following the review of all pertinent safety and tolerability. Together they will make one of the following determinations:

1. To continue with the study as planned.
2. To continue with the study and add additional safety evaluations.
3. To continue with the study by adjusting to a lower dose if 2 patients at any dose level meets any of the following criteria and the patient was determined to have received YPL-001 after unblinding:
   a. Has a drug–related, unexpected SAE.
   b. Experiences drug-related grade ≥ 3 toxicity.
4. The study will be terminated if ≥ 3 patients at any dose level meet any of the following criteria and the patients were determined to have received YPL-001 after unblinding:
   a. Has a drug–related, unexpected SAE.
   b. Experience drug related grade ≥ 3 toxicity.

PK data will not be required for the dose-escalation decision.

When applicable, a written statement fully documenting the reasons for study termination will be provided to the Institutional Review Board (IRB).

13.4.2 Method of Assigning Patients to Treatment Groups

Each patient will be assigned a unique screening identification number upon screening. Patients who complete the study screening assessments, complete the Run-in Period, and meet all the eligibility criteria will be assigned a unique randomization identification number, different from the screening number, and receive the corresponding product, according to a randomization scheme generated at Celerion. Each treatment group will consist of an approximately equal number of current and ex-smokers.

Patients will receive one of the 3 treatments (Treatments A, B, or C) on one occasion.

If replacement patients are used, the replacement patient number will be 100 more than the original (e.g., Patient No. 0101 will replace Patient No. 0001).

13.4.3 Blinding

This is a double-blind, double-dummy, randomized study.

13.4.3.1 Maintenance of Randomization

A computerized randomization scheme will be created by a Celerion unblinded statistician (who is not otherwise involved in the study) and shall be considered blinded (per the following).

The randomization will not be made available to the Sponsor, patients, or members of the staff responsible for the monitoring and evaluation of safety assessments.

The bioanalytical department will also be blinded to the randomization scheme.

13.4.3.2 Procedures for Breaking the Blind Prior to Study Completion

The site Pharmacist/Study Coordinator will receive two sets of randomization code envelopes, one set for “Current Smokers” and another for “Ex-Smokers”. Each individual envelope is marked on the outside with one of the randomization numbers and contains the treatment for that patient. These envelopes must be kept in a secure locked location.

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the patient.

In the event of a medical emergency, it is requested that the Investigator make every effort to contact the medical monitor or designee prior to breaking the blind. If breaking the blind is required because of a medical emergency, the treatment identity would be revealed by the qualified designee, for that patient only. In the event that the emergency is one, in which it appears that the other patients may be at imminent risk, the blind may be broken for all patients dosed at that dose level. The unblinding should be noted in the patient’s electronic case report form (eCRF).

In all cases where the code is broken, the Investigator should record the date, reason for code breaking and his/her name for signature on the envelope.

At the end of the study, the envelopes will be reviewed by the Sponsor.

13.4.3.3 Revealing of Randomization

In the absence of a medical emergency, the blinded randomization for this entire trial will not be revealed until the following conditions are fulfilled:

1. All data are entered in the database, edits checks are performed, queries closed, CRFs signed by the Investigator, and the database is officially locked.
2. All PK/PD samples have been analyzed and quality checked by the responsible analytical associate.

13.4.4 Treatment Compliance

During in-clinic dosing, a qualified designate will be responsible for monitoring the administration of timed oral doses. When appropriate, a mouth check will be performed by the qualified designate to ensure that the patients have swallowed the study medication. Once a patient has finished the water, the qualified designate will use a flashlight and a tongue depressor to check the side of the mouth, the sides of the upper and lower gums and the area under the tongue. Patients' hands will also be verified to ensure that the medication was ingested.

Self-administration by patients at home will be monitored via the e-diary and attempted phone calls will be performed to remind patients to take their medication, if they did not record their self-administration on the e-diary.

14. STUDY PROCEDURES

14.1 Safety Assessments

This study primarily assesses the safety and tolerability of YPL-001. Safety will be determined by evaluating physical examinations, vital signs, pulse oximetry, ECGs, clinical laboratory parameters, and AEs.

If deemed necessary, additional safety measurements will be performed at the discretion of the Investigator.

Study procedures should be completed as close to the prescribed/scheduled time as possible. The Quality of Life questionnaire should be performed prior to any other procedures. When the following procedures are scheduled at the same time, they will be performed in the following order:

1. Vital signs and pulse oximetry
2. ECG
3. Pulmonary function measurement
4. Bronchoscopy and BAL collection

All other procedures can be performed without specific order.

14.1.1 Body Height and Weight

Body height (centimeters) and body weight (kilograms) will be measured as outlined in the Study Events Flow Chart (Section 6).

14.1.2 Physical Examination

All full physical examinations will include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose and throat, respiratory system, cardiovascular system, gastrointestinal system, neurological condition, blood and lymphatic systems, and the musculoskeletal system.

A licensed physician will examine each patient as outlined in the Study Events Flow Chart (Section 6).

Medical history will be recorded at screening.

Physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator.

14.1.3 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate will be measured as outlined in the Study Events Flow Chart (Section 6).

Vital signs may be taken at any other times, if deemed necessary. Blood pressure and heart rate measurements will be performed with patients in a seated position for at least 1 minute, except when they are supine or semi-reclined because of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the Investigator.

When performed prior to the morning dose, blood pressure and heart rate will be measured within 2 hours prior to dosing. When performed prior to the bronchoscopy, blood pressure and heart rate will be measured within 4 hours prior to the bronchoscopy. When scheduled postdose, vital signs readings will be performed within approximately 10 minutes of the scheduled time point. When performing the bronchoscopy, vital signs (body temperature, respiratory rate, blood pressure, and heart rate) will be monitored continuously until the end of the procedure.

14.1.4 Pulse Oximetry

Oxygen saturation (%), and heart rate will be assessed using a pulse oximeter. All readings will be performed with a pulse oximeter (oxygen saturation [%], and heart rate) as outlined in the Study Events Flow Chart in Section 6.

When performed prior to the morning dose, pulse oximetry monitoring will be measured within 2 hours prior to dosing. When performed prior to the bronchoscopy, pulse oximetry monitoring will be measured within 4 hours prior to the bronchoscopy. Readings may be taken at other times, if deemed necessary by the Investigator. When performing the bronchoscopy, oxygen saturation will be monitored continuously until the end of the procedure.

Any clinically relevant oxygen saturation reading below 93% will be documented as an AE, as per Investigator discretion.

14.1.5 Electrocardiogram Monitoring

When performed prior to the morning dose, ECG will be measured within 2 hours prior to dosing. When performed prior to the bronchoscopy, ECG will be measured within 4 hours prior to the bronchoscopy. When performing the bronchoscopy, ECG will be monitored continuously until the end of the procedure.

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6). Patients will be required to lie quietly in a supine position for at least 5 minute prior to ECG measurements. Single 12-lead ECGs may be performed at various unscheduled time points, if deemed necessary by the Investigator.

Single 12-lead ECGs will be interpreted and signed and dated by the Investigator. The ECGs will be classified as normal, having a non-clinically significant abnormality (NCS), or having a clinically significant abnormality (CS). In addition, ECG parameters of ventricular rate, PQ or PR interval, QRS duration, and QT interval (corrected according to Bazett's formula [QTcB] and uncorrected) will be noted on the CRF.

14.1.6 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 6). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator. The clinical laboratory tests include the following:

14.1.6.1 Hematology

- Hemoglobin
- Hematocrit
- RBC count (including a reticulocytes count)
- Platelet count
- Mean Corpuscular Hemoglobin (MCH)
- Mean Corpuscular Volume (MCV)
- Mean Corpuscular Hemoglobin Concentration (MCHC)
- RDW
- White blood cell (WBC) count with differential (including eosinophil, neutrophil, basophil, lymphocytes, and monocytes)

14.1.6.2 Serum Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.

- BUN
- Creatinine*
- Bilirubin (total and direct)
- Uric acid
- Albumin
- Alkaline phosphatase (ALP)
- Creatine kinase (CK)
- Lactate dehydrogenase (LDH)
- Estimated glomerular filtration rate
- Alpha-1 Antitrypsin**
- AST
- ALT
- Amylase
- Lipase
- Glucose (fasting)
- Carbon dioxide (CO_2)/Bicarbonate (HCO_3)
- Sodium
- Potassium
- Chloride

* Creatinine clearance will be calculated using Cockcroft-Gault formula at screening.

** To be performed at screening only.

14.1.6.3 Serology

- HIV
- HBsAg
- HCV
- HCV viral RNA titer

14.1.6.4 Human Chorionic Gonadotropin (Serum Pregnancy Test)

The test will be performed for females only.

14.1.6.5 Follicle-Stimulating Hormone

The test will be performed in postmenopausal females only.

14.1.6.6 Urinalysis

- pH
- Specific gravity
- Protein
- Glucose
- Ketones
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Leukocyte Esterase

If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination will be performed.

14.1.6.7 Urine/Breathalyzer Alcohol Screen

Alcohol levels will be tested using urine dipsticks or breathalyzers.

14.1.6.8 Urine Drug Screen

- Cannabinoids
- Cocaine
- Amphetamines
- Barbiturates
- Benzodiazepines
- Opiates

14.1.6.9 Additional Tests

- Prothrombin time/international normalized ratio (PT/INR)

14.1.7 Chest X-Ray

A baseline chest x-ray will be performed at the screening visit. If the patient has had an x-ray within the last 3 months prior to the screening visit, and the CRU has access to the report and images, this can be used as the baseline chest x-ray and does not need to be repeated.

14.1.8 Berlin Questionnaire

The Berlin Questionnaire is a validated screening questionnaire used to quickly identify the risk (low to high) of sleep disordered breathing. The questionnaire consists of three categories and risk is based on the responses to individual items and overall scores in the symptom categories. Assessments will be performed according to the Study Events Flow Chart (Section 6). The questionnaire will be provided as a separate document and a copy of the questionnaire to be used will be kept in the study binder.

14.1.9 Adverse Events

14.1.9.1 Adverse Event Definition

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.[4]

14.1.9.2 Monitoring

The patients will be instructed to inform the Investigator or clinic staff of any AEs and intercurrent illnesses experienced during the trial. Additionally, a specific inquiry regarding AEs will be conducted prior to each dosing at the CRU, after the last scheduled study procedures on Day 56 (or upon early withdrawal), and at the follow-up phone call. The inquiry will be made in a non-specific manner using open-ended questions so as not to bias the response (e.g., How have you been feeling since your last visit?).

All symptoms will be evaluated by the Investigator.

Any patient who has a clinically significant AE (whether serious or non-serious) or clinically significant abnormal laboratory test value will be evaluated by the Investigator, or other monitoring physician, and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

Treatment of SAEs will be performed by a physician, either at the CRU or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal or unknown (lost to follow-up).

14.1.9.3 Reporting

AEs will be coded using the most current MedDRA® available at Celerion (e.g., 17.0 or higher). The Sponsor will inform the Celerion Global Project Manager which version is to be used prior to initiation of the study.

The Investigator will review each event and assess its relationship to drug treatment (unrelated, unlikely, possible, probable, definite). The severity of each sign or symptom reported will be graded based on the NIH NCI CTCAE toxicity grading scale 5-point severity scale (Grade 1, 2, 3, 4 and 5) [5] and the date and time of onset, time relationship to drug dosing, duration, and outcome (resolved, improved, unchanged, worse, fatal, or unknown/lost to follow-up) of each event will be noted.

The relationship of each AE will be assessed using the following definitions:

Unrelated	▪ Event occurring before dosing. ▪ Event or intercurrent illness due wholly to factors other than drug treatment.
Unlikely	▪ Poor temporal relationship with drug treatment. ▪ Event easily explained by patient's clinical state or other factors.
Possible	▪ Reasonable temporal relationship with drug treatment. ▪ Event could be explained by patient's clinical state or other factors.
Probable	▪ Reasonable temporal relationship with drug treatment. ▪ Likely to be known reaction to agent or chemical group, or predicted by known pharmacology. ▪ Event cannot easily be explained by patient's clinical state or other factors.
Definite	▪ Distinct temporal relationship with drug treatment. ▪ Known reaction to agent or chemical group, or predicted by known pharmacology. ▪ Event cannot be explained by patient's clinical state or other factors.

The following definitions for rating severity will be used:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**. Note**:** An experience may be severe but may not be serious, e.g., severe headache).
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A semi-colon indicates 'or' within the description of the grade; ADL = Activities of Daily Living

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

14.1.9.4 Serious Adverse Events

If any AEs are serious, as defined by the Food and Drug Administration (FDA) Code of Federal Regulations (CFR), Chapter 21, special procedures will be followed. All SAEs will be reported to the Medical Monitor via fax or e-mail within one working day of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012[4]. The institutional review board (IRB) will be notified of the Alert Reports as per FDA regulations.

If an SAE occurs to a patient on this study, the Medical Monitor is to be contacted (see Section 4).

A SAE is any AE or suspected adverse reaction that in the view of either the Investigator or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

14.2 Symptom Assessments

14.2.1 Electronic Diary

On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their self-administered doses, whether the dose was administered with food, and daily respiratory symptoms throughout the Run-in and Treatment Periods. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff.

Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality [e.g., color, consistency] and quantity) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

14.2.2 Peak Expiratory Flow

PEF assessments will be made daily prior to each dose from Day 1 of the Run-in Period to Day 56 of the Treatment Period. Three measurements will be made at each time point using a hand held PEF meter. Readings not performed in the CRU will be recorded in the patient e-diary. All PEF assessments should be performed before administration of a bronchodilator where possible.

14.2.3 Symptoms of Chronic Obstructive Pulmonary Disease Exacerbation

Patient will be asked to record the major (e.g., estimated sputum quality [e.g., color, consistency] and quantity) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation via the e-diary before each dosing.

14.2.4 Dyspnea (Modified Borg Dyspnea Scale)

Severity level of patient's dyspnea will be assessed via the modified Borg dyspnea scale programmed within the e-diary. The modified Borg dyspnea scale is a self-administered categorical scale with a score from 0 to 10, where 0 (as a measure of dyspnea) corresponds to the sensation of normal breathing (absence of dyspnea) and 10 corresponds to the patient's maximum possible sensation of dyspnea.

14.2.5 Activity (Duke Activity Status Index)

Patient's functional capacity and activity status will be assessed via the DASI programmed within the e-diary. DASI is a self-administered 12-item questionnaire that assesses daily activities such as personal care, ambulation, household tasks, sexual function and recreation with respective metabolic costs. Each item has a specific weight based on the metabolic cost. The final score ranges between 0 and 58.2 points. The higher the score, the better the functional capacity.

14.3 Pharmacodynamic Assessments

14.3.1 Pulmonary Function (Spirometry)

Spirometry measures will be taken at the time points delineated in the Study Events Flow Chart (Section 6) using a standard calibrated spirometer to determine the parameters detailed below.

- FEV_1;
- FVC (forced vital capacity);
- FEV_1/FVC;
- IC.

Short acting β2-agonist and anticholinergic bronchodilators (e.g., albuterol, ipratropium bromide) and long acting β2-agonist and anticholinergic bronchodilators (e.g., salmeterol, tiotropium) agents will be withheld approximately 4 and 24 hours, respectively, before each pre-bronchodilator spirometry.

Every effort will be made to perform all assessments for a given patient on the same instrument throughout the study.

At screening, baseline pre-bronchodilator spirometry will be performed (prior to albuterol administration) for a minimum of 3 times and a maximum of 8 times in order to obtain 3 manoeuvers with FEV_1 values within 150 mL of each other, using the manoeuver with the highest value of FEV_1 and FVC as the basis for comparison.

Patients shall receive 4 inhalations of albuterol (100 µg/inhalation) for a total dose of 400 µg via metered-dose inhaler using a spacer. Within approximately 20 to 30 minutes after albuterol administration, the baseline post-bronchodilator spirometry will be performed.

Assessment of FEV_1 stability will take place:

1. Prior to Day 1 dosing of the Treatment Period (Check-in measurement): Predose FEV_1 is defined as the time point prior to Day 1 dosing in the Treatment Period and will be performed pre- and post-bronchodilatator administration. Predose FEV_1 will be compared to the corresponding baseline measurement. If the best FEV_1 measurement at predose at Check-in of the Treatment Period has declined by greater than 20% from the best FEV_1 at screening, the visit may be rescheduled up to 3 times, at the discretion of the Investigator.

2. Following Day 1 dosing: At all other spirometry time point, measurements will be performed once. If the value shows a difference of greater than 150 mL decline than the best FEV_1 value collected predose at Check-in, up to 3 measures will be performed.

   Consideration should be given, if a patient experiences any change in post Day 1 dose FEV_1 from the Day 1 predose FEV_1 value (measured following dosing with albuterol) equal to or greater than 20 % and should alert the Investigator to consider whether individual patients should continue to dose. The pulmonary function manoeuver(s) used to make this assessment must be valid and meet acceptable quality spirometry standards.

The Investigator may also use his or her discretion as to the completion of dosing for any period in which an FEV_1 decline and/or respiratory symptoms occur(s).

14.3.2 Bronchoscopy and Bronchoalveolar Lavage (BAL) Biomarkers

Patients will be fasted for 12 hours before the bronchoscopy procedures. If required, blood pressure medications can be taken with small sip of water based on preapproval of local Investigator.

14.3.2.1 Bronchoscopy

The bronchoscopy with bronchial brushings will be performed at the time points delineated in the Study Events Flow Chart (Section 6) by a licensed physician experienced in conducting the procedure according to guidelines published on the use of bronchoscopy for research on airway diseases such as COPD.[6,7]

Albuterol will be administered 20 minutes prior to the beginning of the bronchoscopy. An intravenous line will also be established to administer conscious sedation, and to administer emergency medications if the need were to arise. During the procedure, oxygen saturation (S_PO_2), blood pressure, and heart rate and rhythm (continuous electrocardiogram) will be monitored. Oxygen 2-4 L via nasal cannula will be administered during bronchoscopy and oxygen saturation will be maintained at ≥95%. Conscious sedation will be achieved with incremental doses of 1–4 mg midazolam and 50-100 µg fentanyl. Local upper and lower airway topical anesthesia will be achieved with 1% or 2% lidocaine. The dose of lidocaine administered during the procedure will not exceed a total of 450 mg. The bronchoscope will usually be inserted preferably through the nares into trachea. The bronchoscope will be wedged into 2 subsegments of the right middle or lower lobe, as deemed appropriate by the Investigator. Emergency treatments for cardiopulmonary arrest and pneumothorax will be immediately available in the bronchoscopy room. The patient will remain in the recovery suite for observation for a minimum of 2 hours after the procedure.

14.3.2.2 Bronchial Brushings

Prior to BAL, a cytology brush is inserted into the bronchoscope channel and brushings are collected twice from each of 4 quadrants of visible subsegments of the right middle or lower lobe, as deemed appropriate by the Investigator, under direct visualization. The cellular material is washed off in saline following each brushing. The brushing is performed a total of 8 times. The liquid is centrifuged and the cell pellet is stored at -70°C.

Samples must be protected from UV light during collection, processing, and storage.

14.3.2.3 Bronchoalveolar Lavage (BAL)

BAL in the right middle or lower lobe, as deemed appropriate by the Investigator, will be performed at the time points delineated in the Study Events Flow Chart (Section 6) by a licensed physician experienced in conducting the procedure. A total of 180 mL BAL, using 6 x 30 mL aliquots of normal saline warmed to room temperature, will be performed using each subsegment of the right middle or lower lobe, as deemed appropriate by the Investigator. BAL fluid will be aspirated following each 30 mL instillation. The lavage material, which averages 25% return in COPD patients, typically yields 1-10 x 10^6 macrophages. The centrifuged cell pellet and supernatant will be kept cooled until processed or stored as indicated in the laboratory manual to be provided as a separate document.

Samples must be protected from UV light during collection, processing, and storage.

14.3.2.4 Biomarkers

BAL samples will be analyzed for:

- YPL-001 component levels in epithelial brushings;
- total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells
- total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils

as absolute inflammatory cell numbers

- concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9.

14.3.3 Blood Biomarkers

Blood samples will be collected via direct venipuncture or an angiocatheter at the time points delineated in the Study Events Flow Chart (Section 6) for PD assessments of biomarkers. Biomarker assessments include:

- inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils, and lymphocytes)
- concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9.

Blood will be drawn into 3 tubes. A manual for blood sampling, collection, processing, and sample shipment will be provided in a separate document.

14.3.4 Quality of Life Questionnaires

14.3.4.1 Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI)

Dyspnea at baseline (Check-in of the Treatment Period) will be assessed with the BDI. This instrument has 3 domains (functional impairment, magnitude of task, and magnitude of effort) with the values added for a combined focal score. Functional impairment determines the impact of breathlessness on the ability to carry out activities; magnitude of task determines the type of task that causes breathlessness, magnitude of effort establishes the level of effort that results in breathlessness. The BDI scores range from 0 (very severe impairment) to 4 (no impairment) for each domain with the baseline focal score consisting of the sum of each domain (0 to 12).

Dyspnea throughout the study will be performed at the time points delineated in the Study Events Flow Chart (Section 6). The change from baseline is measured by the TDI score which ranges from -3 (major deterioration) to +3 (major improvement) for each domain with the TDI focal score consisting in the sum of each domain (-9 to +9).

The same Investigator or designee will interview specifically the patients during the study.

A copy of the questionnaire to be used will be kept in the study binder.

14.3.4.2 COPD Assessment Test (CAT)

CAT is a short and simple questionnaire of 8 items completed by patients to be performed at the time points delineated in the Study Events Flow Chart (Section 6). Scores for each of the 8 items are summed to give a single, final score ranging from 0 (no impact on daily activities) to 40 (very high impact on daily activity). This is a measure of the overall impact of a patient's condition on their life. Scores for the individual items within the questionnaire will provide insight into the relative influence that the different components of COPD have on its overall impact on a patient's life.[8,9]

A copy of the questionnaire to be used will be kept in the study binder.

14.4 Pharmacokinetic Assessments

The sampling schedule and/or collection intervals delineated in the Study Events Flow Chart (Section 6) may be modified based on the results from previously dosed patients.

14.4.1 Blood Sampling and Processing

Samples must be protected from UV light during collection, processing, and storage.

Samples will be collected via direct venipuncture or an angiocatheter at the time points delineated in the Study Events Flow Chart (Section 6).

Blood will be drawn into 4 mL pre-chilled evacuated tubes containing K_2EDTA. A manual for blood sampling, collection, processing, and sample shipment will be provided in a separate document.

14.5 Blood Volume for Study Assessments

Table 5: Blood Volume during Study

Sample Type	Number of Time Points	Volume per Time Point*	Sample Volume Over Course of Study
Screening laboratory safety tests (including hematology, serum chemistry, serology, PT/INR), FSH (for postmenopausal female patients only), and serum pregnancy (for female patients only).	1	~ 17 mL** or 21 mL***	~ 17 mL** or 21 mL***
On-study serum chemistry and serum pregnancy (for female patients only) when scheduled at the same time	3	~ 8.5 mL	~ 25.5 mL
Additional on-study serum pregnancy (for female patients only)	2	~ 3.5 mL	~ 7 mL
On-study hematology	3	~ 4 mL	~ 12 mL
Blood samples for PD biomarkers (except CRP and fibrinogen)	8	~ 6 mL	~ 48 mL
Blood samples for PD biomarker - CRP	8	~ 4 mL	~ 32 mL
Blood samples for PD biomarker - Fibrinogen	8	~ 3.5 mL	~ 28 mL
Blood samples for PK of verproside and picroside II	37	~ 4 mL	~ 148 mL
Total Blood Volume for males† →			~ 310.5 mL** or 314.5 mL***
Total Blood Volume for females† →			~ 317.5 mL **or 321.5 mL***

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

** For patients enrolled at UAB Lung Health Center, Florida Pulmonary Research Institute, LLC, or Temple University School of Medicine.

***For patients enrolled at Aventiv Research Inc. only.

† If an angiocatheter is used, up to 5 mL of blood will be used to flush the catheter prior to each collection of PK and/or PD blood samples. Hence the total blood volume collected may increase by approximately 205 mL.

15. DATA ANALYSIS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCPs.

15.1 Statistical Analysis

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a SAP. The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP.

15.1.1 Sample Size Calculation

According to the exploratory nature of this study no formal statistical hypotheses will be tested. However, a sample size of 60 evaluable patients is deemed to be sufficient to assess the safety and tolerability and to provide an indication of the potential effect of YPL-001 on COPD exacerbation symptoms, selected biomarkers and pulmonary function parameters.

15.1.2 Patients to Analyze

Safety population: the safety population data set will include all available data for patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo. Safety data for all discontinued patients will be included in this set for the time points for which their data are available.

Symptom monitoring population: the symptom monitoring population data set will include all available data for patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo. Symptom monitoring data for all discontinued patients will be included in this set for the time points for which their data are available.

PK population:

- The PK full data set will include all patients receiving at least one dose of YPL-001 and having at least one measurable plasma concentration of verproside and picroside II.
- The PK per-protocol data set will include all patients receiving all scheduled doses of YPL-001 and having sufficient samples collected to determine PK parameters from plasma concentrations of verproside and picroside II on Day 1 and/or Day 54 (± 1 day).

PD population:

- The PD full data set will include all patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo and provide at least 1 post-baseline PD measurement.

- The PD per-protocol data set will include all patients receiving all scheduled doses of the investigational product (i.e., YPL-001) or placebo and having measurable PD data.

PK/PD population: All patients who receive at least one dose of YPL-001 and having any measurable concentration of verproside and picroside II and measurable PD data will be included in the PK/PD relationship assessment, as applicable.

15.1.3 Safety Analysis

The following analyses will be performed. Safety analyses will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data, when appropriate.

Medical History:

Medical history will be listed by patient.

Adverse Events:

AEs will be coded using the most current MedDRA® available at Celerion (e.g., 17.0 or higher) and data will be summarized by SOC and preferred term. The number of TEAEs will be reported. In addition, the number and percent of patients reporting each TEAE will be summarized separately for each treatment.

A by-patient AE data listing, including verbatim term, preferred term, treatment, severity, outcome, and relationship to treatment, will be provided.

Physical Examination:

Changes in physical examinations will be described in the text of the final report and significant findings will be reported as AEs.

Clinical Laboratory Tests, Electrocardiograms, Vital Signs and Pulse Oximetry:

All clinical laboratory tests, 12-lead ECGs, vital signs, and pulse oximetry measurements and their change from baseline, if applicable, will be summarized by treatment and time point of collection.

A shift table describing out-of-normal range shifts will be provided for clinical laboratory results.

A normal-abnormal shift table will be presented for ECGs.

Peak Expiratory Flow:

PEF measurements and its change from baseline, will be summarized by treatment and time point of collection.

Concomitant Medications:

Concomitant medications will be listed by patient and coded using the most current WHO drug dictionary available at Celerion (e.g., 01-MAR-2014 or later).

15.1.4 Symptom Monitoring Analysis

Symptom free days and overall symptom burden will be evaluated and compared across treatment groups. Secondary outcome analysis will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative data and frequency counts will be compiled for classification of qualitative data, when appropriate.

Peak Expiratory Flow and Symptoms of COPD Exacerbation:

PEF measurements and symptoms of COPD exacerbation and their change from baseline will be summarized by treatment and time point of collection.

Dyspnea and Activity:

The Modified Borg Dyspnea Scale and DASI scores will be listed and presented descriptively.

Additional analysis may be performed if deemed appropriate.

15.1.5 Pharmacodynamic Analysis

15.1.5.1 Biomarkers

When applicable, the following PD biomarkers will be summarized by treatment group using descriptive statistics (arithmetic means, SD, CV, N, minimum, maximum, and median). Figures will be created to display mean and individual level or activity as a function of time, as appropriate:

- Pulmonary biomarker (i.e., Pulmonary Function measurements [Spirometry]): pre- and post-bronchodilator change in activity by time point will be calculated relative to the pre- and post-bronchodilator baseline activity;
- BAL biomarkers (i.e., total cell count [cells/mL] of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; total cell count [cells/mL] of neutrophils, macrophages, lymphocytes and eosinophils as absolute inflammatory cell numbers; and concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9): raw and % change from baseline levels; and
- Blood biomarkers (i.e., inflammatory markers [total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes] and concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9): raw and % change from baseline levels.

PK/PD relationship may be explored graphically using scatter plots and an appropriate regression model.

15.1.5.2 Quality of Life

The quality of life parameters reported from the BDI/TDI and CAT questionnaires will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.

15.1.6 Pharmacokinetic Analysis

15.1.6.1 Pharmacokinetic Parameters

15.1.6.1.1 Plasma

PK parameters will be computed from the individual plasma verproside and picroside II concentrations using a noncompartmental approach. Appropriate validated PK software (e.g., WinNonlin Professional) will be used. PK parameters for other components of YPL-001 and its metabolites may also be computed, as appropriate.

The following PK parameters will be computed following Day 1 morning dose:

$AUC_{0\text{-}12}$	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to 12 hours.
$AUC_{0\text{-}t}$	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (C_t). This parameter will be reported only if plasma concentrations fall below the lower limit of quantitation before the last time point prior to the evening drug administration on Day 1 for at least one patient. Otherwise, only $AUC_{0\text{-}12}$ will be reported.
$AUC_{0\text{-}inf}$	Area under the drug concentration-time curve from time zero to infinity, $AUC_{0\text{-}inf} = AUC_{0\text{-}t} + C_t/k_{el}$, where k_{el} is the terminal elimination rate constant. †
C_{max}	Maximum observed drug concentration.
t_{max}	Time of the maximum drug concentration (obtained without interpolation).
k_{el}	Apparent terminal elimination rate constant, calculated by linear regression of the terminal linear portion of the log concentration vs. time curve. †
$t_{1/2}$	Apparent elimination half-life, calculated as $\ln(2)/k_{el}$. †
CL/F	Oral clearance [$Dose/AUC_{0\text{-}inf}$]. †
V_Z/F	Apparent volume of distribution at the terminal phase, calculated as $Dose/(k_{el} * AUC_{0\text{-}inf})$.†

† All k_{el} and related PK parameters ($AUC_{0\text{-}inf}$, $t_{1/2}$, CL/F, and V_z/F) will be reported only if the half-life of verproside or picroside II can be appropriately estimated from a 12-hour sampling period following dosing.

The following PK parameters will be computed following Day 54 (± 1 day) morning dose:

AUC_{τ}	The area under the plasma concentration versus time curve over the final dosing interval, as calculated by the log-linear trapezoidal method (e.g., 0-12 hours).
$AUC_{0\text{-}t}$	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (C_t).
C_{max_ss}	Maximum observed drug concentration at steady-state.
$C_{min,ss}$	Minimum observed/measured non-zero concentration at steady-state.
C_{trough}	Concentration at the end of a dosing interval.
C_{avg}	Ratio of AUC_{τ} to the dosing interval, τ.
%Fluc	Percent fluctuation will be calculated as follows: $\frac{C_{\max\_ss} - C_{\min\_ss}}{C_{avg}} \; x \; 100$
Swing	Percent swing will be calculated as follows: $\frac{C_{\max\_ss} - C_{\min\_ss}}{C_{\min\_ss}} \; x \; 100$
t_{max_ss}	Time to reach the maximum drug concentration (obtained without interpolation) at steady-state.
CL_{ss}/F	Total body clearance estimated at steady-state after oral administration, calculated as Dose/AUC_{τ}.
V_{z_ss}/F	Apparent volume of distribution at steady-state, calculated as (CL_{ss}/F)/k_{el}.*

* All k_{el} and related PK parameters ($t_{1/2}$ or V_{z_ss}/F) will not be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

If metabolite data are available, metabolite to parent ratios may be calculated for $AUC_{0\text{-}t}$, AUC_{τ}, and C_{max_ss}.

15.1.6.1.2 Bronchoalveolar Lavage

Levels of YPL-001 components in epithelial brushing will be listed.

15.1.6.2 Statistical Methods for Pharmacokinetic Analyses

PK parameters will be summarized by treatment group using descriptive statistics (arithmetic means, SD, CV, N, minimum, maximum, and median). In addition, geometric means will be calculated for AUC_{τ} and C_{max_ss}, as appropriate. Figures will be created to display mean and individual verproside and picroside II concentration-time curves. Additional PK analyses may be performed if deemed appropriate.

No value for k_{el}, $t_{1/2}$, and V_{z_ss}/F, as appropriate, will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

An estimate of the relative systemic exposure of AUC_{τ} and C_{max_ss} will be performed by dose normalized ratio analysis expressing the geometric mean ratio and 90% CI of the geometric mean ratio.

Steady-state will be assessed by visual inspection of predose plasma C_{trough} values on Days 15 (± 2 days), 29 (± 2 days), 43 (± 2 days), and 54 (± 1 day) following multiple oral dose administration of YPL-001.

Additional analyses will be performed as deemed necessary upon review of the data.

15.1.7 Assessment of Efficacy

Efficacy will not be assessed in this study.

16. STUDY ADMINISTRATION

16.1 Ethics

16.1.1 Institutional Review Board

This protocol will be reviewed by an IRB and the study will not start until the Board has approved the protocol or a modification thereof. The Board is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The board is ICH compliant.

16.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, GCP, 21 CFR Parts 50, 56, and 312, the ethical princliples set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

16.1.3 Patient Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the patients in non-technical terms. Patients will be required to read, sign and date an informed consent form summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Patients will be given a copy of their informed consent form.

16.2 Termination of the Study

The Sponsor reserves the right to discontinue this study and the Investigator reserves the right to terminate their participation at any time.

16.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion relevant to the quality of this study. Designated personnel of Celerion will be responsible for maintaining quality assurance (QA) and quality control (QC) to ensure that the trial is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and Good Laboratory Practice requirements as well as applicable regulatory requirements.

The Clinical Study Report will be audited by the QA department and the quality assurance audit certificate will be included in the study report.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to statistical database lock.

Patient compliance will be monitored throughout the study via procedures such as questioning at check-in to review inclusion and exclusion criteria, urine drug screen at

check-in, mouth check following dosing, and confinement for all conduct procedures with clinical research staff on site at all times.

16.4 Direct Access to Source Data/Documents

The Investigator must maintain, at all times, the primary records (i.e., source documents) of each patient's data. Examples of source documents are laboratory reports, drug inventory, study drug label records, and eCRFs that are used as the source.

Celerion will ensure that the sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6] 5.1.2 & 6.10). In the event that other trial-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

16.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of YPL-001 80 mg tablets, and matching placebo tablets to allow completion of this study. The lot numbers and expiration dates (where available) of the drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the drugs supplied. At the conclusion of the study, any unused drugs (including placebo) will either be retained by the CRU, or returned to the Sponsor, depending on the specific requirements of the regulatory bodies to whom the study report will be submitted. If no supplies remain, this fact will be indicated in the Drug Accountability section of the final report.

16.6 Data Handling and Record Keeping

Celerion standard eCRFs will be used. Each eCRF is reviewed and signed off by the Investigator.

All raw data generated in connection with this study, together with the original copy of the final report, will be retained at each CRU in a designated storage facility, until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

16.7 Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be discussed between Sponsor and the Investigator. All revisions and/or amendments to the protocol in writing must be approved by the Sponsor, the Investigator, and the IRB before implementation.

16.8 Finance and Insurance

Finance and insurance will be addressed in a separate document.

16.9 Publication Policy

All unpublished information given to Celerion by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor's written consent to publish the article.

17. REFERENCES

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[9] The COPD Assessment Test healthcare professional user guide: expert guidance on frequently asked questions (issue 3: February 2012). Jones PW, Jenkins C, Bauerle O (on behalf of the CAT Development Steering Group).

18. APPENDICES

18.1 Appendix 1 - SULT Drug Interaction Table

The following list provides medications that are substrates and inhibitors of sulfotransferase. Adapted from Zhang H, Cui D, Wang B, Han YH, et al. Pharmacokinetic drug interactions involving 17alpha-ethinylestradiol: a new look at an old drug. Clin Pharmacokinet. 2007;46(2):133-57; Coughtrie MW, Johnston LE. Interactions between dietary chemicals and human sulfotransferases-molecular mechanisms and clinical significance. Drug Metab Dispos. 2001;29(4 Pt 2):522-528; King RS, Ghosh AA, and Wu J Inhibition of human phenol and estrogen sulfotransferase by certain non-steroidal anti-inflammatory agents. Curr Drug Metab. 2006;7(7):745–753; Nagai M, et al. Inhibitory effects of herbal extracts on the activity of human sulfotransferase isoform sulfotransferase 1A3 (SULT1A3). Biol Pharm Bull. 2009;32(1):105-109; and Harris, R. M.; Waring, R. H. Sulfotransferase inhibition: potential impact of diet and environmental chemicals on steroid metabolism and drug. Current Drug Metabolism 2008;9(4):269-275.

Inhibitors
17-beta-estradiol glucuronide
Vitamin C
Brown rice
Beer
Meclofenamate
Nimesulide
Salicylic acid
Acetylsalicylic acid
Naproxen
Banaba extract
Rafuma extract
Grape seed extract
Peanut seed coat extract
Gingko extract
Biloba leaf extract
St. John’s wort
Gymnema
Milk thistle

Celerion Project No.: AA98497

Sponsor Project No.: YPL-001-YJP-130403

IND No.: 114903

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

1. PROTOCOL REVISION HISTORY

DATE/NAME	DESCRIPTION
05-Nov-2015 by Caroline Engel	Final Protocol, Amendment 5 This protocol amendment is generated to add the following Investigator and clinical site: Samir Arora, MD Aventiv Research Inc. 99 North Brice Road, Suite 260 Columbus, Ohio 43213 United States Tel: + 1 614 501-6164 Therefore, Section 3 Investigators Signature was updated accordingly. Section 4 Additional Key Contacts for the Study was also updated to add the correcponding certified clinical laboratory. All 3 sites clinical sites will be using the Western Institutional Review Board. Section 4 Additional Key Contacts for the Study was updated accordingly. Minor editorial corrections were made where applicable.
16-Sep-2015 by Caroline Engel	Final Protocol, Amendment 4 This protocol amendment is generated to clarify and adjust study procedures as listed below: 1. Brigham and Women's Hospital Investigator signature and contact information was removed throughout the protocol since the center will not be participating during this study. The following sections were updated accordingly: • Section 3 Investigators Signatures • Section 4 Additional Key Contacts for the Study 2. The age limits were changed from 40 - 80 years of age, inclusively, to 30 - 85 years of age, inclusively. The following sections were updated accordingly: • Section 5 Synopsis - Study Population • Section 13.3.2 Inclusion Criteria – Inclusion criterion #1 3. To provide scheduling flexibility to the patients, a ±2-day window was added to the return visits on Days 15, 29, and 43. The following sections were updated accordingly: • Section 5 Synopsis - Summary of Study Design and Exploratory Outcome Measures • Section 6 Study Events Flow Chart • Section 13.1 Overall Study Design and Plan

DATE/NAME	DESCRIPTION
16-Sep-2015 by Caroline Engel	• Section 13.4.1.2 Drug Administration During Treatment Period • Section 15.1.6.2 Statistical Methods for Pharmacokinetic Analyses 4. Breathalyzer was added as an alternative method to the urine dipstick for the alcohol screen. The following sections were updated accordingly: • Section 6 Study Events Flow Chart • Section 13.3.3 Exclusion Criteria – Exclusion criterion #13 • Section 14.1.6.7 Urine/Breathalyzer Alcohol Screen was added • Section 14.1.6.8 (previously 14.1.6.7) was renamed Urine Drug Screen (previously Urine Drug/Alcohol Screen). 5. Only patients suffering from severe sleep apnea, as assessed by the Berlin Questionnaire, will be excluded from the study; The following sections were updated accordingly: • Section 6 Study Events Flow Chart • Section 13.3.3 Exclusion Criteria - exclusion criterion #8. • Section 14.1.8 Berlin Questionnaire was added. 6. The body mass index upper limit was increased from 32.0 kg/m^2 to 40.0 kg/m^2 inclusively. Therefore inclusion criterion #5 of Section 13.3.2 Inclusion Criteria was revised accordingly. 7. Drug screen false positive will be allowed if they are due to the use of prescription medication following approval from the PI and the medical monitor, the exclusion criterion #13 of Section 13.3.3 Exclusion Criteria was revised accordingly. 8. Smoking restriction prior to the bronchoscopy procedures was removed. Therefore, Section 14.3.2 Bronchoscopy and Bronchoalveolar Lavage (BAL) Biomarkers was updated accordingly. 9. Only strong and moderate inhibitors of UDP-glucuronosyltransferase and/or sulfotransferases are prohibited, therefore to prevent confusion with the list of substrats that was provided in Appendix 1, Appendix 1 was remove and the only 3 inhibitors listed in that table was enumarated in exclusion criterion #18. The list of substrate in appendix 2 (now rename Appendix 1) was also remove. This change will prevent possible confusion with the lists provided in the appendices. Exclusion criterion #18 of Section 13.3.3 Exclusion Criteria was revised accordingly. 10. To be consistent with Section 6 Study Events Flow Chart, pulse oximetry was added to the order of procecedures listed in Section 14.1 Safety Assessments. 11. Typographic and editorial corrections were made where applicable.

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	Final Protocol, Amendment 3 This protocol amendment is generated to clarify and adjust study procedures as listed below. The changes to the protocol are presented with new text in **bold** font and deleted text in ~~strikethrough~~ font. **Serious Adverse Event Contact Information** Drug Safety Solution's Medical Monitor will be contacted in case of serious adverse events. Hence the information under Sponsor Contact for Serious Adverse Events (Medical Monitor) in Section 4 Additional Key Contacts for the Study was corrected as follows: ~~Primary Contact:~~ ~~Yongnam Lee, Ph.D.~~ ~~Principal Scientist,~~ ~~Yungjin Pharm. CO., LTD.~~ ~~#451-20 Cheonho-3 dong, Gangdong-gu, Seoul, 134-721, Republic of Korea~~ ~~Tel.: +82 (31) 546-6980 ext. 220~~ ~~Fax: +82 (31) 546-6983~~ ~~E-mail: nami0209@yungjin.co.kr~~ ~~Mobile: +82 (10) 6311-4228~~ ~~Secondary Contact:~~ ~~Kangrae Ha, B.Sc.~~ ~~E-mail: hakr@yungjin.co.kr~~ **Dr. Kathy Smith** **Drug Safety Solution** **Tel.: +1 919 264-5626** **E-mail: ksmith@drugsafety.biz** Section 14.1.8.4 Serious Adverse Events and Section 13.4.3.2 Procedures for Breaking the Blind Prior to Study Completion was also corrected accordingly. **Certified Clinical Laboratory:** Brigham and Women's Hospital and UAB Lung Health Center clinical laboratories contact information were added to Section 4 Additional Key Contacts for the Study. **Clinical Indication:** As indicated in the objectives of the study, the study will examine the pharmacodynamic (PD) effect of YPL-001 in patients with chronic obstructive pulmonary disease (COPD) only. Therefore, to prevent potential confusion and to capture the intended indication of the study specifically "asthma" was removed from the Clinical Indication in Section 5 synopsis and Section 10.1 Purpose of the Study.

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	**Study Population:** As indicated throughout the protocol, patients will be will be adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3). Hence to be consistent with the GOLD Stage standards, the first sentence under Study Population from Section 5, Synopsis was corrected as follow: "Patients will be adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3) with a predominant bronchitic component ~~and a history of frequent (>2/year) COPD exacerbations,~~ between 40 and 80 years of age (inclusive)." **Randomization and Drug Dispensing** Instruction for randomization and drug dispensing are provided in a separate document. To be consistent with this document, which states that two sets of randomization code envelopes will be provided to site pharmacist/study coordinators and patients will received appropriately labeled kits and/or any unused wallets from previously provided kits (when applicable) for YPL-001 home dosing in addition to the containers for tiotropium/albuterol home dosing, the following section were modified accordingly: • Section 5 Synopsis under Summary of Study Design and Study Products • Section 6 Study Event Flow Chart, Day 1 Study Drug Administration at CRU - Footnotes "k" and "p" • Section 6 Study Event Flow Chart, Days 2 to 55 Study Drug Administration at Home – Footnotes "j" and "o" • Section 13.1 Overall Study Design and Plan • Section 13.4.1.2 Drug Administration During Treatment Period • Section 13.4.3.1 Maintenance of Randomization • Section 13.4.3.2 Procedures for Breaking the Blind Prior to Study Completion In addition, and "X" was also added in the "Randomization" row under Day 1 predose in Section 6 Study Events Flow Chart. **Fasting Conditions** As indicated throughout the protocol, subjects will be required to fast for at least 8 hours before and 4 hours after YPL-001/placebo morning administration on Days 1 and 56. For clarity, footnote "q" was added to Day 1 Study Drug Administration at CRU and footnote "k" was added to Day 56 Study Drug Administration at CRU in Section 6 Study Events Flow Chart.

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	**Analytes to be Measured** As indicated throughout the protocol, blood samples will be collected for the analyses of verproside and picroside II in plasma. Hence, the row identified as "Blood for Verproside Phamacokinetics" on Day 56 of Section 6 Study Events Flow Chart, was corrected to read: "Blood for Verproside **& Picroside II PK**". **End-of-Treatment – Early Termination Procedures** All procedures listed under End-of-Treatment/Early Termination column in Section 6 Study Events Flow Chart are also scheduled to be performed on Day 55 before the bronchoscopy procedures. Therefore, as it is not required to repeat these procedures for two consecutive days, End-of-Treatment procedures were removed on Day 56, however early termination (ET) procedures were listed under the new ET column. Hence, the following sections were corrected accordingly. • Section 6 Study Events Flow Chart • Section 13.2.4.2 End-of-Treatment or Early Termination (Day 56), (renamed Section 13.2.4.2 Early Termination). • Section 13.3.2 Inclusion Criteria – Criterion #16 • Section 13.3.4 Removal of Patients from the Study • Section 13.3.5.1.1 Prohibited Therapy • Section 13.3.5.1.2 Permitted Therapy • Section 14.1.8.2 Monitoring • Section 14.5 Blood Volume for Study Assessments (Table 5: Blood Volume during Study) In addition, the following sentence was added to Section 13.2.4.2 End-of-Treatment or Early Termination (Day 56), (renamed Section 13.2.4.2 Early Termination): "Patients who want to terminate from the study and are not currently on-site will be contacted and asked to return to the CRU to perform the early termination procedures" **Investigator's Brochure Version** In Section 9.1 YPL-001, the Investigator's Brochure version was updated to reflect the reference section and the most recent version of the Investigator's Brochure. **Method of Blood Collection** Throughout the protocol, the option of using an angiocatheter was added. Hence, the following sections were corrected accordingly: • Section 11 Risk/Benefit • Section 14.3.3 Blood Biomarkers • Section 14.4.1 Blood Sampling and Processing • Section 14.5 Blood Volume for Study Assessments

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	**Recording of Meal** To be consistent with clinical sites standard procedures, the last sentence of Section 13.2.4.1 Meal Schedule was corrected as follow: "Meals are not required to be completed by patients ~~and all meals and snacks eaten by patients will be recorded on the CRFs~~.' **Coffee, Tea and Alcohol Prohibition** As indicated in Section 13.3.5.2 Prohibitions, coffee tea, and red wine will be restricted for 7 days prior to Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample. Beer will be restricted for 14 days prior to Day 1 of the Treatment Period through collection of Day 56 last PK sample. Any other product containing xanthines or caffeine will be restricted 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample. Any other alcohol product will be restricted 48 hours prior to each CRU visit, 48 hours prior to dosing on Days 1 and 56 last PK sample. Hence, the xanthines/caffeine prohibition and the alcohol prohibition were corrected as follows for clarification: "Xanthines/caffeine **(other than coffee and tea)**: 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample." "Alcohol **(other than red wine and beer)**: 48 hours prior to each CRU visit, 48 hours prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample." **e-Diary** Home dosing will be recorded using a yes/no answer in the e-diary. Therefore the last sentence of the second to last paragraph of Section 13.4.1.2 Drug Administration During Treatment Period was corrected as follows: ***"***Patients will be given instructions on ~~recording of dosing times~~ **how to record their drug administration** in their e-diary on home-dosing days.' In addition, estimation of sputum quantity was added to the list of major symptoms of COPD exacerbation recorded daily by the patients on their e-diary, "color" and "consistency" was moved as example of sputum quality, and a statement indicating that the e-diary device will be return in case of early termination was also added. Hence, the following sections were corrected accordingly: • Section 5 Synopsis under Secondary Outcome Measures • Section 5 Synopsis under Summary of Study Design • Section 6 Study Events Flow Chart – Day 1, Footnote "j" • Section 6 Study Events Flow Chart – Days 2-55, Footnote "i" • Section 6 Study Events Flow Chart – Day 56, Footnotes "g" and "h" • Section 12.2 Study Endpoints • Section 13.1 Overall Study Design and Plan

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	• Section 13.2.3 Run-In Period (Days 1 to 14 [± 2 days]) • Section 13.2.4 Treatment Period (Days 1 to 56) • Section 14.2.1 Electronic Diary • Section 14.2.3 Symptoms of Chronic Obstructive Pulmonary Disease Exacerbation **Treatment Compliance** Drug administration at home will be monitored by HGE Technologies Inc. via the e-diary. Therefore, the last sentence of Section 13.4.4. Treatment Compliance was corrected as follow: "Self-administration by patients at home will be monitored ~~by the CRU~~ via the e-diary and attempted phone calls will be performed to remind patients to take their medication, if they did not record their self-administration on the e-diary." **Oxygen Saturation** For consistency throughout the protocol, "oxygen levels, saturation (%)" was replaced with "oxygen saturation (%)." **Tiotropium Treatment** As indicated in Section 13.3.2 Inclusion Criteria and Section 13.3.5.1.2 Permitted Therapy, tiotropium will be withheld 24 hours prior to pulmonary function (spirometry) measurements. Hence, the 2nd paragraph of Section 14.3.1 Pulmonary Function (Spirometry), was corrected to read: "Short acting β2-agonist and anticholinergic bronchodilators (e.g., albuterol, ipratropium bromide) and long acting β2-agonist and anticholinergic bronchodilators (e.g., salmeterol, tiotropium) agents will be withheld approximately 4 and ~~12~~ **24** hours, respectively, before each pre-bronchodilator spirometry." **Spirometer Across Clinical Site** The 3rd paragraph of Section 14.3.1 Pulmonary Function (Spirometry) was corrected as follow: "Every effort will be made to perform all assessments for a given patient on the same instrument throughout the study~~ and all sites should be using the same brand and model of spirometer for this study~~." **Bronchoalveolar Lavage (BAL) Collection** It is planned that a maximum of 180 mL BAL will be performed during each planned bronchoscopy procedures. Therefore, to prevent confusion, the second sentence of Section 14.3.2.3, Bronchoalveolar Lavage (BAL) was corrected to read: "A **total of** 180 mL BAL**, using 6 x 30 mL aliquots of normal saline warmed to room temperature,** will be performed ~~in~~ **using** each subsegment of the right middle or lower lobe, as deemed appropriate by the Investigator~~, using 6 x 30 mL aliquots of normal saline warmed to~~

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	~~room temperature~~." **Blood Volume for Clinical Safety Laboratory Tests, Pharmacodynamic (PD) Markers and Pharmacokinetic (PK) Samples:** Blood collection volume for PD markers, as indicated in Section 14.3.3 Blood Biomarkers and Section 14.5 Blood Volume for Study Assessments, only accounts for 1 tube. However, 3 tubes will be required to assess CRP (4 mL tube), fibrinogen (3.5 mL tube) and the rest of the PD biomarkers (6 mL tube). The blood volume per time point will be approximately 13.5 mL instead of 4.5 mL. As indicated above, End-of-Treatment listed on Day 56 were removed as the same tests are scheduled on Day 55 before the bronchoscopy procedures. Hence one sample was removed for a total of 3 on-study hematology and serum chemistry tests to be performed throughout the study. In addition, 4 mL of blood will be sufficient for the determination of verproside and picroside II concentration in plasma at each time point. Therefore the total blood volume was corrected to 310.5 mL for males and 317.5 mL for females. Section 14.3.3 Blood Biomarkers, Section 14.4.1 Blood Sampling and Processing, and Section 14.5 Blood Volume for Study Assessments were corrected accordingly. Minor typographic and editorial corrections were made where applicable.
16-Feb-2015 by Caroline Engel	Final Protocol, Amendment 2 This protocol amendment is generated to clarify and adjust study procedures as listed below. **Number of Subjects:** The sample size was revised to 60 subjects as it is sufficient to meet the objectives of the study. In case of dropouts, discontinued patients may be replaced at the discretion of the Sponsor as indicated throughout the protocol. Therefore the following sections were corrected accordingly to indicate that at least 60 subjects are planned to be enrolled and randomized with 20 patients to receive one of the 3 treatments: • Section 5 Synopsis (the 1st sentence of the 2nd paragraph under Summary of Study Design and the 1st and 2nd sentences under Number of Patients). • The 1st sentence of the 2nd paragraph of Section 13.1 Overall Study Design and Plan. • The 1st and 3rd sentences of Section 13.3.1 Number of Patients. • The last sentence of Section 15.1.1 Sample Size Calculation. **Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) and COPD Assessment Test (CAT):** BDI/TDI and CAT questionnaires will not be used as a diagnostic tool to

DATE/NAME	DESCRIPTION
16-Feb-2015 by Caroline Engel	assess the patient's potential to meet all inclusion criteria and none of the exclusion criteria. Therefore these questionnaires are not required at screening. In addition, it is not required to perform them for 2 consecutive days to meet the study objectives and therefore, Day 55 assessments were removed. Section 6 Study Events Flow Chart was corrected accordingly. The first sentence in Section 14.3.4.1 Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) was also corrected to be consistent with Section 6. **Early Termination Procedures:** Weight, and oxygen levels, saturation (%), and heart rate assessed using a pulse oximeter were added to the procedures performed at the end of the Treatment Period on Day 56 or prior to early termination from the study to monitor subject's safety appropriately. A pulmonary function (spirometry) test was also added prior to early termination for safety monitoring. Section 6 Study Events Flow Chart was corrected accordingly. **Recording Concomitant Medication:** Concomitant medication will be recorded at each study visit by the clinical staff in to the electronic data capture system. Therefore, concomitant medications was removed from the list of events that will be recorded by the patients via their e-diary throughout the protocol. The following sections were corrected accordingly: • Footnotes in Section 6 Study Events Flow Chart. • The first sentence of the 4th paragraph of Section 13.2.3 Run-In Period (Days 1 to 14 [± 2 days]). • The 2nd sentence of the 2nd paragraph of Section 13.2.4 Treatment Period (Days 1 to 56). • The 2nd sentence of the first paragraph of Section 14.2.1 Electronic Diary. **Subject Numbering:** The first paragraph of Section 13.4.2 Method of Assigning Patients to Treatment Groups was modified to clarify that the screening number and randomization number are two separate identification number given to each subject at different stages of the study. **Adverse Events Reporting** Footnotes were added to clarify the rating severity definitions in Section 14.1.8.3 Reporting. Minor editorial and typographical corrections were made where applicable.

DATE/NAME	DESCRIPTION
20-Nov-2014 by Ziv Machnes	Final Protocol, Amendment 1 This protocol amendment is generated to update the study population with regards to smoking frequency, to update the handling procedures for BAL samples, and to clarify other study procedures as listed below. **Study Population:** Section 13.3.2 - Inclusion Criteria, bullet 11 was updated to indicate that the study population will consist only of current and ex-smokers with a history of >10 pack years. As such, the indications for 'packs/year' were replaced with 'pack years' and the allowance for current smokers with <10 pack/years was removed. Wording was added to indicate an approximately equal number of current and ex-smokers will be enrolled, and that each treatment group will consist of an approximately equal number of smokers and ex-smokers. In addition, the stratification criteria for the randomization was updated to consist of either current or ex-smokers. The following sections were affected: • Section 5 – Synopsis (under Study Population and Number of Patients) • Section 13.1 - Overall Study Design and Plan (second paragraph) • Section 13.3.1 – Number of Patients. • Section 13.4.2 - Method of Assigning Patients to Treatment Groups. **BAL Sample Handling:** Section 14.3.2.3 - Bronchoalveolar Lavage (BAL) was updated to indicate that sample handling, processing and storage procedures will be provided in a separate document. **Follow-up Procedures:** The wording in regards to follow-up procedures to be conducted on 14 days (± 2 day), after the last study drug administration, was updated to indicated a phone-call and not a visit, as indicated correctly in Section 6 – Study Event Flow Chart. Study event were updated accordingly. The following sections were affected: • Section 5 – Synopsis (under Duration of Participation for Patients, and Exploratory Outcome Measures [under Blood Assessments, Pulmonary Assessment, and Quality of Life Assessments]) • Section 13.3.5.2 – Prohibitions (under Alcohol) • Section 14.1.8.2 – Monitoring (first paragraph). **Study Duration:** The total duration of the study indicated in Section 5 – Synopsis (under Duration of Participation for Patients) was corrected to 12 weeks to correspond with the actual study duration as indicated throughout the protocol.

DATE/NAME	DESCRIPTION
20-Nov-2014 by Ziv Machnes	**Inflammatory Markers in Blood Samples:** The list of cell types to be evaluated as part of the inflammatory markers in the blood was updated to include monocytes instead of macrophages, as macrophages are not expected to be present in blood. The following sections were affected: • Section 5 – Synopsis (under Study Objectives, fourth exploratory objective, and under Exploratory Outcome Measures [under Pharmacodynamic Assesments, Blood Assessments, first bullet]) • Section 12.1 - Study Objectives (fourth exploratory objective) • Section 12.2 - Study Endpoints (third exploratory endpoint) • Section 14.3.3 - Blood Biomarkers (first bullet) • Section 15.1.5.1 - Biomarkers (third bullet) **Neutrophil Evaluation in BAL Samples** Neutrophils were added to the list of cell types to be evaluated as a percentage of the total cell count in BAL samples. The following sections were affected: • Section 5 – Synopsis (under Study Objectives, second exploratory objective and under Exploratory Outcome Measures [under Pharmacodynamic Assessments, Bronchoalveolar Lavage Assessments, second bullet]) • Section 12.1 - Study Objectives (second exploratory objective) • Section 12.2 - Study Endpoints (second exploratory endpoint) • Section 14.3.2.4 - Biomarkers (second bullet) • Section 15.1.5.1 – Biomarkers (second bullet) **Location of Study Drug Administration**: Wording was added in Section 6 – Study Events Flow Chart for Day 56, to clarify that the study drug will be administered at the CRU. **Meal Schedule**: The indication for fasting requirement in Section 13.2.4.1 – Meal Schedule, was corrected to indicate patients will fast overnight for at least 12 hours before bronchoscopy and BAL collection on Days -1 and 55 instead of Days -1 and 56, as correctly indicated in Section 6 – Study Events Flow Chart. **ECG Monitoring:** Following an update in Celerion's standard operating procedure, Section 14.1.5 – Electrocardiogram Monitoring was updated to include at least 5 minutes of rest prior to each ECG measurement (instead of at least 1 minute as previously indicated).

DATE/NAME	DESCRIPTION
20-Nov-2014 by Ziv Machnes	**Hematology:** The tests included in the hematology panel Section 14.1.6.1 – Hematology were updated to indicate that the red blood cell (RBC) count will include a reticulocytes count, and that the white blood cell (WBC) count with differential will include monocytes but will not include reticulocytes. **Bronchoscopy and BAL:** Due to the sensitivity of YPL-001 components to UV light, a warning was added to protect all samples from exposure to UV light, as indicated for the PK blood samples. The following sections were affected: • Section 14.3.2.2 - Bronchial Brushings • Section 14.3.2.3 - Bronchoalveolar Lavage (BAL) **PK Population:** The indication for measurable concentration of verproside and picroside II in urine was removed from the definition of PK population in Section 15.1.2 - Patients to Analyze, as there is no urine PK sampling planned for this study. Minor typographic and editorial corrections were made where applicable.
18-Sep-2014 by Caroline Engel	Final Protocol

2. SPONSOR – SIGNATORIES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

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Signature

Jan. 27. 2016
Date

3. INVESTIGATORS SIGNATURES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

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11/10/15

Date

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INVESTIGATORS SIGNATURES (*CONTINUED*)

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

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05 Nov 2015
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4. ADDITIONAL KEY CONTACTS FOR THE STUDY

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5. SYNOPSIS

Compound:	YPL-001
Clinical Indication:	Treatment of inflammatory diseases of the respiratory tract such chronic obstructive pulmonary disease (COPD)
Study Type:	Phase 2a, proof of concept
Study Objectives:	The **primary objective** of the study is to assess the safety and tolerability of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients. The **secondary objective** of the study is to assess the number and magnitude of daily respiratory symptoms of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients. The **exploratory objectives** of the study are to evaluate the following in moderate to severe COPD patients: 1. To assess bronchoalveolar lavage (BAL) epithelial brushings for YPL-001 component levels. 2. To compare BAL samples for total cell count (cells/mL) macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; neutrophil, macrophage, lymphocyte and eosinophil counts as absolute inflammatory cell numbers in YPL-001 groups versus placebo group. 3. To compare BAL samples for tumor necrosis factors alpha (TNF-α), interleukin (IL)-1β, IL-4, IL-5, IL-6, IL-8, IL-13, myeloperoxidase (MPO), neutrophil elastase, monocyte chemotactic protein (MCP)-1, and matrix metalloproteinase (MMP)-9 in YPL-001 groups versus placebo group. 4. To compare blood inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) and concentrations of C-reactive protein (CRP), fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9 in YPL-001 groups versus placebo group. 5. To compare spirometric functions (forced expiratory volume in one second [FEV_1], forced vital capacity [FVC], FEV_1/FVC, and inspiratory capacity [IC]) in YPL-001 groups versus placebo group. 6. To compare patient reported outcomes (Baseline Dyspnea Index [BDI]/Transition Dyspnea Index [TDI], COPD Assessment Test [CAT]) in YPL-001 groups versus placebo group. 7. To assess verproside and picroside II concentration in plasma and BAL and verproside and picroside II pharmacokinetics (PK) in plasma following multiple oral doses administration of two YPL-001 dose levels.

Summary of Study Design:	This is a Phase 2a, proof-of-concept, multicenter, randomized, double-blind, double-dummy, 3-treatment, parallel study, with low and high YPL-001 doses (80 mg and 160 mg twice daily [BID]) and a placebo control in moderate to severe COPD patients. At least 60 patients will be enrolled and randomized into 3 treatment groups (20 patients per group). Patients will participate only once. Safety and tolerability will be assessed throughout the study. Assessment of respiratory symptoms and symptom burden in YPL-001 and placebo treatments will be performed daily through patient self-report of peak expiratory flow (PEF), major and minor symptoms of COPD exacerbation, dyspnea, and activity in their electronic diary (e-diary). Spirometry measurement, bronchoalveolar lavage (BAL), and blood samples will be collected for the pharmacodynamic (PD) assessment of YPL-001 and placebo treatments. Serial blood samples will also be collected for PK assessment of verproside (the principal active ingredient of YPL-001) and picroside II. Other components of YPL-001 and its metabolites may also be analyzed in plasma. Following screening, eligible patients will discontinue non permitted respiratory drugs if already receiving them and enter a 14 ± 2 days Run-in Period during which patients will be given albuterol taken on an as required basis and daily tiotropium 18 µg (one capsule inhaled daily in the morning) to be administered at home. On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their daily symptoms throughout the Run-in Period. Patients will return to the clinical research unit (CRU) on the morning of Day -1 of the Treatment Period to confirm their eligibility and assess their health conditions. If they still meet all of the inclusion criteria and none of the exclusion criteria, they will undergo Day -1 scheduled study procedures. Patients will return to the CRU the next day (Day 1) to be randomized and receive one of the 3 treatments and undergo all scheduled study procedures. Patients will return on the morning of Days 15 (± 2 days), 29 (± 2 days), 43 (± 2 days), 55, and 56 of the Treatment Period for study drug administration and procedures. Prior to each release from the CRU, patients will receive a properly labeled YPL-001 kit (and/or any unused wallets from previously provided kits [when applicable]) and tiotropium/albuterol container with sufficient doses which will be self-administered by patients at home until the next morning visit at the CRU. Patients will continue recording their daily symptoms via the e-diary throughout the Treatment Period. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff. The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any adverse event (AE) has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary. Patients will be instructed to call the Investigator if breathing worsens or if they need to take more than 8 puffs per day of albuterol for more than 2 consecutive days. If the Investigator determines that the patient is too unstable to continue in the study, he/she will be discontinued. Rescue medication will be used for any patient with an exacerbation of COPD and

	will be administered in accordance with the study center standard of care.
Study Population:	Patients will be adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3) with a predominant bronchitic component, between 30 and 85 years of age (inclusive). An approximately equal number of current and ex-smokers will be enrolled.
Number of Patients:	The study is planned to enroll at least 60 patients. Patients will be divided in 3 treatment groups with 20 patients to receive one of the 3 treatments (i.e., low and high YPL-001 doses [80 mg and 160 mg BID] and a placebo control) as per the randomization schedule. Each treatment group will consist of an approximately equal number of current and ex-smokers.
Duration of Participation for Patients:	The planned length of participation in the study for each patient is approximately 12 weeks (from Day 1 of the Run-in Period through completion of the follow-up procedures on Day 70 [± 2 days]).
Duration of Study Conduct:	The study is planned to take place over approximately 12 to 24 months (from screening of the first patient through completion of all study procedures for the last patient). This time period may change in the event that the study is terminated early, additional time is required to review safety, or a decision is made to complete an unscheduled analysis for a group.
Study Products:	YPL-001 will be supplied as 80 mg tablets for oral administration. Placebo will be supplied as YPL-001 80 mg matching placebo tablets for oral administration. YPL-001 or placebo will be dispensed in accordance with the Randomization and Drug Dispensing Instructions provided in a separate document.
Dosage, Dosage Form, Route, and Dose Regimen:	Treatments are described as follows: Treatment A: Multiple oral YPL-001 80 mg doses (1 x 80 mg tablet + 1 x 1 YPL-001 80 mg matching placebo tablet) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56. Treatment B: Multiple oral YPL-001 160 mg doses (2 x 80 mg tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56. Treatment C: Multiple oral matching placebo (2 x 1 YPL-001 80 mg matching placebo tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56. In all treatments, one tiotropium (Spiriva® HandiHaler®) 18 µg capsule will also be administered QD every morning prior to study drugs administration. Albuterol will be administered on an as needed basis. Each dose of Treatments A, B, and C will be administered orally with approximately 240 mL of water.

Stopping Rules:	A decision to stop or suspend the study will be made jointly by the Sponsor and the Investigator following the review of all pertinent safety and tolerability. Together they will make one of the following determinations: 1. To continue with the study as planned. 2. To continue with the study and add additional safety evaluations. 3. To continue with the study by adjusting to a lower dose if 2 patients at any dose level meets any of the following criteria and the patient was determined to have received YPL-001 after unblinding: a. Has a drug–related, unexpected serious adverse event (SAE). b. Experiences drug-related grade ≥ 3 toxicity. 4. The study will be terminated if ≥ 3 patients at any dose level meet any of the following criteria and the patients were determined to have received YPL-001 after unblinding: a. Has a drug–related, unexpected SAE. b. Experience drug related grade ≥ 3 toxicity.
Primary Outcome Measures	Safety and tolerability will be monitored through physical examinations, vital signs, pulse oximetry, ECGs, clinical laboratory tests, and AEs.
Safety and Tolerability Analysis	The following analyses will be performed. Safety analyses will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data, when appropriate. **Medical History:** Medical history will be listed by patient. **Adverse Events:** AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion (e.g., 17.0 or higher) and data will be summarized by System organ class (SOC) and preferred term. The number of treatment-emergent AEs (TEAEs) will be reported. In addition, the number and percent of patients reporting each TEAE will be summarized separately for each treatment. A by-patient AE data listing, including verbatim term, preferred term, treatment, severity, outcome, and relationship to treatment, will be provided. **Physical Examination:** Changes in physical examinations will be described in the text of the final report and significant findings will be reported as AEs. **Clinical Laboratory Tests, Electrocardiograms, Vital Signs, and Pulse Oximetry Measurements:** All clinical laboratory tests, 12-lead ECGs, vital signs, and pulse oximetry measurements and their change from baseline, if applicable, will be summarized by treatment and time point of collection. A shift table describing out-of-normal range shifts will be provided for clinical laboratory results. A normal-abnormal shift table will be presented for ECGs.

Safety and Tolerability Analysis (continued):	**Concomitant Medications:** Concomitant medications will be listed by patient and coded using the most current World Health Organization (WHO) drug dictionary available at Celerion (e.g., 01-MAR-2014 or later).
Secondary Outcome Measures:	PEF, major (e.g., estimated sputum quality (e.g., color, consistency), and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (Duke Activity Status Index [DASI]) self-reported daily by the patients using an e-diary.
Symptom Monitoring Analysis:	Symptom free days and overall symptom burden will be evaluated and compared across treatment groups. Secondary outcome analysis will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative data and frequency counts will be compiled for classification of qualitative data, when appropriate. **Peak Expiratory Flow and Symptoms of COPD Exacerbation:** PEF measurements and symptoms of COPD exacerbation and their change from baseline will be summarized by treatment and time point of collection. **Dyspnea and Activity:** The Modified Borg Dyspnea Scale and DASI scores will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.
Exploratory Outcome Measures:	**Pharmacodynamic Assessments:** <u>Bronchoalveolar Lavage Assessments:</u> BAL samples will be collected at baseline and again at the completion of the study for PD assessments of biomarkers. Biomarker assessments include: 1. epithelial brushings for YPL-001 component levels; 2. total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells 3. total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers 4. concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9. <u>Blood Assessments:</u> Blood samples will be collected at screening, and throughout the study for PD assessments of biomarkers. Biomarker assessments include: 1. inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) 2. concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9. <u>Pulmonary Assessment:</u> Pulmonary function measurements (spirometry [FEV_1, FVC, FEV_1/FVC, and

Exploratory Outcome Measures (continued):	IC] will be performed at screening, and throughout the study. Quality of Life Assessments: Patient reported outcomes (e-diary, BDI/TDI, CAT) will be performed at baseline, and throughout the study. **Pharmacokinetic Assessments:** Bronchoalveolar Lavage Assessments: BAL samples will be collected at baseline and again at the completion of the study to determine verproside and picroside II concentrations in BAL. Other components of YPL-001 and its metabolites may also be analyzed. Plasma Assessments: Serial blood samples will be collected prior to the initial dosing and through 12 hours following dosing on Days 1 and 56 to determine verproside and picroside II concentrations in plasma. Predose samples will also be collected in the morning of Days 15 (± 2 days), 29 (± 2 days), 43 (± 2 days) and 56 for C_{trough} determination. Other components of YPL-001 and its metabolites may also be analyzed. The sampling schedule and/or collection intervals may be modified based on the results as the study progress.
Pharmacodynamic Analysis:	**Blood, Plasma, and Pulmonary biomarkers:** When applicable, the raw data and % change from baseline or placebo, as appropriate, for PD markers (BAL biomarkers, blood biomarkers, and pulmonary biomarker) will be summarized by time point and treatment using descriptive statistics (arithmetic means, standard deviations [SD], coefficients of variation [CV], sample size [N], minimum, maximum, and median). Figures will be created to display mean and individual level or activity as a function of time. **Quality of Life:** The quality of life parameters will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.
Pharmacokinetic Parameters and Analysis:	Noncompartmental PK parameters, including AUC_{0-t}, AUC_{0-inf}, AUC_{τ}, k_{el}, C_{max}, C_{max_ss}, C_{min_ss}, C_{trough}, t_{max}, t_{max_ss}, CL/F, CL_{ss}/F, V_z/F, V_{z_ss}/F, and $t_{1/2}$, as appropriate, will be calculated from plasma concentrations of verproside and picroside II from patients who received YPL-001 only. Additional PK parameters may be calculated if deemed appropriate. Plasma PK parameters may also be calculated for other components of YPL-001 and its metabolites. PK parameters will be summarized by treatment using descriptive statistics. Relative exposure of verproside and picroside II will be assessed between the two YPL-001 dose levels, and steady-state will be assessed by visual inspection in the active treatment groups. Verproside and picroside II concentration in BAL samples from patients who received YPL-001 only will be listed.

6. STUDY EVENTS FLOW CHART

Study Procedures[a]	Screen[b]	Run-in Period		Treatment Period																		
Days →		1	2-14 (±2)	-1	1																	
Hours →					Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12
Administrative Procedures																						
Informed Consent	X																					
Inclusion/Exclusion Criteria	X	X																				
Medical History	X																					
Randomization					X																	
Safety Evaluations																						
Physical Examination[c]	X			X[d]																		
Height	X																					
Weight	X			X[d]																		
Chest X-ray[e]	X																					
Berlin Questionnaire	X																					
12-Lead Electrocardiogram	X			X[f]																		
Vital Signs[g]	X			X[f]	X						X		X						X			
Pulse Oximetry	X			X[f]																		
Hem, Chem, and UA[h]	X			X[d]																		
Serum Pregnancy Test (♀ only)	X			X[d]																		
Serum FSH (postmenopausal ♀ only)	X																					
Urine Drug Screen	X			X[d]																		
Urine or Breathalyzer Alcohol Screen	X			X[d]																		
HIV/Hepatitis Screen	X																					
AE Inquiries																						
AE Monitoring										X												
ConMeds Monitoring	X									X												
Symptoms Monitoring																						
Diary Training		X																				
Diary Use[l]										X												
PEF, COPD exacerbation, dyspnea and activity[j]										X												
Study Drug Administration																						
Tiotropium Administration[p]		X	X	X	X																	
Study Drug Administration at CRU[k,q]						X																X

Study Procedures[a]	Screen[b]	Run-in Period		Treatment Period																		
Days →		1	2-14 (±2)	-1	1																	
Hours →					Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12
Pharmacodynamic																						
Pulmonary Function (Spirometry)[l]	X			X[d]																		
Pharmacodynamic																						
Bronchoscopy and BAL Biomarkers[m]				X																		
Blood Biomarkers	X				X						X											
BDI/TDI & CAT				X[d]																		
Pharmacokinetic																						
Blood for Verproside & Picroside II PK					X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]
Other Procedures																						
Visit & Return Visits[o]	X	X		X	X																	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.
b. Within 14 days of Day 1 (inclusive) of the Run-in Period.
c. A full physical examination will be performed at screening. Symptom-driven physical examinations will be performed at other scheduled times, and may be performed at other times at the Investigator's discretion.
d. To be performed prior to the bronchoscopy procedures.
e. To be performed at screening or within 3 months (inclusive) of screening.
f. ECGs, vital sign and pulse oximetry will be measured within 2 hours of bronchoscopy procedures. During the bronchoscopy procedures and BAL sample collection, patients will be continuously monitored for ECGs, vital signs (blood pressure, heart rate, respiration rate, and body temperature), and oxygen saturation.
g. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
h. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.
i. Patients will be provided with an e-diary device to record their self-administered doses, whether the dose was administered with food, and daily respiratory symptoms.
j. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).
k. Prior to release from the CRU, patients will receive a properly labeled kit with sufficient study drug for their assigned treatment which will be self-administered by patients at home until the next morning visit at the CRU. Patients must return the used and unused wallets at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.
l. Pulmonary function will be performed prior to and 20 to 30 minutes after inhalation of approximately 400 µg albuterol.
m. Bronchoscopy and BAL sample collection will be performed following a 12-hour fast.
n. To be performed prior to dosing.
o. Patients will be admitted to the CRU at the time indicated by the CRU.
p. Patients will receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. They must return the container (empty or not) at the next schedule visit.
q. On Day 1, patients will be required to fast overnight for at least 8 hours before and 4 hours after YPL-001/placebo morning administration.

STUDY EVENTS FLOW CHART *(CONTINUED)*

Study Procedures[a]	Treatment Period											
Days →	2-14	15 (± 2)		16-28	29 (± 2)		30-42	43 (± 2)		44-54	55	
Hours →		AM	PM		AM	PM		AM	PM		AM	PM
Safety Evaluations												
Physical Examination[b]					X[c]						X[d]	
Weight					X[c]						X[d]	
12-Lead Electrocardiogram					X[c]						X[e]	
Vital Signs[f]		X[c]			X[c]			X[c]			X[e]	
Pulse Oximetry											X[e]	
Hem, Chem, and UA[g]					X[c]						X[d]	
Serum Pregnancy Test (♀ only)		X[c]			X[c]			X[c]			X[d]	
Urine Drug Screen		X[c]			X[c]			X[c]			X[d]	
Urine or Breathalyzer Alcohol Screen		X[c]			X[c]			X[c]			X[d]	
AE Inquiries		X[c]			X[c]			X[c]			X[d]	
AE Monitoring	X											
ConMeds Monitoring	X											
Symptoms Monitoring												
Diary Use[n]	X											
PEF, COPD exacerbation, dyspnea and activity[i]	X											
Study Drug Administration												
Tiotropium Administration[o]	X											
Study Drug Administration at CRU		X			X			X			X	
Study Drug Administration at Home[j]	X		X	X		X	X		X	X		X
Pharmacodynamic												
Pulmonary Function (Spirometry)[k]		X[c]			X[c]			X[c]			X[n]	
Bronchoscopy and BAL Biomarkers[l]											X[c]	
Blood Biomarkers		X[c]			X[c]			X[c]				
BDI/TDI & CAT		X[d]			X[d]			X[d]				
Pharmacokinetic												
Blood for Verproside & Picroside II PK		X[c]			X[c]			X[c]				
Other Procedures												
Return Visits[m]		X			X			X			X	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.
b. Symptom-driven physical examinations will be performed at scheduled times, and may be performed at other times at the Investigator's discretion.
c. To be performed or completed prior to dosing.
d. To be performed or completed prior to bronchoscopy procedures and/or dosing.
e. ECGs, vital sign and pulse oximetry will be measured within 2 hours of bronchoscopy procedures. During the bronchoscopy procedures and BAL sample collection, patients will be continuously monitored for ECGs, vital signs (blood pressure, heart rate, respiration rate, and body temperature), and oxygen saturation.
f. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
g. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.
h. Patients will be provided with an e-diary device to record their self-administered doses, whether the dose was administered with food, and daily respiratory symptoms.
i. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).
j. Prior to release from the CRU on Days 15 (± 2 days), 29 (± 2 days), 43 (± 2 days), and 55 patients will receive a properly labeled kit and/or any unused wallets from previously provided kits (when applicable) with sufficient study drug for their assigned treatment which will be self-administered by patients at home until the next morning visit at the CRU. Patients must return the used and unused wallets at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.
k. Pulmonary function will be performed prior to and 20 to 30 minutes after inhalation of approximately 400 µg albuterol.
l. Bronchoscopy and BAL sample collection will be performed following a 12-hour fast.
m. Patients will be admitted to the CRU at the time indicated by the CRU.
n. To be completed prior to bronchoscopy procedures and dosing.
o. Patients will receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. They must return the container (empty or not) at the next schedule visit.

STUDY EVENTS FLOW CHART *(CONTINUED)*

Study Procedures[a]	Treatment Period																		ET[b]	FU[c]
Days →	56																			
Hours →	Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12		
Safety Evaluations																				
Physical Examination[d]																			X	
Weight																			X	
12-Lead Electrocardiogram																			X	
Vital Signs[e]	X						X		X						X			X	X	
Pulse Oximetry																			X	
Hem, Chem, and UA[f]																			X	
Serum Pregnancy Test (females only)																				
UrineDrug Screen	X																			
Urine or Breathalyzer Alcohol Screen	X																			
AE Inquiries	X																		X	
AE Monitoring	X																			X
Concomitant Medication Monitoring	X																			
Symptoms Monitoring																				
Diary Use[g]	X																		X	
PEF, COPD exacerbation, dyspnea and activity[h]	X																			
Study Drug Administration																				
Tiotropium Administration	X																			
Study Drug Administration at CRU[k]		X																		
Pharmacodynamic																				
Pulmonary Function (Spirometry)																			X	
Blood Biomarkers	X[i]						X													
BDI/TDI & CAT	X[i]																			
Pharmacokinetic																				
Blood for Verproside & Picroside II PK	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Other Procedures																				
Return Visits[j]	X																		X	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.

b. To be performed prior to early termination from the study.

c. The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

d. Symptom-driven physical examinations will be performed at scheduled times, and may be performed at other times at the Investigator's discretion.

e. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.

f. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.

g. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff.

h. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

i. To be performed at predose on Day 56 or upon early termination.

j. Patients will be admitted to the CRU at the time indicated by the CRU.

k. On Day 56, patients will be required to fast overnight for at least 8 hours before and 4 hours after YPL-001/placebo morning administration.

Abbreviations: ♀ = Female, AE = Adverse events, AM = Morning, BAL = bronchoalveolar lavage, BDI/TDI = Baseline Dyspnea Index/Transition Dyspnea Index Test, CAT = COPD Assessment Test, Chem = Serum chemistry, COPD = chronic obstructive pulmonary disease, CRU = Clinical research unit, ConMeds = Concomitant medication, DASI = Duke Activity Status Index, ECG = Electrocardiogram, e-diary = electronic diary, ET = Early termination, FSH = Follicle-stimulating hormone, Hem = Hematology, HIV = Human immunodeficiency virus, IL= interleukin, PEF = Peak expiratory flow, PK = Pharmacokinetics, PM = Evening, Preg = Serum pregnancy, Screen = Screening, UA = Urinalysis.

7. TABLE OF CONTENTS

8. ABBREVIATIONS

Only those uncommon abbreviations specific to this study are listed. Pharmacokinetic (PK) parameter abbreviations and definitions may be found in Section 15.1.6.1.

AE	Adverse event
AHR	Airway hyper-responsiveness
ALD	Approximate lethal dose
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
BALF	Bronchoalveolar lavage fluid
BDI	Baseline Dyspnea Index
BID	Twice daily
BLQ	Below the lower limit of quantification
BMI	Body mass index
bpm	Beat per minute
BUN	Blood urea nitrogen
°C	Degrees Celsius
CAT	COPD Assessment Test
Chem	Chemistry
CFR	Code of Federal Regulations
CK	Creatine kinase
CNS	Central nervous system
CO_2	Carbon dioxide
Coag	Coagulation
COPD	Chronic obstructive pulmonary disease
CRO	Contract Research Organization
CRP	C-reactive protein
CRU	Clinical research unit

CS	Clinically significant abnormality
CSC	Cigarette smoking condensate
CXCL	Chemokine (C-X-C motif) ligand
CV	Coefficient of variation
DASI	Duke Activity Status Index
dL	Deciliter
DRF	Dose range finding
e-diary	Electronic diary
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
ERS	European Respiratory Society
F	Female
°F	Degrees Fahrenheit
FDA	Unites States Foods and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FU	Follow-up
FVC	Forced vital capacity
g	gram
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HBsAg	hepatitis B surface antigen
HCO_3	Bicarbonate
HCV	hepatitis C antibodies
HED	Human equivalent dose
Hem	Hematology
HIV	Human immunodeficiency virus
hr	Hour
IC	Inspiratory capacity
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroid

IgE	Immunoglobulin E
IL	Interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
kg	Kilogram
kg/m^2	Kilogram per meter squared
LABA	long acting beta agonist
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
LOQ	Limit of quantitation
LPS	Lipopolysaccharide
LSM	Least-squares means
µg	Microgram
m^2	Square meter
M	Male
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCO	Myeloperoxidase
MCP	Monocyte chemotactic protein
MCV	Mean Corpuscular Volume
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
MIP	Monocyte inhibitory protein
mL	Milliliter
mmHg	Millimeter of mercury
MMP	Matrix metalloproteinase
msec	Millisecond
MTD	Maximum Tolerated Dose
N	Sample size
NCS	Not clinically significant

ng	Nanogram
No.	Number
NOAEL	No observed adverse effect levels
OTC	Over-the-counter
OVA	Ovalbumin
PD	Pharmacodynamic(s)
PEF	Peak expiratory flow
PK	Pharmacokinetic(s)
QA	Quality Assurance
QC	Quality Control
QT	Interval between the Q and T waves on the electrocardiogram tracing
QTcF	Corrected QT interval with Fridericia's formula
RBC	Red blood cell
RDW	Red cell distribution width
Resp	Respiration
ROS	Reactive oxygen species
SABA	Short-acting β2-agonist
SAD	Single ascending dose
SAE	Serious adverse event
SAMA	Short-acting anticholinergic agent
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SULT	Sulfotranferase
TBIL	Total bilirubin
TDI	Transition Dyspnea Index
TEAE	Treatment-emergent adverse event
Th	T helper
TNF-α	Tumor necrosis factors alpha
UA	Urinalysis
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal

US	United States
WBC	White blood cell
WHO	World Health Organization

9. INTRODUCTION AND BACKGROUND

This study is being conducted as the third in a series of studies for the clinical development of YPL-001. The trial will be conducted in compliance with the protocol, GCP, and applicable regulatory requirements. The patient population will be comprised of moderate to severe (GOLD Stage 2-3) COPD patients.

9.1 YPL-001

YPL-001 drug product is an oral dosage form of an herbal extract from the aerial parts of the plant Speedwell (*Pseudolysimachion rotundum* subsp. *Subintegrum*). *Pseudolysimachion* (*Veronica*) is a perennial herb which has been used as a traditional medicine in Korea and China for the treatment of inflammatory diseases of the respiratory tract such as asthma and COPD.

As a botanical drug product, the drug substance is a mixture of chemical species (iridoids [including verproside] and other related compounds) and biological activity is considered to be from the mixture and not from an individual component. It is unknown if the total activity from individual components is additive or synergistic. Five active constituents, classified as iridoids, have been identified in the herbal extract: verproside, picroside II, catalpolside, isovanilloyl catalpol, and 6-*O*-veratroylcatalpol. Recent experimentation has revealed that the principal active ingredient in *Pseudolysimachion* is verproside, a dihydroxylated catalpol derivative.

YPL-001, containing verproside and other active ingredients, is being developed as a potential oral treatment for long term inflammatory diseases of the respiratory tract such as asthma or bronchitic COPD. Current long term control medications include corticosteroids, cromolyn sodium, immunomodulators, long acting beta agonists, (LABAs), methylxanthines, and leukotriene modifiers. YPL-001 belongs most closely with the leukotriene modifier class of drug.

A brief overview of available information regarding YPL-001 follows below. Details can be found in the YPL-001 Investigator's Brochure of June 3, 2014. [1]

9.1.1 Preclinical Trials

9.1.1.1 Pharmacology

Five *in vivo* primary pharmacology studies have been completed.

In ovalbumin-sensitized mice, an animal model for asthma, YPL-001 reduced elevated immunoglobulin E (IgE), IL-4, IL-5, IL-13, airway hyper-responsiveness, and mucus hyper-secretion.

In the lipopolysaccharide (LPS)- and cigarette smoking condensate (CSC)-induced COPD mice model, verproside and roflumilast treatment inhibited the accumulation of neutrophils in Bronchoalveolar lavage fluid (BALF) as well as the increase of several proinflammatory cytokines and chemokines. Neutrophil infiltration induced by LPS and CSC treatments was associated with a significant increase in BALF levels of the chemoattractants, TNF-α, chemokine (C-X-C motif) ligand (CXCL)-1, and monocyte inhibitory protein (MIP)-2. These data also demonstrated that the effect of YPL-001 and verproside involves down-regulation of the influx of neutrophils and production of TNF-α,

CXCL-1, and MIP-2 molecules which play a major role in tissue remodeling.

YPL-001 significantly suppressed the increase of inflammatory cell counts, particularly neutrophils in BALF and also effectively suppressed elevated levels of TNF-α, CXCL-1 and MIP-2 with the reduction in airway inflammatory responses in CSC- and LPS-induced COPD mice.

YPL-001 also effectively suppressed the increased inflammatory cell count, particularly neutrophils in BALF and also significantly inhibited elevated levels of TNF-α, IL-1β and IL-6 with the reduction in reactive oxygen species (ROS) production and elastase activity in cigarette smoke- and LPS-induced COPD mice.

In the LPS- and cigarette smoke-induced COPD rats model, YPL-001 significantly inhibited the increase of inflammatory cell count, particularly neutrophils in BALF and also effectively suppressed elevated levels of TNF-α, IL-1β, IL-6, MIP-2 and CRP.

YPL-001 effectively inhibited development of both T helper (Th)2 and Th1/Th17 type asthma in these murine models. These effects resulted from inhibition of cytokine and chemokine production by infiltrated inflammatory cells and antigen specific T cells in lymph nodes. YPL-001 did not inhibit development of COPD which was induced by *E.coli* extracellular vesicles.

9.1.1.2 Pharmacokinetics

After oral administration of YPL-001 at 12.5, 25, and 50 mg/kg doses (5.225, 10.45, and 20.9 mg/kg as verproside) in rats, verproside was rapidly absorbed; verproside was detected at the first blood sampling time (5 min) and absorbed rapidly, with the t_{max} achieved at 0.46-0.61 hour for all three doses. The post-absorption phase of the mean plasma verproside concentration-time profiles showed a poly-exponential decay.

The area under the plasma concentration-time curve (AUC) and the maximum plasma concentration (C_{max}) of verproside were linearly increased as the oral dose of YPL-001 increased. Alternately, the dose normalized (based on 12.5 mg/kg) AUCs and C_{max} of verproside were comparable among different doses studied. The elimination half-lives ($t_{1/2}$), 2.14 – 3.91 hours, and other PK parameters of verproside for all three doses were also comparable. These findings indicate that the PK parameters of verproside were independent of doses.

The fraction of dose of verproside excreted unchanged in urine at 24 hours was less than 0.10%. Verproside was not detected in the 24 hours feces sample for all three doses studied. These results indicate that verproside is almost completely eliminated by the first pass metabolism due to O-methylation, glucuronidation, sulfation, and intestinal microflora-mediated metabolism. Verproside is metabolized to verproside glucuronides (M1 and M2), verproside sulfates (M3 and M4), O-methylverproside such as picroside II (M5) and isovanilloylcatalpol (M6), 3,4-dihydroxybenzoic acid (M11), 3-methyoxy-4-hydroxybenzoic acid (M15) and 3-hydroxy-4-methoxybenzoic acid (M16), which are further metabolized to their glucuronides and sulfates including M5 glucuronide (M7), M5 sulfate (M9), M6 glucuronide (M8), M6 sulfate (M10), M11 glucuronide (M12), M11 sulfates (M13 and M14), M15 glucuronides (M17 and M18), M15 sulfate (M20), M16 glucuronide (M19), and M16 sulfate (M21). The O-methylation of verproside to picroside II (M5) and isovanilloylcatalpol (M6) followed by glucuronidation and sulfation

were identified as the major metabolic pathway in bile and urine samples.

Picroside II, a major metabolite of verproside, was detected in plasma samples but most plasma concentrations in 12.5 and 25 mg/kg YPL-001 treated groups were below the lower limit of quantification (LLOQ, 2.5 ng/mL) compared to 50 mg/kg YPL-001 treated group. The picroside II-to-verproside AUC ratios in the 50 mg/kg YPL-001 treated group were 13.9-65.1%, suggesting that picroside II may be one of the major YPL-001 metabolites. Plasma concentrations of isovanilloylcatalpol, a metabolite of verproside and isomer of picroside II, were below LLOQ (2.5 ng/mL) after oral administration of all three YPL-001doses tested.

Verproside, catalposide, and picroside II were not considerably bound to human plasma proteins; the binding values were 36.3-55.0% at verproside concentrations of 0.1, 1.0, and 10.0 μg/mL, 31.2-49.5% at catalposide concentrations of 0.5, 1, and 10 μg/mL, and 34.0-41.2% at picroside II concentrations of 0.5, 1, and 10 μg/mL.

9.1.1.3 Toxicology

Two single dose toxicity studies with YPL-001 have been completed in rat and dog. In the rat study, polyuria was observed in the 5,000 mg/kg dosing group of each sex between 2-4 hours after YPL-001 administration. Discolored stool was observed dose-dependently in the all dosing groups of each sex at 1-3 days post administration. Soft stool, mucous stool and soiled perineal region were observed at 1 day after administration in the 2,500 and 5,000 mg/kg dosing group of each gender. There were no notable changes of body weight in any study group. There were no notable gross necropsy findings in any of the study groups. Based on the results above, when YLP-001 is administered orally to Sprague-Dawley rats, the approximate lethal dose (ALD) is higher than 5,000 mg/kg. In the dog study, There were no changes with respect to the toxicity of the test article in the clinical signs, body weight change and necropsy findings after a single dose. Vomiting and discoloration of stool was noted. The Maximum Tolerated Dose (MTD) was determined to be 2,000 mg/kg for males and 1,000 mg/kg for females.

Two dose range finding (DRF) studies with YPL-001 have been completed in rat and dog, followed by two pivotal, 4-week, GLP repeated-dose toxicology studies in the same species. In the rat DRF study, YPL-001 induced anemia and hemolysis at 667 mg/kg/d and at higher doses. In addition, enlargement of cecum was observed at 667 mg/kg/d and at higher doses. The NOEL for this study was 74 mg/kg/d in both genders. In the dog DRF study, decreases in red blood cell (RBC) values were present in males at the high dose level (1000 mg/kg/d). In females the TBIL values were elevated at the 1000 mg/kg/d dose levels. Females had enlarged spleens at 125, 250 and 1000 mg/kg dose levels without dose relationship (trend was toward significance). The MTD for this study was 1000 mg/kg/d.

Primary results from the pivotal, 4-week rat study included:

There were no abnormal clinical signs observed in any group during dosing or the recovery periods and no mortality was reported.

Hematology: Compared to controls, there were decreases in values of RBC, hematocrit, and hemoglobin at all dose levels of both genders in a dose-dependent fashion. The

values of hemoglobin distribution width, red cell distribution width (RDW) and reticulocyte at all dose levels of both genders were higher or significantly higher than those of vehicle control.

Clinical Biochemistry: There were significant increases in the values of TBIL at all dose levels of both genders when compared with that of vehicle control. After the recovery period, there were no noticeable changes related to the test article.

Organ Weights: Slight increase in absolute & relative weights of the spleen at 540 mg/kg/d in males and notable increase in absolute & relative weights of the spleen at all dose levels of females were observed. Weights of left and right kidneys in female at 540 mg/kg/d were significantly higher than that of vehicle control. After the recovery period, the absolute weights of the spleen and both kidneys in both genders at 540 mg/kg/d were significantly higher than that of vehicle control.

Necropsy Findings: At necropsy, 6 cases of dark reddish discoloration of spleen were observed at 540 mg/kg/d in both genders, and 1 case of enlargement of cecum was observed at 540 mg/kg/d in female. After the recovery period, one case of dark reddish discoloration of spleen was observed at 540 mg/kg/d in the female. The histopathology examination revealed increased hematopoiesis of spleen at the high dose in both genders.

No Observed Adverse Effect Levels (NOAEL): The NOAEL for this study was 180 mg/kg/d for both genders.

Primary results from the pivotal, 4-week dog study included:

YPL-001 colored stool with/without soft stool or diarrhea was persistently observed in both sexes at 1000 mg/kg/d during the dosing period. It was not observed during the recovery period. No mortality was reported.

Hematology: There were no treatment-related changes.

Clinical Biochemistry: The TBIL increased in a dose-dependent manner in both genders at 111, 333 and 1000 mg/kg/d, and it was not recovered completely after the 2-week recovery period.

Organ Weights: There were no treatment-related changes.

Necropsy Findings: Slight red discoloration of mucous membranes in the stomach or duodenum was observed in female treatment groups but not observed after the 2-week recovery period.

NOAEL: The NOAEL for this study was 1000 mg/kg/d for both genders.

9.1.2 Clinical Experience

To date, 2 studies have been conducted in healthy subjects, a randomized, double-blind, placebo-controlled, sequential single ascending dose (SAD) clinical study (AA98496) and a randomized, double-blind, placebo-controlled, sequential multiple ascending dose (MAD) clinical study (AA98495).

9.1.2.1 SAD study

All 5 cohorts of 8 subjects (6 active and 2 placebo), with one cohort crossing over to assess food effect, were dosed and completed. All dosed levels (i.e., 40, 80, 160, 240, and 320 mg) were well tolerated with no SAEs reported during the conduct of the study. All 9 AEs reported in 7 subjects were mild in severity and the most frequent AE reported, regardless of causality, was headache. Of the 7 AEs experienced by subjects receiving the active drug, the Investigator considered 2 of these to be possibly related (nausea, and vomiting), 2 unlikely related, and 3 unrelated. Of the 2 AEs experienced by subjects receiving placebo, the Investigator considered 1 of these to be possibly related (headache), and 1 unrelated.

Plasma samples were analyzed using a validated bioanalytical method. Verproside concentrations were lower than concentrations observed from the animal PK data. The limit of quantitation (LOQ) was approximately 20% of the C_{max} after a single 160 mg dose and approximately 10% of the C_{max} after a single 320 mg dose. Therefore, the half-life could not be well characterized since only a few PK concentrations were available for the estimation.

Verproside appeared to be rapidly absorbed following oral administration and independent on dose, as suggested by median t_{max} values of approximately 0.5 to 0.67 hours under fasting conditions. Verproside appeared to be cleared rapidly from plasma, with mean $t_{1/2}$ values under 1 hour; plasma verproside concentrations were below the lower limit of quantification (BLQ) for all subjects by 6 hours postdose. Table 1 below summaries the PK parameters of verproside following single-dose administrations of YPL-001 at each dose level:

Table 1 Summary of PK Parameters

Pharmacokinetic Parameters	Dose Level Mean ± SD					
	40 mg (N = 1)[a]	80 mg (N = 6)[b]	160 mg (fasting) (N = 6)[c]	160 mg (fed) (N = 6)[d]	240 mg (N = 6)[e]	320 mg (N = 6)[f]
C_{max} (ng/mL)	1.19	1.14 ± 0.328	2.90 ± 1.76	1.08 ± 0.287	4.78 ± 5.66	4.49 ± 1.44
t_{max} (hr)[g]	0.4969	0.6682 (0.5158, 1.0025)	0.5074 (0.3331, 0.6700)	1.2538 (0.9994, 2.0008)	0.5867 (0.3486, 1.5022)	0.5057 (0.3419, 1.5014)
AUC_{0-t} (ng·hr/mL)	0.7422	0.7520 ± 0.3818	2.5616 ± 1.7947	1.2822 ± 0.3599	5.4567 ± 5.0158	5.3612 ± 0.8664
AUC_{0-inf} (ng·hr/mL)	·	·	3.8048 ± 1.8238	·	8.2199 ± 5.3327	6.2162 ± 0.7776
$t_{1/2}$ (hr)	·	·	0.677 ± 0.263	·	0.919 ± 0.176	0.713 ± 0.100

[a] Individual values are presented for the 40 mg dose level
[b] N=5 for AUC_{0-t}
[c] N=3 for AUC_{0-inf} and $t_{1/2}$,
[d] N=4 for AUC_{0-t}
[e] N=3 for AUC_{0-inf}, and $t_{1/2}$,
[f] N=5 for AUC_{0-inf}, and $t_{1/2}$,
[g] t_{max} is presented as Median (Minimum, Maximum)
· = Value missing or not reportable

9.1.2.2 MAD Study

In total, 2 cohorts of 8 subjects and 1 cohort of 10 subjects received multiple YPL-001 doses of 80, 160, or 240 mg BID. Each cohort was constituted of 2 subjects receiving placebo and the remaining subjects receiving the active drug. All dose levels were well tolerated. There were no deaths or SAEs in this study. One (1) subject was discontinued due to the AE of chest pain. Overall, TEAEs were experienced by 38% of subjects in this study. The Investigator considered 1 AE (chest pain) to be possibly related to study drug and the remaining AEs unlikely or unrelated. There were no treatment-related trends in physical examination, laboratory, vital sign, or ECG assessments in this study.

Verproside appeared to be rapidly absorbed following multiple-dose oral administration, as suggested by median t_{max} values of approximately 0.5 - 0.9 hours and independent of dose. Following a multiple oral doses of YPL-001, verproside appeared to be cleared rapidly from plasma, with mean $t_{½}$ values under 1.6 hours, and plasma verproside concentrations were BLQ for most subjects by 12 hours postdose.

Picroside II appeared to be also rapidly absorbed following single- and multiple-dose oral administration, as suggested by median t_{max} values of approximately 0.6 to 0.9 hours and independent of dose. Following a single oral dose of YPL-001, picroside II appeared to be cleared rapidly from plasma, with mean $t_{½}$ values under 1 hour, CL/F values of 14000 – 18500 L/hour, and plasma picroside II concentrations BLQ by 10 - 12 hours postdose. Following multiple oral doses, mean $t_{½}$ values were under 2.5 hours, and plasma picroside II concentrations were BLQ for most subjects by 12 hours postdose.

For all 3 dose levels, minimal to modest accumulation of verproside and picroside II was observed following BID administration of YPL-001 for 2 weeks. The mean peak and total exposure of verproside and picroside II in plasma appeared to increase in a dose-dependent manner between 80 and 160 mg of YPL-001, but no increase in plasma bioavailability was observed between 160 and 240 mg dose levels. Table 2 and Table 3 below summaries the PK parameters of verproside and picroside II, respectively, following multiple-dose administrations of YPL-001 at each dose level:

Table 2 Summary of Verproside PK Parameters

Pharmacokinetic Parameters	YPL-001 Dose Level Mean ± SD		
	80 mg	**160 mg**	**240 mg**
AUC_t (pg*hr/mL)	4709 ± 4080 (N=6)	10860 ± 11424 (N=6)	9658 ± 9246 (N=5)
AUC_{0-t} (pg*hr/mL)	4596 ± 4127 (N=6)	10770 ± 11489 (N=6)	9566 ± 9298 (N=5)
C_{max_ss} (pg/mL)	2414 ± 1281 (N=6)	6737 ± 7342 (N=6)	5458 ± 4387 (N=5)
t_{max_ss} (hr)*	0.756 (0.252, 2.00) (N=6)	0.759 (0.329, 1.50) (N=6)	0.528 (0.272, 0.751) (N=5)
$t_{½}$ (hr)	1.47 ± 0.425 (N=6)	1.30 ± 0.406 (N=6)	1.57 ± 0.236 (N=5)

* = t_{max_ss} is presented as median (minimum, maximum)

Table 3 Summary of Picroside II PK Parameters

Pharmacokinetic Parameters	YPL-001 Dose Level Mean ± SD		
	80 mg	**160 mg**	**240 mg**
AUC_{τ} (pg*hr/mL)	2556 ± 599 (N=2)†	4287 ± 4369 (N=4)†	1985 ± 1024 (N=5)
AUC_{0t} (pg*hr/mL)	1124 ± 1044 (N=6)	3024 ± 3877 (N=6)	1804 ± 949 (N=5)
C_{max_ss} (pg/mL)	419 ± 240 (N=6)	1116 ± 1391 (N=6)	751 ± 490 (N=5)
t_{max_ss} (hr)*	0.756 (0.252, 2.00) (N=6)	0.759 (0.329, 1.50) (N=6)	0.748 (0.524, 0.751) (N=5)
$t_{½}$ (hr)	2.23 ± 0.254 (N=6)	1.84 ± 0.395 (N=6)	2.08 ± 0.793 (N=5)

* = t_{max_ss} is presented as median (minimum, maximum)
. = Value missing or not reportable

10. RATIONALE

10.1 Purpose of the Study

This study will be the initial exploration of multiple-dose administration of YPL-001 in COPD patients. The assessments of the safety, tolerability, COPD symptoms, PD, and PK of verproside and picroside II following administration of multiple doses of YPL-001 will guide decisions to further develop the drug and support the compound as a useful clinical candidate in the treatment of inflammatory diseases of the respiratory tract such as COPD and the data generated will support larger studies in patients with inflammatory diseases of the respiratory tract such COPD to demonstrate safety and evidence of efficacy and clinical benefit.

10.2 Dose Selection

This will be the first COPD patient study of YPL-001.

YPL-001 appeared well tolerated in a panel of standard animal toxicology studies. In the initial studies in humans, the initial dose of YPL-001 was justified conservatively according to the United States (US) Food and Drug Administration (FDA) guidance document “Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers”.[2]

Accordingly, the single and multiple dose escalation study (AA98496) initiated single doses at the 40 mg and 80 mg level, respectively. Dose escalations up to 320 mg and 240 mg in the SAD and MAD studies, respectively, were reached. All cohorts have been completed and all doses administered were well tolerated in human subjects and no clear pattern of toxicity is apparent.

Based on the review of safety, tolerability, and PK data from Cohorts 1 to 5 of the SAD study (AA98496) and Cohorts 1 to 3 of the MAD study, and the in vivo efficacy data in rat and mouse models, it is predicted that the therapeutic range should be between 1.2 mg/kg and 4.8 mg/kg which is equivalent to 84 mg to 336 mg daily in a 70 kg patient. Therefore, a low YPL-001 dose of 80 mg BID and the high YPL-001 dose of 160 mg BID were selected for this proof-of-concept study.

The total strength (23.75 mg) of identified compounds in YPL-001 as a whole in the 40 mg starting dose administered in the first-time-in-human dose escalation study (AA98496) corresponded to approximately 35% of the dosages that have been used in the traditional medicine setting in China (68.65 mg). In this present proof-of-concept study the total strength (47.50 mg) of identified compounds in the initial starting dose of 80 mg is still lower than the dosages that have been used in the traditional medicine setting in China, as shown in Table 4, corresponding to 70% of the traditional Chinese medicine.

Table 4: Traditional Chinese Medicine Use Versus Proposed Clinical Starting Dose

Identified Compounds in YPL-001	1.40 g (Single Dose) Traditional Chinese Medicine[a] (mg)	2.80 g/day (Divided Dose) Traditional Chinese Medicine[a] (mg)	80 mg (Single Dose) for MAD Study[b] (mg)
Verproside	47.94	95.88	30.64
Veratric acid	2.10	4.20	1.08
Catalpolside	3.77	7.54	4.08
Picroside II	3.43	6.86	3.36
Isovanilloyl catalpol	3.53	7.06	4.72
6-*O*-veratroyl catalpol	7.88	15.76	3.62
Total	68.65	137.30	47.50

[a] Traditional medicine dosage from Chinese Medical Great Dictionary; Zhong Yao Da Ci Dian.
[b] Proposed dosage of YPL-001 in MAD study

11. RISK/BENEFIT

YPL-001 is being developed as a potential oral treatment for long term control of persistent asthma and COPD. YPL-001 belongs most closely with the leukotriene modifier class of drug and has the potential to inhibit the accumulation of neutrophils the increase of several proinflammatory cytokines and chemokines which play a major role in tissue remodeling. The development of a product to improve the treatment of asthma and COPD will be of benefit to the wider community/patients with respiratory disease.

The safety monitoring practices employed by this protocol (i.e., physical examination, vital signs, pulse oximetry, 12-lead ECG, hematology, serum chemistry, urinalysis, AE monitoring, and AE questioning) are deemed adequate to protect the patients' safety and should detect all expected TEAEs. The procedures employed in this study to assess efficacy are primarily non-invasive and present no undue risk to the patient.

The approximate volume of blood planned for collection from each patient over the course of the study (see Section 14.5), presents no undue risk to the patients nor does the possibility of collection (for wasting to ensure clean sample) of additional blood in the event an angiocatheter is utilized and the possibility of additional blood collection for recheck of safety labs if deemed necessary by the Investigator.

12. STUDY OBJECTIVES AND ENDPOINTS

12.1 Study Objectives

The primary objective of the study is to assess the safety and tolerability of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients.

The secondary objective of the study is to assess the number and magnitude of daily respiratory symptoms of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients.

The exploratory objectives of the study are to evaluate the following in moderate to severe COPD patients:

1. To assess BAL epithelial brushings for YPL-001 component levels.
2. To compare BAL samples for total cell count (cells/mL) macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; neutrophil, macrophage, lymphocyte, and eosinophil counts as absolute inflammatory cell numbers in YPL-001 groups versus placebo group.
3. To compare BAL samples for TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9 in YPL-001 groups versus placebo group.
4. To compare blood inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) and concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9 in YPL-001 groups versus placebo group.
5. To compare spirometric functions (FEV_1, FVC, FEV_1/FVC, and IC) in YPL-001 groups versus placebo group.
6. To compare patient reported outcomes (BDI/TDI, CAT) in YPL-001 groups versus placebo group.
7. To assess verproside and picroside II concentration in plasma and BAL and verproside and picroside II PK in plasma following multiple oral doses administration of two YPL-001 dose levels.

12.2 Study Endpoints

The primary endpoint is the number and severity of TEAEs following multiple oral doses of YPL-001 or placebo.

The secondary endpoint is the number of symptom free days and overall symptom burden following multiple oral doses of YPL-001 or placebo, assessed by measuring:

- daily PEF;
- major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation;

- dyspnea (using the Modified Borg Dyspnea Scale); and
- activity (using the DASI).

The exploratory endpoints are:

1. YPL-001 component levels in epithelial brushings;
2. BAL biomarkers following multiple oral doses of YPL-001 or placebo, measuring:
   - total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells
   - total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers
   - concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9.
3. Blood biomarkers following multiple oral doses of YPL-001 or placebo, measuring:
   - inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils, and lymphocytes)
   - concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9.
4. Pulmonary function results (spirometry) following multiple oral doses of YPL-001 or placebo.
5. Quality of life scores using the BDI/TDI, CAT questionnaires.
6. Concentrations and PK of verproside and picroside II in plasma following multiple oral doses of YPL-001.
7. Concentrations of verproside and picroside II in BAL following multiple oral doses of YPL-001.

13. INVESTIGATIONAL PLAN

13.1 Overall Study Design and Plan

This is a Phase 2a, proof-of-concept, multicenter, randomized, double-blind, double-dummy, 3-treatment, parallel study, with low and high YPL-001 doses (80 mg and 160 mg BID) and a placebo control, in moderate to severe COPD patients.

At least 60 patients will be enrolled and randomized into 3 treatment groups (20 patients per group). Patients will participate only once. An approximately equal number of current and ex-smokers will be enrolled in the study.

Safety and tolerability will be assessed throughout the study. Assessment of respiratory symptoms and symptom burden in YPL-001 and placebo treatments will be performed daily through patient self-report of PEF, major and minor symptoms of COPD exacerbation, dyspnea, and activity in their e-diary. Spirometry measurement, BAL, and blood samples will be collected for the PD assessment of YPL-001 and placebo treatments. Serial blood samples will also be collected for PK assessment of verproside (the principal active ingredient of YPL-001) and picroside II. Other components of YPL-001 and its metabolites may also be analyzed in plasma.

Following screening, eligible patients will discontinue non permitted respiratory drugs if already receiving them and enter a 14 ± 2 days Run-in Period during which patients will be given albuterol taken on an as required basis and daily tiotropium 18 µg (one capsule inhaled daily in the morning) to be administered at home. On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their daily symptoms throughout the Run-in Period.

Patients will return to the CRU on the morning of Day -1 of the Treatment Period to confirm their eligibility and assess their health conditions. If they still meet all of the inclusion criteria and none of the exclusion criteria, they will undergo Day -1 scheduled study procedures. Patients will return to the CRU the next day (Day 1) to be randomized and receive one of the 3 treatments and undergo all scheduled study procedures. Patients will return on the morning of Days 15 (± 2 days), 29 (± 2 days), 43 (± 2 days), 55, and 56 of the Treatment Period for study drug administration and procedures. Prior to each release from the CRU, patients will receive a properly labeled kit and/or any unused wallets from previously provided kits (when applicable) with sufficient doses which will be self-administered by patients at home until the next morning visit at the CRU. Patients will continue recording their daily symptoms via the e-diary throughout the Treatment Period. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff.

The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

Patients will be instructed to call the Investigator if breathing worsens or if they need to take more than 8 puffs per day of albuterol for more than 2 consecutive days. If the Investigator determines that the patient is too unstable to continue in the study, he/she

will be discontinued. Rescue medication will be used for any patient with an exacerbation of COPD and will be administered in accordance with the study center standard of care.

Discontinued patients may be replaced at the discretion of the Sponsor.

13.2 Study Conduct

Please see the Study Events Flow Chart for a summary of the schedule of study participation and procedures in Section 6.

13.2.1 Screening

Screening will begin within 14 days of Day 1 (inclusive) of the Run-in Period. Informed consent will be obtained at screening (see Section 16.1.3) and prior to any study procedures being performed. Patients will have to meet all eligibility criteria before being enrolled in the study (see Section 13.3). Patients will be informed of the study restrictions (see Section 13.3.5).

The following will be recorded at screening: medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI, and history of tobacco use (including number of pack-year and cigarette smoked per day).

Screening procedures are listed in Section 6.

13.2.2 Patient Confinement

Patients will be admitted to the CRU on the morning of each scheduled visit at a time designated by the CRU as delineated in the Study Events Flow Chart (Section 6). Patients will remain in the clinic through completion of all scheduled study procedures.

13.2.3 Run-In Period (Days 1 to 14 [± 2 days])

Eligible patients will be admitted to the CRU on the morning of Day 1 of the Run-in Period at a time designated by the CRU. Patients will discontinue all restricted concomitant medications as indicated in Section 13.3.5.1 and undergo the Run-in procedures as listed in Section 6.

During the Run-in Period, patients will self-administer tiotropium (Spiriva® HandiHaler®) daily for 14 ± 2 days before Day 1 of the Treatment Period. Patients will be instructed to inhale 1 capsule of tiotropium (Spiriva® HandiHaler®) every morning. Patients will also receive albuterol for as needed use. Patient will keep this rescue albuterol throughout the Run-in Period.

Prior to release from the CRU, patients will receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. They must return the container (empty or not) at the next schedule visit, which is scheduled after 14 ± 2 days.

Each patient will also be issued and trained on the use of the e-diary to record their self-administered doses and their daily respiratory symptoms. Prior to each morning dose, patients will record at home their daily PEF, major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat,

nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

13.2.4 Treatment Period (Days 1 to 56)

Patients who completed the Run-in Period and still meet all the inclusion criteria and none of the exclusion criteria will be randomized to receive one of the assigned treatments (80 mg or 160 mg YPL-001 BID, or placebo BID) on Day 1 through Day 56 (see Section 13.4.1 and Section 13.4.2).

Safety and tolerability will be monitored throughout the Treatment Period as listed in Section 6. Patients will continue to record their self-administered doses and their daily respiratory symptoms on their e-diary. Prior to each morning dose, patients will record at home their daily PEF, major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

BAL samples for YPL-001 concentrations and PD assessments will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

Spirometry and quality of life questionnaires for PD assessments will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

Blood samples for PD and PK assessment will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

13.2.4.1 Meal Schedule

Patients will be required to fast overnight for at least 12 hours before bronchoscopy and BAL collection on Days -1 and 55. On Days 1 and 56, patients will be required to fast overnight for at least 8 hours before and for at least 4 hours after the morning dose. On all other days, patients will be asked to fast for at least 2 hours before and 2 hours after each morning dose. Patients will also be asked to fast for at least 2 hours before and after each evening dose.

Patients will also be required to fast for at least 8 hours before the scheduled serum chemistry tests at the time points delineated in the Study Events Flow Chart (Section 6).

During in-clinic dosing, water (except that administered with dosing) will not be permitted from 1 hour before until 1 hour after each dosing. Water will be allowed as desired at all other times. On all other days, patients will be informed to follow the same restrictions.

On Days 1 and 56, patients will fast from all food and drink except water between meals and snacks. Foods and beverages containing alcohol, xanthines, caffeine, vegetables from the mustard green family, mustard, tea (especially speedwell tea), or grapefruit/Seville oranges will not be served in the CRU. Across all CRUs, menus should be similar in content. The same menu and meal (except for snacks) schedule will be administered uniformly for all patients confined within the same CRU, across all treatment groups. Meals are not required to be completed by patients.

13.2.4.2 Early Termination

Early termination evaluations will be performed on patients prior to early termination. Patients who want to terminate from the study and are not currently on-site will be contacted and asked to return to the CRU to perform the early termination procedures.

The early termination procedures are listed in Section 6.

13.2.5 Follow-up Call (14 ± 2 days)

The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

13.2.6 Scheduled End of Study

The end of the study is scheduled after completion of the evaluations in the 3 treatment groups or after dose-limiting clinical safety endpoints have been reached to preclude continuation of the study. The clinical conduct of the study is intended to last approximately 12 to 24 months.

This time period may change in the event that the study is terminated early, additional time is required to review safety, or a decision is made to complete an unscheduled analysis for a group.

13.3 Selection of Study Population

13.3.1 Number of Patients

The study is planned to enroll at least 60 patients. An approximately equal number of current and ex-smokers will be enrolled. Patients will be divided in 3 treatment groups with 20 patients to receive one of the 3 treatments (i.e., low and high YPL-001 doses [80 mg and 160 mg BID] and a placebo control) as per the randomization schedule. Each treatment group will consist of an approximately equal number of current and ex-smokers.

13.3.2 Inclusion Criteria

Patient candidates must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Adult males and/or females, 30 to 85 years of age (inclusive).
2. History of COPD for at least 12 months prior to screening.
3. Diagnosed with COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines with symptoms compatible with COPD for at least 12 months prior to screening.

4. Classified as moderate to severe COPD based on the current severity classification GOLD Stage 2-3 disease in terms of post-bronchodilator spirometry at screening:
   - Post-bronchodilator FEV_1/FVC ratio of <70%
   - Post-bronchodilator FEV_1 ≥30 % and <80 % of predicted normal values
5. Weigh at least 52 kg for males and 45 kg for females and within the normal range according to accepted normal values of the Body Mass Index (BMI) chart 18.5-40.0 kg/m^2 inclusive.
6. In the judgment of the Investigator, the patient is medically stable with no change in symptoms, medication, or with clinical laboratory results that in the Investigator's opinion are compatible with the diagnosis of either COPD or a complication thereof and are judged acceptable for inclusion with predominantly bronchitic symptoms at screening.
7. Must be on a stable medical regimen for COPD ≥ 30 days prior to screening.
8. In the Investigator's opinion patients should be able to withhold tiotropium 24 hours prior to Day 1 of the Run-in Period, if already receiving it and prior to each scheduled CRU visit.
9. Must have oxygen saturation on room air > 93%.
10. Hemoglobin must be equal to or above the lower limit of normal at screening and check-in.
11. Current or ex-smoker with a history of >10 pack years. Ten pack years are defined as: 20 cigarettes a day for 10 years; 10 cigarettes a day for 20 years; or 40 cigarettes a day for 5 years (i.e., [number of cigarettes smoked per day × number of years smoked]/20). Patients, who undergo smoking cessation therapy, must be completed 3 months prior to screening visit and smoking status should not change between the patient's screening visit and patient's last study visit.
12. For a female of childbearing potential: either be sexually inactive (abstinent) for 14 days prior to the first dose and throughout the study or be using one of the following acceptable birth control methods:
    a. non-hormone releasing intrauterine device in place for at least 3 months prior to the first dose.
    b. surgical sterilization of the partner (vasectomy for 4 months minimum).
    c. physical barrier method (e.g., condom, diaphragm) with spermicide for at least 14 days prior to the first dose and throughout the study.
13. A female patient who claims to be sexually inactive, but becomes sexually active during the course of the study must agree to use a physical barrier method (e.g., condom, diaphragm) with spermicide from the time of the start of sexual activity through to the completion of the study.

14. For a female of non-childbearing potential: must have undergone one of the following sterilization procedures at least 6 months prior to the first dose:

    a. hysteroscopic sterilization;

    b. bilateral tubal ligation or bilateral salpingectomy;

    c. hysterectomy;

    d. bilateral oophorectomy;

    or be postmenopausal with amenorrhea for at least 1 year prior to the first dose and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status as per Investigator judgment.

15. Non-vasectomized males must agree to be sexually abstinent or to use a condom with spermicide when engaging in sexual activity from the first dose through completion of the last scheduled study procedures on Day 56 or upon early termination. Patients will be advised to use a condom with spermicide for 90 days following the last administration of the study drug, and to not donate sperm during this same period of time. In the event that the sexual partner is surgically sterile, use of a condom with spermicide is not necessary. No restrictions are required for vasectomized males provided their vasectomy has been performed 120 days or more prior to study start. Males who have been vasectomized less than 120 days prior to study start must follow the same restrictions as non-vasectomized males.

16. Understands study procedures and provides written informed consent for the trial.

17. Be able to comply with the protocol, such as all the study restrictions, and the assessments therein.

13.3.3 Exclusion Criteria

Patients will be excluded from the study if there is evidence of any of the following criteria at screening or check-in, as appropriate.

1. History of life-threatening COPD including respiratory arrest, intensive care unit admission and/or requiring intubation.
2. History of more than 2 hospitalizations for COPD within 12 months prior to screening.
3. Presentation of an acute exacerbation of COPD that will be associated with increase sputum volume or change in sputum color within 4 weeks before Day 1 of the Run-in Period.
4. Evidence of cor pulmonale, or clinically significant pulmonary hypertension.
5. Continuous use of more than 2L/day of oxygen.
6. History or presence of other respiratory disorders, such as asthma, α-1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis or other chronic pulmonary diseases.
7. A chest X-ray at screening (or within 3 months prior to screening) showing abnormalities, which in the opinion of the Investigator are clinically significant and unrelated to COPD.

8. A history of chronic disease including, but not limited to, unstable or uncontrolled hypertension (or been diagnosed with hypertension in the 6 months before screening), severe sleep apnea (assessed using the Berlin Questionnaire [refer to Section 14.1.8]), cardiovascular, endocrine, neurological, hepatic, gastrointestinal, renal, hematological, urological, immunological or ophthalmic diseases that the Investigator believes are clinically significant e.g., unstable and could impact patient safety by participation in the study.
9. History or presence of:
    - significant cardiac arrhythmia;
    - prostatic hyperplasia;
    - bladder-neck obstruction;
    - urinary retention;
    - narrow-angle glaucoma.
10. Evidence of clinically relevant abnormal baseline hematology, serum chemistry, or urinalysis. Patients with an AST > 2 x ULN, ALT > 2 x ULN, bilirubin > 2 x ULN or creatinine > 2 x ULN (confirmation of results may be done once).
11. Evidence of hepatic impairment with a Child-Pugh class A score or higher.
12. Lung resection or lung reduction surgery within 12 months.
13. Positive alcohol (using urine dipstick or breathalyzer) and/or urine drug testing at screening or at each CRU visit, unless the positive drug screen is due to prescription drug use and is approved by the PI and the medical monitor.
14. Positive testing for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C antibodies (HCV).
15. History or presence of alcoholism or drug abuse within the 2 years prior to Day 1 of the Treatment Period.
16. Hypersensitivity or idiosyncratic reaction to compounds related to YPL-001, including Speedwell tea and herbal remedies.
17. Requires one (or more) routine therapies for COPD during the indicated restricted time period as listed in Section 13.3.5.1.1.
18. Use of any drugs or substances known to be significant inhibitors (strong or moderate) of UDP-glucuronosyltransferase (UGT) (such as 17-beta-estradiol glucuronide, flavonoids [citrus fruit], silybin [herb supplement milk thistle]) and/or sulfotransferases (SULT) (refer to Appendix 1), within 12 hours prior to Day 1 of the Run-in Period. Additional sources may be consulted by the PI or medical monitor to confirm lack of PK/PD interaction with study drug.
19. Blood donation or significant blood loss within 56 days prior to Day 1 of the Treatment Period.
20. Plasma donation within 7 days prior to Day 1 of the Treatment Period.

21. Participation in another clinical trial within 30 days prior to Day 1 of the Run-in Period.
22. Females who are pregnant or lactating.
23. Surgery within the past 3 months prior to Day 1 of the Treatment Period determined by the Investigator to be clinically relevant.
24. Active or history of any disease or condition that would, in the opinion of the Investigator and/or medical monitor, place the patient at an unacceptable risk to participate in this study.

13.3.4 Removal of Patients from the Study

Patient participation in this trial may be discontinued for any of the following reasons:

1. Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol.
2. Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient.
3. The patient interrupts trial study drug administration for more than 7 consecutive days of dosing or missed a total of 17 doses (15%) throughout the Treatment Period.
4. Patient's decision to withdraw.
5. Requirement for prohibited concomitant medication.
6. Patient failure to comply with protocol requirements or study related procedures.
7. Termination of the study by the Investigator, Sponsor, FDA, Celerion, or other regulatory authorities.

The clinical report will include reason(s) for patient withdrawals as well as details relevant to the patient withdrawal. If a patient is withdrawn from the trial prior to study completion, the patient will undergo all procedures scheduled for study completion (early termination evaluations) as the situation allows (see Section 13.2.4.2). Any patient withdrawn due to an AE (whether serious or non-serious) or clinically significant abnormal laboratory test values will be evaluated by the Investigator and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

Patients withdrawn may be replaced at the Sponsor’s discretion.

13.3.5 Study Restrictions

13.3.5.1 Concomitant Therapy

All medications taken during the 30 days prior to the first dose will be recorded and reviewed by the Investigator.

Any medication taken by patients during the course of the study will be recorded. Concomitant medication will be coded using the most current WHO drug dictionary available at Celerion (e.g., 01-MAR-2014 or later). If drug therapy other than that specified by the protocol is taken, a joint decision will be made by the Investigator and Sponsor to continue or discontinue the patient.

13.3.5.1.1 Prohibited Therapy

The following medications are not permitted within the time delineated below and during the study (from Day 1 of the Run-in Period to the completion of the last scheduled study procedures on Day 56 or upon early termination). Intake of these medications during the Run-in Period constitutes a non-eligibility criterion and the patients will not be randomized into the study. If any of these medications are taken during the Treatment Period, the need for this patient to be withdrawn from the study will be carefully evaluated by the Investigator and the Sponsor on the basis of the potential impact on efficacy or safety evaluation and in the patient's best interest:

1. Any medications administered for the treatment of worsening of COPD within 4 weeks prior to Day 1 of the Run-in Period:
   - nebulized, inhaled, oral, IV, IM corticosteroids;
   - oral or parenteral β2 agonists;
   - Antibiotics.
2. Inhaled corticosteroids (ICS), LABA, and/or inhaled ICS/LABA fixed combinations within 12 hours prior to Day 1 of the Run-in Period;
3. Inhaled long acting anticholinergic agents other than tiotropium within 2 weeks prior to Day 1 of the Run-in Period;
4. Inhaled short-acting β2-agonists (SABA) other than albuterol (e.g., terbutaline, fenoterol) within 12 hours prior to Day 1 of the Run-in Period;
5. Inhaled short-acting anticholinergic agents (SAMA) (e.g., ipratropium) within 12 hours prior to Day 1 of the Run-in Period;
6. PDE inhibitors (including roflumilast) within 2 weeks prior to Day 1 of the Run-in Period.
7. Leukotriene modifiers and xanthines derivatives within 2 weeks prior to Day 1 of the Run-in Period.
8. Drugs or substances known to be significant inhibitors (strong or moderate) of UGT and/or SULT, within 12 hours prior to Day 1 of the Run-in Period and through collection of the final PK sample.
9. Acetaminophen will be prohibited 24 hours prior to Day 1 of the Treatment Period and through collection of the final PK sample.
10. Vitamin supplements and herbal products (especially Speedwell) will be prohibited 7 days prior Day 1 of the Treatment Period and through collection of the final PK sample.

13.3.5.1.2 Permitted Therapy

Throughout the study Period (from Day 1 of the Run-in Period to the completion of the last scheduled study procedures on Day 56 or upon early termination) patients will be permitted to take the following medications in addition to the study drugs:

1. Albuterol, as required (except approximately 4 hours before schedule pulmonary function test);
2. Tiotropium (Spiriva® HandiHaler®) 18 µg once a day (except approximately 24 hours before schedule pulmonary function test);
3. Ibuprofen, as required, up to 1200 mg per day for intercurrent illness or AEs. Ibuprofen should not be taken for 2 hours before or after each dosing.
4. In the case of a concomitant disease, appropriate treatment will be permitted if it does not interfere with the study evaluation parameters and does not qualify under the section "Prohibited Therapy" (see Section 13.3.5.1.1)

13.3.5.2 Prohibitions

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/caffeine (other than coffee and tea): 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Alcohol (other than red wine and beer): 48 hours prior to each CRU visit, 48 hours prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts), and mustard: 14 days prior to Day 1 of the Treatment Period through collection of Day 56 last PK sample.
- Fruit Juice: 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Tea (especially Speedwell tea), coffee, and red wine: 7 days prior to Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Grapefruit/Seville orange and beer: 14 days prior to Day 1 of the Treatment Period through collection of Day 56 last PK sample.

13.3.5.3 Activity

Patients will remain ambulatory or seated upright for 1 hour following each study medication administration.

Patients will be advised to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

13.4 Treatments

13.4.1 Treatments administered

13.4.1.1 Drug Administration During Run-in Period

Tiotropium (Spiriva® HandiHaler®) will be supplied as 18 µg capsules for inhalation.

Albuterol will be supplied as 100 µg albuterol base (1 actuation = 100 µg albuterol base) for oral inhalation. Albuterol may be administered via a nebulizer or a metered-dose inhaler.

Multiple oral inhalation of tiotropium (Spiriva® HandiHaler®) 18 µg capsule will be administered QD every morning for 14 ± 2 days during the Run-in Period. Albuterol will be administered on an as needed basis.

13.4.1.2 Drug Administration During Treatment Period

YPL-001 will be supplied as 80 mg tablets for oral administration.

Placebo will be supplied as YPL-001 80 mg matching placebo tablets for oral administration.

Treatments A, B, and C are described as follows:

Treatment A: Multiple oral YPL-001 80 mg doses (1 x 80 mg tablet + 1 x 1 YPL-001 80 mg matching placebo tablet) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56.

Treatment B: Multiple oral YPL-001 160 mg doses (2 x 80 mg tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56.

Treatment C: Multiple oral matching placebo (2 x 1 YPL-001 80 mg matching placebo tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56.

Each dose of Treatments A, B and C will be administered with approximately 240 mL of water.

In all treatments, one tiotropium (Spiriva® HandiHaler®) 18 µg capsule will also be administered QD every morning prior to study drugs administration. Albuterol will be administered on an as needed basis.

YPL-001 or placebo will be dispensed in accordance with the Randomization and Drug Dispensing Instructions provided in a separate document.

Prior to release from the CRU on Days 1, 15 (± 2 days), and 29 (± 2 days), of the Treatment Period, patients will receive a properly labeled new kit, which contains 4 wallets of 2 blister cards, with the appropriate doses which will be self-administered by

patients at home. Any unused wallets from previously provided kits will also be dispensed to patients on Days 15 (± 2 days) and 29 (± 2 days). Prior to release from the CRU on Days 43 (± 2 days), and 55, patients will received unused wallets from previously provided kits with the appropriate doses which will be self-administered by patients at home. Patients will also receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. Patients will record their self-administered doses in their e-diary, and whether the dose was administered with food, and must return the YPL-001 used and unused wallets and the tiotropium and albuterol container (empty or not) at the next schedule visit at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.

Patients will be instructed not to crush, split or chew the study drug.

The exact clock time of dosing will be recorded on on-site dosing days. Patients will be given instructions on how to record their drug administration in their e-diary on home-dosing days.

Each dose will be administered under fasting conditions as described in Section 13.2.4.1.

13.4.1.3 Stopping Rules

A decision to stop or suspend the study will be made jointly by the Sponsor and the Investigator following the review of all pertinent safety and tolerability. Together they will make one of the following determinations:

1. To continue with the study as planned.
2. To continue with the study and add additional safety evaluations.
3. To continue with the study by adjusting to a lower dose if 2 patients at any dose level meets any of the following criteria and the patient was determined to have received YPL-001 after unblinding:
   a. Has a drug–related, unexpected SAE.
   b. Experiences drug-related grade ≥ 3 toxicity.
4. The study will be terminated if ≥ 3 patients at any dose level meet any of the following criteria and the patients were determined to have received YPL-001 after unblinding:
   a. Has a drug–related, unexpected SAE.
   b. Experience drug related grade ≥ 3 toxicity.

PK data will not be required for the dose-escalation decision.

When applicable, a written statement fully documenting the reasons for study termination will be provided to the Institutional Review Board (IRB).

13.4.2 Method of Assigning Patients to Treatment Groups

Each patient will be assigned a unique screening identification number upon screening. Patients who complete the study screening assessments, complete the Run-in Period, and meet all the eligibility criteria will be assigned a unique randomization identification number, different from the screening number, and receive the corresponding product, according to a randomization scheme generated at Celerion. Each treatment group will consist of an approximately equal number of current and ex-smokers.

Patients will receive one of the 3 treatments (Treatments A, B, or C) on one occasion.

If replacement patients are used, the replacement patient number will be 100 more than the original (e.g., Patient No. 0101 will replace Patient No. 0001).

13.4.3 Blinding

This is a double-blind, double-dummy, randomized study.

13.4.3.1 Maintenance of Randomization

A computerized randomization scheme will be created by a Celerion unblinded statistician (who is not otherwise involved in the study) and shall be considered blinded (per the following).

The randomization will not be made available to the Sponsor, patients, or members of the staff responsible for the monitoring and evaluation of safety assessments.

The bioanalytical department will also be blinded to the randomization scheme.

13.4.3.2 Procedures for Breaking the Blind Prior to Study Completion

The site Pharmacist/Study Coordinator will receive two sets of randomization code envelopes, one set for “Current Smokers” and another for “Ex-Smokers”. Each individual envelope is marked on the outside with one of the randomization numbers and contains the treatment for that patient. These envelopes must be kept in a secure locked location.

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the patient.

In the event of a medical emergency, it is requested that the Investigator make every effort to contact the medical monitor or designee prior to breaking the blind. If breaking the blind is required because of a medical emergency, the treatment identity would be revealed by the qualified designee, for that patient only. In the event that the emergency is one, in which it appears that the other patients may be at imminent risk, the blind may be broken for all patients dosed at that dose level. The unblinding should be noted in the patient’s electronic case report form (eCRF).

In all cases where the code is broken, the Investigator should record the date, reason for code breaking and his/her name for signature on the envelope.

At the end of the study, the envelopes will be reviewed by the Sponsor.

13.4.3.3 Revealing of Randomization

In the absence of a medical emergency, the blinded randomization for this entire trial will not be revealed until the following conditions are fulfilled:

1. All data are entered in the database, edits checks are performed, queries closed, CRFs signed by the Investigator, and the database is officially locked.
2. All PK/PD samples have been analyzed and quality checked by the responsible analytical associate.

13.4.4 Treatment Compliance

During in-clinic dosing, a qualified designate will be responsible for monitoring the administration of timed oral doses. When appropriate, a mouth check will be performed by the qualified designate to ensure that the patients have swallowed the study medication. Once a patient has finished the water, the qualified designate will use a flashlight and a tongue depressor to check the side of the mouth, the sides of the upper and lower gums and the area under the tongue. Patients' hands will also be verified to ensure that the medication was ingested.

Self-administration by patients at home will be monitored via the e-diary and attempted phone calls will be performed to remind patients to take their medication, if they did not record their self-administration on the e-diary.

14. STUDY PROCEDURES

14.1 Safety Assessments

This study primarily assesses the safety and tolerability of YPL-001. Safety will be determined by evaluating physical examinations, vital signs, pulse oximetry, ECGs, clinical laboratory parameters, and AEs.

If deemed necessary, additional safety measurements will be performed at the discretion of the Investigator.

Study procedures should be completed as close to the prescribed/scheduled time as possible. The Quality of Life questionnaire should be performed prior to any other procedures. When the following procedures are scheduled at the same time, they will be performed in the following order:

1. Vital signs and pulse oximetry
2. ECG
3. Pulmonary function measurement
4. Bronchoscopy and BAL collection

All other procedures can be performed without specific order.

14.1.1 Body Height and Weight

Body height (centimeters) and body weight (kilograms) will be measured as outlined in the Study Events Flow Chart (Section 6).

14.1.2 Physical Examination

All full physical examinations will include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose and throat, respiratory system, cardiovascular system, gastrointestinal system, neurological condition, blood and lymphatic systems, and the musculoskeletal system.

A licensed physician will examine each patient as outlined in the Study Events Flow Chart (Section 6).

Medical history will be recorded at screening.

Physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator.

14.1.3 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate will be measured as outlined in the Study Events Flow Chart (Section 6).

Vital signs may be taken at any other times, if deemed necessary. Blood pressure and heart rate measurements will be performed with patients in a seated position for at least 1 minute, except when they are supine or semi-reclined because of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the Investigator.

When performed prior to the morning dose, blood pressure and heart rate will be measured within 2 hours prior to dosing. When scheduled postdose, vital signs readings will be performed within approximately 10 minutes of the scheduled time point. When performing the bronchoscopy, vital signs (body temperature, respiratory rate, blood pressure, and heart rate) will be monitored continuously until the end of the procedure.

14.1.4 Pulse Oximetry

Oxygen saturation (%), and heart rate will be assessed using a pulse oximeter. All readings will be performed with a pulse oximeter (oxygen saturation [%], and heart rate) as outlined in the Study Events Flow Chart in Section 6.

When performed prior to the morning dose, pulse oximetry monitoring will be measured within 2 hours prior to dosing. Readings may be taken at other times, if deemed necessary by the Investigator. When performing the bronchoscopy, oxygen saturation will be monitored continuously until the end of the procedure.

Any clinically relevant oxygen saturation reading below 93% will be documented as an AE, as per Investigator discretion.

14.1.5 Electrocardiogram Monitoring

When performed prior to the morning dose, ECG will be measured within 2 hours prior to dosing. When performing the bronchoscopy, ECG will be monitored continuously until the end of the procedure.

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6). Patients will be required to lie quietly in a supine position for at least 5 minute prior to ECG measurements. Single 12-lead ECGs may be performed at various unscheduled time points, if deemed necessary by the Investigator.

Single 12-lead ECGs will be interpreted and signed and dated by the Investigator. The ECGs will be classified as normal, having a non-clinically significant abnormality (NCS), or having a clinically significant abnormality (CS). In addition, ECG parameters of ventricular rate, PQ or PR interval, QRS duration, and QT interval (corrected according to Bazett's formula [QTcB] and uncorrected) will be noted on the CRF.

14.1.6 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 6). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator. The clinical laboratory tests include the following:

14.1.6.1 Hematology

- Hemoglobin
- Hematocrit
- RBC count (including a reticulocytes count)
- Platelet count
- Mean Corpuscular Hemoglobin (MCH)
- Mean Corpuscular Volume (MCV)
- Mean Corpuscular Hemoglobin Concentration (MCHC)
- RDW
- White blood cell (WBC) count with differential (including eosinophil, neutrophil, basophil, lymphocytes, and monocytes)

14.1.6.2 Serum Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.

- BUN
- Creatinine*
- Bilirubin (total and direct)
- Uric acid
- Albumin
- Alkaline phosphatase (ALP)
- Creatine kinase (CK)
- Lactate dehydrogenase (LDH)
- Estimated glomerular filtration rate
- Alpha-1 Antitrypsin**
- AST
- ALT
- Amylase
- Lipase
- Glucose (fasting)
- Carbon dioxide (CO_2)/Bicarbonate (HCO_3)
- Sodium
- Potassium
- Chloride

* Creatinine clearance will be calculated using Cockcroft-Gault formula at screening.

** To be performed at screening only.

14.1.6.3 Serology

- HIV
- HBsAg
- HCV

14.1.6.4 Human Chorionic Gonadotropin (Serum Pregnancy Test)

The test will be performed for females only.

14.1.6.5 Follicle-Stimulating Hormone

The test will be performed in postmenopausal females only.

14.1.6.6 Urinalysis

- pH
- Specific gravity
- Protein
- Glucose
- Ketones
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Leukocyte Esterase

If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination will be performed.

14.1.6.7 Urine/Breathalyzer Alcohol Screen

Alcohol levels will be tested using urine dipsticks or breathalyzers.

14.1.6.8 Urine Drug Screen

- Cannabinoids
- Cocaine
- Amphetamines
- Barbiturates
- Benzodiazepines
- Opiates

14.1.7 Chest X-Ray

A baseline chest x-ray will be performed at the screening visit. If the patient has had an x-ray within the last 3 months prior to the screening visit, and the CRU has access to the report and images, this can be used as the baseline chest x-ray and does not need to be repeated.

14.1.8 Berlin Questionnaire

The Berlin Questionnaire is a validated screening questionnaire used to quickly identify the risk (low to high) of sleep disordered breathing. The questionnaire consists of three categories and risk is based on the responses to individual items and overall scores in the symptom categories. Assessments will be performed according to the Study Events Flow Chart (Section 6). The questionnaire will be provided as a separate document and a copy of the questionnaire to be used will be kept in the study binder.

14.1.9 Adverse Events

14.1.9.1 Adverse Event Definition

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.[3]

14.1.9.2 Monitoring

The patients will be instructed to inform the Investigator or clinic staff of any AEs and intercurrent illnesses experienced during the trial. Additionally, a specific inquiry regarding AEs will be conducted prior to each dosing at the CRU, after the last scheduled study procedures on Day 56 (or upon early withdrawal), and at the follow-up phone call. The inquiry will be made in a non-specific manner using open-ended questions so as not to bias the response (e.g., How have you been feeling since your last visit?).

All symptoms will be evaluated by the Investigator.

Any patient who has a clinically significant AE (whether serious or non-serious) or clinically significant abnormal laboratory test value will be evaluated by the Investigator, or other monitoring physician, and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

Treatment of SAEs will be performed by a physician, either at the CRU or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal or unknown (lost to follow-up).

14.1.9.3 Reporting

AEs will be coded using the most current MedDRA® available at Celerion (e.g., 17.0 or higher). The Sponsor will inform the Celerion Global Project Manager which version is to be used prior to initiation of the study.

The Investigator will review each event and assess its relationship to drug treatment (unrelated, unlikely, possible, probable, definite). The severity of each sign or symptom reported will be graded based on the NIH NCI CTCAE toxicity grading scale 5-point severity scale (Grade 1, 2, 3, 4 and 5)[4] and the date and time of onset, time relationship to drug dosing, duration, and outcome (resolved, improved, unchanged, worse, fatal, or unknown/lost to follow-up) of each event will be noted.

The relationship of each AE will be assessed using the following definitions:

Unrelated	▪ Event occurring before dosing. ▪ Event or intercurrent illness due wholly to factors other than drug treatment.
Unlikely	▪ Poor temporal relationship with drug treatment. ▪ Event easily explained by patient's clinical state or other factors.
Possible	▪ Reasonable temporal relationship with drug treatment. ▪ Event could be explained by patient's clinical state or other factors.

Probable	▪ Reasonable temporal relationship with drug treatment. ▪ Likely to be known reaction to agent or chemical group, or predicted by known pharmacology. ▪ Event cannot easily be explained by patient's clinical state or other factors.
Definite	▪ Distinct temporal relationship with drug treatment. ▪ Known reaction to agent or chemical group, or predicted by known pharmacology. ▪ Event cannot be explained by patient's clinical state or other factors.

The following definitions for rating severity will be used:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**. Note**:** An experience may be severe but may not be serious, e.g., severe headache).
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A semi-colon indicates 'or' within the description of the grade; ADL = Activities of Daily Living

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

14.1.9.4 Serious Adverse Events

If any AEs are serious, as defined by the Food and Drug Administration (FDA) Code of Federal Regulations (CFR), Chapter 21, special procedures will be followed. All SAEs will be reported to the Medical Monitor via fax or e-mail within one working day of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012[3]. The institutional review board (IRB) will be notified of the Alert Reports as per FDA regulations.

If an SAE occurs to a patient on this study, the Medical Monitor is to be contacted (see Section 4).

A SAE is any AE or suspected adverse reaction that in the view of either the Investigator or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

14.2 Symptom Assessments

14.2.1 Electronic Diary

On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their self-administered doses, whether the dose was administered with food, and daily respiratory symptoms throughout the Run-in and Treatment Periods. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff.

Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

14.2.2 Peak Expiratory Flow

PEF assessments will be made daily prior to each dose from Day 1 of the Run-in Period to Day 56 of the Treatment Period. Three measurements will be made at each time point using a hand held PEF meter. Readings not performed in the CRU will be recorded in the patient e-diary. All PEF assessments should be performed before administration of a bronchodilator where possible.

14.2.3 Symptoms of Chronic Obstructive Pulmonary Disease Exacerbation

Patient will be asked to record the major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation via the e-diary before each dosing.

14.2.4 Dyspnea (Modified Borg Dyspnea Scale)

Severity level of patient's dyspnea will be assessed via the modified Borg dyspnea scale programmed within the e-diary. The modified Borg dyspnea scale is a self-administered categorical scale with a score from 0 to 10, where 0 (as a measure of dyspnea) corresponds to the sensation of normal breathing (absence of dyspnea) and 10 corresponds to the patient's maximum possible sensation of dyspnea.

14.2.5 Activity (Duke Activity Status Index)

Patient's functional capacity and activity status will be assessed via the DASI programmed within the e-diary. DASI is a self-administered 12-item questionnaire that assesses daily activities such as personal care, ambulation, household tasks, sexual function and recreation with respective metabolic costs. Each item has a specific weight based on the metabolic cost. The final score ranges between 0 and 58.2 points. The higher the score, the better the functional capacity.

14.3 Pharmacodynamic Assessments

14.3.1 Pulmonary Function (Spirometry)

Spirometry measures will be taken at the time points delineated in the Study Events Flow Chart (Section 6) using a standard calibrated spirometer to determine the parameters detailed below.

- FEV_1;
- FVC (forced vital capacity);
- FEV_1/FVC;
- IC.

Short acting β2-agonist and anticholinergic bronchodilators (e.g., albuterol, ipratropium bromide) and long acting β2-agonist and anticholinergic bronchodilators (e.g., salmeterol, tiotropium) agents will be withheld approximately 4 and 24 hours, respectively, before each pre-bronchodilator spirometry.

Every effort will be made to perform all assessments for a given patient on the same instrument throughout the study.

At screening, baseline pre-bronchodilator spirometry will be performed (prior to albuterol administration) for a minimum of 3 times and a maximum of 8 times in order to obtain 3 manoeuvers with FEV_1 values within 150 mL of each other, using the manoeuver with the highest value of FEV_1 and FVC as the basis for comparison.

Patients shall receive 4 inhalations of albuterol (100 µg/inhalation) for a total dose of

400 µg via metered-dose inhaler using a spacer. Within approximately 20 to 30 minutes after albuterol administration, the baseline post-bronchodilator spirometry will be performed.

Assessment of FEV_1 stability will take place:

1. Prior to Day 1 dosing of the Treatment Period (Day -1 measurement): Predose FEV_1 is defined as the time point prior to Day 1 dosing in the Treatment Period and will be performed pre- and post-bronchodilatator administration. Predose FEV_1 will be compared to the corresponding baseline measurement. If the best FEV_1 measurement at predose on Day -1 of the Treatment Period has declined by greater than 20% from the best FEV_1 at screening, the visit may be rescheduled up to 3 times, at the discretion of the Investigator.

2. Following Day 1 dosing: At all other spirometry time point, measurements will be performed once. If the value shows a difference of greater than 150 mL decline than the best FEV_1 value collected predose on Day -1, up to 3 measures will be performed.

   Consideration should be given, if a patient experiences any change in post Day 1 dose FEV_1 from the Day 1 predose FEV_1 value (measured following dosing with albuterol) equal to or greater than 20 % and should alert the Investigator to consider whether individual patients should continue to dose. The pulmonary function manoeuver(s) used to make this assessment must be valid and meet acceptable quality spirometry standards.

The Investigator may also use his or her discretion as to the completion of dosing for any period in which an FEV_1 decline and/or respiratory symptoms occur(s).

14.3.2 Bronchoscopy and Bronchoalveolar Lavage (BAL) Biomarkers

Patients will be fasted for 12 hours before the bronchoscopy procedures. If required, blood pressure medications can be taken with small sip of water based on preapproval of local Investigator.

14.3.2.1 Bronchoscopy

The bronchoscopy with bronchial brushings will be performed at the time points delineated in the Study Events Flow Chart (Section 6) by a licensed physician experienced in conducting the procedure according to guidelines published on the use of bronchoscopy for research on airway diseases such as COPD.[5,6]

Albuterol will be administered 20 minutes prior to the beginning of the bronchoscopy. An intravenous line will also be established to administer conscious sedation, and to administer emergency medications if the need were to arise. During the procedure, oxygen saturation (S_PO_2), blood pressure, and heart rate and rhythm (continuous electrocardiogram) will be monitored. Oxygen 2-4 L via nasal cannula will be administered during bronchoscopy and oxygen saturation will be maintained at ≥95%. Conscious sedation will be achieved with incremental doses of 1–4 mg midazolam and

50-100 µg fentanyl. Local upper and lower airway topical anesthesia will be achieved with 1% or 2% lidocaine. The dose of lidocaine administered during the procedure will not exceed a total of 450 mg. The bronchoscope will usually be inserted preferably through the nares into trachea. The bronchoscope will be wedged into 2 subsegments of the right middle or lower lobe, as deemed appropriate by the Investigator. Emergency treatments for cardiopulmonary arrest and pneumothorax will be immediately available in the bronchoscopy room. The patient will remain in the recovery suite for observation for a minimum of 2 hours after the procedure.

14.3.2.2 Bronchial Brushings

Prior to BAL, a cytology brush is inserted into the bronchoscope channel and brushings are collected twice from each of 4 quadrants of visible subsegments of the right middle or lower lobe, as deemed appropriate by the Investigator, under direct visualization. The cellular material is washed off in saline following each brushing. The brushing is performed a total of 8 times. The liquid is centrifuged and the cell pellet is stored at -70°C.

Samples must be protected from UV light during collection, processing, and storage.

14.3.2.3 Bronchoalveolar Lavage (BAL)

BAL in the right middle or lower lobe, as deemed appropriate by the Investigator, will be performed at the time points delineated in the Study Events Flow Chart (Section 6) by a licensed physician experienced in conducting the procedure. A total of 180 mL BAL, using 6 x 30 mL aliquots of normal saline warmed to room temperature, will be performed using each subsegment of the right middle or lower lobe, as deemed appropriate by the Investigator. BAL fluid will be aspirated following each 30 mL instillation. The lavage material, which averages 25% return in COPD patients, typically yields 1-10 x 10^6 macrophages. The centrifuged cell pellet and supernatant will be kept cooled until processed or stored as indicated in the laboratory manual to be provided as a separate document.

Samples must be protected from UV light during collection, processing, and storage.

14.3.2.4 Biomarkers

BAL samples will be analyzed for:

- YPL-001 component levels in epithelial brushings;
- total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells
- total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers
- concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9.

14.3.3 Blood Biomarkers

Blood samples will be collected via direct venipuncture or an angiocatheter at the time points delineated in the Study Events Flow Chart (Section 6) for PD assessments of biomarkers. Biomarker assessments include:

- inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils, and lymphocytes)
- concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9.

Blood will be drawn into 3 tubes. A manual for blood sampling, collection, processing, and sample shipment will be provided in a separate document.

14.3.4 Quality of Life Questionnaires

14.3.4.1 Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI)

Dyspnea at baseline (Day -1 of the Treatment Period) will be assessed with the BDI. This instrument has 3 domains (functional impairment, magnitude of task, and magnitude of effort) with the values added for a combined focal score. Functional impairment determines the impact of breathlessness on the ability to carry out activities; magnitude of task determines the type of task that causes breathlessness, magnitude of effort establishes the level of effort that results in breathlessness. The BDI scores range from 0 (very severe impairment) to 4 (no impairment) for each domain with the baseline focal score consisting of the sum of each domain (0 to 12).

Dyspnea throughout the study will be performed at the time points delineated in the Study Events Flow Chart (Section 6). The change from baseline is measured by the TDI score which ranges from -3 (major deterioration) to +3 (major improvement) for each domain with the TDI focal score consisting in the sum of each domain (-9 to +9).

The same Investigator or designee will interview specifically the patients during the study.

A copy of the questionnaire to be used will be kept in the study binder.

14.3.4.2 COPD Assessment Test (CAT)

CAT is a short and simple questionnaire of 8 items completed by patients to be performed at the time points delineated in the Study Events Flow Chart (Section 6). Scores for each of the 8 items are summed to give a single, final score ranging from 0 (no impact on daily activities) to 40 (very high impact on daily activity). This is a measure of the overall impact of a patient's condition on their life. Scores for the individual items within the questionnaire will provide insight into the relative influence that the different components of COPD have on its overall impact on a patient's life.[7,8]

A copy of the questionnaire to be used will be kept in the study binder.

14.4 Pharmacokinetic Assessments

The sampling schedule and/or collection intervals delineated in the Study Events Flow Chart (Section 6) may be modified based on the results from previously dosed patients.

14.4.1 Blood Sampling and Processing

Samples must be protected from UV light during collection, processing, and storage.

Samples will be collected via direct venipuncture or an angiocatheter at the time points delineated in the Study Events Flow Chart (Section 6).

Blood will be drawn into 4 mL pre-chilled evacuated tubes containing K_2EDTA. A manual for blood sampling, collection, processing, and sample shipment will be provided in a separate document.

14.5 Blood Volume for Study Assessments

Table 5: Blood Volume during Study

Sample Type	Number of Time Points	Volume per Time Point*	Sample Volume Over Course of Study
Screening laboratory safety tests (including hematology, serum chemistry, serology), FSH (for postmenopausal female patients only) and serum pregnancy (for female patients only).	1	~ 17 mL	~ 17 mL
On-study serum chemistry and serum pregnancy (for female patients only) when scheduled at the same time	3	~ 8.5 mL	~ 25.5 mL
Additional on-study serum pregnancy (for female patients only)	2	~ 3.5 mL	~ 7 mL
On-study hematology	3	~ 4 mL	~ 12 mL
Blood samples for PD biomarkers (except CRP and fibrinogen)	8	~ 6 mL	~ 48 mL
Blood samples for PD biomarker - CRP	8	~ 4	~ 32
Blood samples for PD biomarker - Fibrinogen	8	~ 3.5	~ 28
Blood samples for PK of verproside and picroside II	37	~ 4 mL	~ 148 mL
Total Blood Volume for males →			~ 310.5 mL**
Total Blood Volume for females →			~ 317.5 mL**

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

** If an angiocatheter is used, up to 5 mL of blood will be used to flush the catheter prior to each collection of PK and/or PD blood samples. Hence the total blood volume collected may increase by approximately 205 mL.

15. DATA ANALYSIS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCPs.

15.1 Statistical Analysis

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a SAP. The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP.

15.1.1 Sample Size Calculation

According to the exploratory nature of this study no formal statistical hypotheses will be tested. However, a sample size of 60 evaluable patients is deemed to be sufficient to assess the safety and tolerability and to provide an indication of the potential effect of YPL-001 on COPD exacerbation symptoms, selected biomarkers and pulmonary function parameters.

15.1.2 Patients to Analyze

Safety population: the safety population data set will include all available data for patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo. Safety data for all discontinued patients will be included in this set for the time points for which their data are available.

Symptom monitoring population: the symptom monitoring population data set will include all available data for patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo. Symptom monitoring data for all discontinued patients will be included in this set for the time points for which their data are available.

PK population:

- The PK full data set will include all patients receiving at least one dose of YPL-001 and having at least one measurable plasma concentration of verproside and picroside II.
- The PK per-protocol data set will include all patients receiving all scheduled doses of YPL-001 and having sufficient samples collected to determine PK parameters from plasma concentrations of verproside and picroside II on Days 1 and/or 56.

PD population:

- The PD full data set will include all patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo and provide at least 1 post-baseline PD measurement.
- The PD per-protocol data set will include all patients receiving all scheduled doses of

the investigational product (i.e., YPL-001) or placebo and having measurable PD data.

PK/PD population: All patients who receive at least one dose of YPL-001 and having any measurable concentration of verproside and picroside II and measurable PD data will be included in the PK/PD relationship assessment, as applicable.

15.1.3 Safety Analysis

The following analyses will be performed. Safety analyses will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data, when appropriate.

Medical History:

Medical history will be listed by patient.

Adverse Events:

AEs will be coded using the most current MedDRA® available at Celerion (e.g., 17.0 or higher) and data will be summarized by SOC and preferred term. The number of TEAEs will be reported. In addition, the number and percent of patients reporting each TEAE will be summarized separately for each treatment.

A by-patient AE data listing, including verbatim term, preferred term, treatment, severity, outcome, and relationship to treatment, will be provided.

Physical Examination:

Changes in physical examinations will be described in the text of the final report and significant findings will be reported as AEs.

Clinical Laboratory Tests, Electrocardiograms, Vital Signs and Pulse Oximetry:

All clinical laboratory tests, 12-lead ECGs, vital signs, and pulse oximetry measurements and their change from baseline, if applicable, will be summarized by treatment and time point of collection.

A shift table describing out-of-normal range shifts will be provided for clinical laboratory results.

A normal-abnormal shift table will be presented for ECGs.

Peak Expiratory Flow:

PEF measurements and its change from baseline, will be summarized by treatment and time point of collection.

Concomitant Medications:

Concomitant medications will be listed by patient and coded using the most current WHO drug dictionary available at Celerion (e.g., 01-MAR-2014 or later).

15.1.4 Symptom Monitoring Analysis

Symptom free days and overall symptom burden will be evaluated and compared across treatment groups. Secondary outcome analysis will be based on treatment actually

received by patients. Descriptive statistics will be calculated for quantitative data and frequency counts will be compiled for classification of qualitative data, when appropriate.

Peak Expiratory Flow and Symptoms of COPD Exacerbation:

PEF measurements and symptoms of COPD exacerbation and their change from baseline will be summarized by treatment and time point of collection.

Dyspnea and Activity:

The Modified Borg Dyspnea Scale and DASI scores will be listed and presented descriptively.

Additional analysis may be performed if deemed appropriate.

15.1.5 Pharmacodynamic Analysis

15.1.5.1 Biomarkers

When applicable, the following PD biomarkers will be summarized by treatment group using descriptive statistics (arithmetic means, SD, CV, N, minimum, maximum, and median). Figures will be created to display mean and individual level or activity as a function of time, as appropriate:

- Pulmonary biomarker (i.e., Pulmonary Function measurements [Spirometry]): pre- and post-bronchodilator change in activity by time point will be calculated relative to the pre- and post-bronchodilator baseline activity;
- BAL biomarkers (i.e., total cell count [cells/mL] of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; total cell count [cells/mL] of neutrophils, macrophages, lymphocytes and eosinophils as absolute inflammatory cell numbers; and concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9): raw and % change from baseline levels; and
- Blood biomarkers (i.e., inflammatory markers [total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes] and concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9): raw and % change from baseline levels.

PK/PD relationship may be explored graphically using scatter plots and an appropriate regression model.

15.1.5.2 Quality of Life

The quality of life parameters reported from the BDI/TDI and CAT questionnaires will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.

15.1.6 Pharmacokinetic Analysis

15.1.6.1 Pharmacokinetic Parameters

15.1.6.1.1 Plasma

PK parameters will be computed from the individual plasma verproside and picroside II concentrations using a noncompartmental approach. Appropriate validated PK software (e.g., WinNonlin Professional) will be used. PK parameters for other components of YPL-001 and its metabolites may also be computed, as appropriate.

The following PK parameters will be computed following Day 1 morning dose:

AUC_{0-12}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to 12 hours.
AUC_{0-t}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (C_t). This parameter will be reported only if plasma concentrations fall below the lower limit of quantitation before the last time point prior to the evening drug administration on Day 1 for at least one patient. Otherwise, only AUC_{0-12} will be reported.
AUC_{0-inf}	Area under the drug concentration-time curve from time zero to infinity, $AUC_{0-inf} = AUC_{0-t} + C_t/k_{el}$, where k_{el} is the terminal elimination rate constant. †
C_{max}	Maximum observed drug concentration.
t_{max}	Time of the maximum drug concentration (obtained without interpolation).
k_{el}	Apparent terminal elimination rate constant, calculated by linear regression of the terminal linear portion of the log concentration vs. time curve. †
$t_{1/2}$	Apparent elimination half-life, calculated as $\ln(2)/k_{el}$. †
CL/F	Oral clearance [$Dose/AUC_{0-inf}$]. †
V_Z/F	Apparent volume of distribution at the terminal phase, calculated as $Dose/(k_{el} * AUC_{0-inf})$.†

† All k_{el} and related PK parameters (AUC_{0-inf}, $t_{1/2}$, CL/F, and V_z/F) will be reported only if the half-life of verproside or picroside II can be appropriately estimated from a 12-hour sampling period following dosing.

The following PK parameters will be computed following Day 56 morning dose:

AUC_{τ}	The area under the plasma concentration versus time curve over the final dosing interval, as calculated by the log-linear trapezoidal method (e.g., 0-12 hours).
AUC_{0-t}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (C_t).
C_{max_ss}	Maximum observed drug concentration at steady-state.
$C_{min,ss}$	Minimum observed/measured non-zero concentration at steady-state.
C_{trough}	Concentration at the end of a dosing interval.
C_{avg}	Ratio of AUC_{τ} to the dosing interval, τ.
%Fluc	Percent fluctuation will be calculated as follows: $\frac{C_{\max\_ss} - C_{\min\_ss}}{C_{avg}} x\ 100$
Swing	Percent swing will be calculated as follows: $\frac{C_{\max\_ss} - C_{\min\_ss}}{C_{\min\_ss}} \text{ x } 100$
t_{max_ss}	Time to reach the maximum drug concentration (obtained without interpolation) at steady-state.
CL_{ss}/F	Total body clearance estimated at steady-state after oral administration, calculated as Dose/AUC_{τ}.
V_{z_ss}/F	Apparent volume of distribution at steady-state, calculated as $(CL_{ss}/F)/k_{el}$.*

* All k_{el} and related PK parameters ($t_{1/2}$ or V_{z_ss}/F) will not be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

If metabolite data are available, metabolite to parent ratios may be calculated for AUC_{0-t}, AUC_{τ}, and C_{max_ss}.

15.1.6.1.2 Bronchoalveolar Lavage

Levels of YPL-001 components in epithelial brushing will be listed.

15.1.6.2 Statistical Methods for Pharmacokinetic Analyses

PK parameters will be summarized by treatment group using descriptive statistics (arithmetic means, SD, CV, N, minimum, maximum, and median). In addition, geometric means will be calculated for AUC_{τ} and C_{max_ss}, as appropriate. Figures will be created to display mean and individual verproside and picroside II concentration-time curves. Additional PK analyses may be performed if deemed appropriate.

No value for k_{el}, $t_{1/2}$, and V_{z_ss}/F, as appropriate, will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

An estimate of the relative systemic exposure of AUC_{τ} and C_{max_ss} will be performed by dose normalized ratio analysis expressing the geometric mean ratio and 90% CI of the geometric mean ratio.

Steady-state will be assessed by visual inspection of predose plasma C_{trough} values on Days 15 (± 2 days), 29 (± 2 days), 43 (± 2 days), and 56 following multiple oral dose administration of YPL-001.

Additional analyses will be performed as deemed necessary upon review of the data.

15.1.7 Assessment of Efficacy

Efficacy will not be assessed in this study.

16. STUDY ADMINISTRATION

16.1 Ethics

16.1.1 Institutional Review Board

This protocol will be reviewed by an IRB and the study will not start until the Board has approved the protocol or a modification thereof. The Board is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The board is ICH compliant.

16.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, GCP, 21 CFR Parts 50, 56, and 312, the ethical princliples set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

16.1.3 Patient Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the patients in non-technical terms. Patients will be required to read, sign and date an informed consent form summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Patients will be given a copy of their informed consent form.

16.2 Termination of the Study

The Sponsor reserves the right to discontinue this study and the Investigator reserves the right to terminate their participation at any time.

16.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion relevant to the quality of this study. Designated personnel of Celerion will be responsible for maintaining quality assurance (QA) and quality control (QC) to ensure that the trial is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and Good Laboratory Practice requirements as well as applicable regulatory requirements.

The Clinical Study Report will be audited by the QA department and the quality assurance audit certificate will be included in the study report.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to statistical database lock.

Patient compliance will be monitored throughout the study via procedures such as questioning at check-in to review inclusion and exclusion criteria, urine drug screen at

check-in, mouth check following dosing, and confinement for all conduct procedures with clinical research staff on site at all times.

16.4 Direct Access to Source Data/Documents

The Investigator must maintain, at all times, the primary records (i.e., source documents) of each patient's data. Examples of source documents are laboratory reports, drug inventory, study drug label records, and eCRFs that are used as the source.

Celerion will ensure that the sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6] 5.1.2 & 6.10). In the event that other trial-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

16.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of YPL-001 80 mg tablets, and matching placebo tablets to allow completion of this study. The lot numbers and expiration dates (where available) of the drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the drugs supplied. At the conclusion of the study, any unused drugs (including placebo) will either be retained by the CRU, or returned to the Sponsor, depending on the specific requirements of the regulatory bodies to whom the study report will be submitted. If no supplies remain, this fact will be indicated in the Drug Accountability section of the final report.

16.6 Data Handling and Record Keeping

Celerion standard eCRFs will be used. Each eCRF is reviewed and signed off by the Investigator.

All raw data generated in connection with this study, together with the original copy of the final report, will be retained at each CRU in a designated storage facility, until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

16.7 Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be discussed between Sponsor and the Investigator. All revisions and/or amendments to the protocol in writing must be approved by the Sponsor, the Investigator, and the IRB before implementation.

16.8 Finance and Insurance

Finance and insurance will be addressed in a separate document.

16.9 Publication Policy

All unpublished information given to Celerion by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor's written consent to publish the article.

17. REFERENCES

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[3] FDA Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies-Small Entity Compliance Guide. December 2012. Available online: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332846.pdf

[4] National Cancer Institute. Common Terminology Criteria for Adverse Events v4.0. NCI, NIH, DHHS. May 29, 2009. NIH publication # 09-7473. Available online at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm The quick reference guide is available online at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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[6] Jarjour NN, Peters SP, Djukanović R, and Calhoun WJ. Investigative use of bronchoscopy in asthma. Am J Respir Crit Care Med. 1998;157(3 Pt 1):692-697.

[7] Jones PW, et al. Development and First Validation of the COPD Assessment Test. Eur Respir J. 2009;34:648-654.

[8] The COPD Assessment Test healthcare professional user guide: expert guidance on frequently asked questions (issue 3: February 2012). Jones PW, Jenkins C, Bauerle O (on behalf of the CAT Development Steering Group).

18. APPENDICES

18.1 Appendix 1 - SULT Drug Interaction Table

The following list provides medications that are substrates and inhibitors of sulfotransferase. Adapted from Zhang H, Cui D, Wang B, Han YH, et al. Pharmacokinetic drug interactions involving 17alpha-ethinylestradiol: a new look at an old drug. Clin Pharmacokinet. 2007;46(2):133-57; Coughtrie MW, Johnston LE. Interactions between dietary chemicals and human sulfotransferases-molecular mechanisms and clinical significance. Drug Metab Dispos. 2001;29(4 Pt 2):522-528; King RS, Ghosh AA, and Wu J Inhibition of human phenol and estrogen sulfotransferase by certain non-steroidal anti-inflammatory agents. Curr Drug Metab. 2006;7(7):745–753; Nagai M, et al. Inhibitory effects of herbal extracts on the activity of human sulfotransferase isoform sulfotransferase 1A3 (SULT1A3). Biol Pharm Bull. 2009;32(1):105-109; and Harris, R. M.; Waring, R. H. Sulfotransferase inhibition: potential impact of diet and environmental chemicals on steroid metabolism and drug. Current Drug Metabolism 2008;9(4):269-275.

Inhibitors
17-beta-estradiol glucuronide
Vitamin C
Brown rice
Beer
Meclofenamate
Nimesulide
Salicylic acid
Acetylsalicylic acid
Naproxen
Banaba extract
Rafuma extract
Grape seed extract
Peanut seed coat extract
Gingko extract
Biloba leaf extract
St. John’s wort
Gymnema
Milk thistle

Celerion Project No.: AA98497

Sponsor Project No.: YPL-001-YJP-130403

IND No.: 114903

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

1. PROTOCOL REVISION HISTORY

DATE/NAME	DESCRIPTION
16-Sep-2015 by Caroline Engel	Final Protocol, Amendment 4 This protocol amendment is generated to clarify and adjust study procedures as listed below: 1. Brigham and Women's Hospital Investigator signature and contact information was removed throughout the protocol since the center will not be participating during this study. The following sections were updated accordingly: • Section 3 Investigators Signatures • Section 4 Additional Key Contacts for the Study 2. The age limits were changed from 40 - 80 years of age, inclusively, to 30 - 85 years of age, inclusively. The following sections were updated accordingly: • Section 5 Synopsis - Study Population • Section 13.3.2 Inclusion Criteria – Inclusion criterion #1 3. To provide scheduling flexibility to the patients, a ±2-day window was added to the return visits on Days 15, 29, and 43. The following sections were updated accordingly: • Section 5 Synopsis - Summary of Study Design and Exploratory Outcome Measures • Section 6 Study Events Flow Chart • Section 13.1 Overall Study Design and Plan • Section 13.4.1.2 Drug Administration During Treatment Period • Section 15.1.6.2 Statistical Methods for Pharmacokinetic Analyses 4. Breathalyzer was added as an alternative method to the urine dipstick for the alcohol screen. The following sections were updated accordingly: • Section 6 Study Events Flow Chart • Section 13.3.3 Exclusion Criteria – Exclusion criterion #13 • Section 14.1.6.7 Urine/Breathalyzer Alcohol Screen was added • Section 14.1.6.8 (previously 14.1.6.7) was renamed Urine Drug Screen (previously Urine Drug/Alcohol Screen). 5. Only patients suffering from severe sleep apnea, as assessed by the Berlin Questionnaire, will be excluded from the study; The following sections were updated accordingly: • Section 6 Study Events Flow Chart

DATE/NAME	DESCRIPTION
16-Sep-2015 by Caroline Engel	• Section 13.3.3 Exclusion Criteria - exclusion criterion #8. • Section 14.1.8 Berlin Questionnaire was added. 6. The body mass index upper limit was increased from 32.0 kg/m^2 to 40.0 kg/m^2 inclusively. Therefore inclusion criterion #5 of Section 13.3.2 Inclusion Criteria was revised accordingly. 7. Drug screen false positive will be allowed if they are due to the use of prescription medication following approval from the PI and the medical monitor, the exclusion criterion #13 of Section 13.3.3 Exclusion Criteria was revised accordingly. 8. Smoking restriction prior to the bronchoscopy procedures was removed. Therefore, Section 14.3.2 Bronchoscopy and Bronchoalveolar Lavage (BAL) Biomarkers was updated accordingly. 9. Only strong and moderate inhibitors of UDP-glucuronosyltransferase and/or sulfotransferases are prohibited, therefore to prevent confusion with the list of substrats that was provided in Appendix 1, Appendix 1 was remove and the only 3 inhibitors listed in that table was enumarated in exclusion criterion #18. The list of substrate in appendix 2 (now rename Appendix 1) was also remove. This change will prevent possible confusion with the lists provided in the appendices. Exclusion criterion #18 of Section 13.3.3 Exclusion Criteria was revised accordingly. 10. To be consistent with Section 6 Study Events Flow Chart, pulse oximetry was added to the order of procecedures listed in Section 14.1 Safety Assessments. 11. Typographic and editorial corrections were made where applicable.
23-Apr-2015 by Caroline Engel	Final Protocol, Amendment 3 This protocol amendment is generated to clarify and adjust study procedures as listed below. The changes to the protocol are presented with new text in **bold** font and deleted text in ~~strikethrough~~ font. **Serious Adverse Event Contact Information** Drug Safety Solution's Medical Monitor will be contacted in case of serious adverse events. Hence the information under Sponsor Contact for Serious Adverse Events (Medical Monitor) in Section 4 Additional Key Contacts for the Study was corrected as follows: ~~Primary Contact:~~ ~~Yongnam Lee, Ph.D.~~ ~~Principal Scientist,~~ ~~Yungjin Pharm. CO., LTD.~~ ~~#451-20 Cheonho-3 dong, Gangdong-gu, Seoul, 134-721, Republic of Korea~~ ~~Tel.: +82-(31) 546-6980 ext. 220~~ ~~Fax: +82-(31) 546-6983~~ ~~E-mail: nami0209@yungjin.co.kr~~

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	~~Mobile: +82 (10) 6311-4228~~ ~~Secondary Contact:~~ ~~Kangrae Ha, B.Sc.~~ ~~E-mail: hakr@yungjin.co.kr~~ **Dr. Kathy Smith** **Drug Safety Solution** **Tel.: +1 919 264-5626** **E-mail: ksmith@drugsafety.biz** Section 14.1.8.4 Serious Adverse Events and Section 13.4.3.2 Procedures for Breaking the Blind Prior to Study Completion was also corrected accordingly. **Certified Clinical Laboratory:** Brigham and Women's Hospital and UAB Lung Health Center clinical laboratories contact information were added to Section 4 Additional Key Contacts for the Study. **Clinical Indication:** As indicated in the objectives of the study, the study will examine the pharmacodynamic (PD) effect of YPL-001 in patients with chronic obstructive pulmonary disease (COPD) only. Therefore, to prevent potential confusion and to capture the intended indication of the study specifically “asthma” was removed from the Clinical Indication in Section 5 synopsis and Section 10.1 Purpose of the Study. **Study Population:** As indicated throughout the protocol, patients will be will be adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3). Hence to be consistent with the GOLD Stage standards, the first sentence under Study Population from Section 5, Synopsis was corrected as follow: “Patients will be adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3) with a predominant bronchitic component ~~and a history of frequent (>2/year) COPD exacerbations,~~ between 40 and 80 years of age (inclusive).” **Randomization and Drug Dispensing** Instruction for randomization and drug dispensing are provided in a separate document. To be consistent with this document, which states that two sets of randomization code envelopes will be provided to site pharmacist/study coordinators and patients will received appropriately labeled kits and/or any unused wallets from previously provided kits (when applicable) for YPL-001 home dosing in addition to the containers for tiotropium/albuterol home dosing, the following section were modified

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	accordingly: • Section 5 Synopsis under Summary of Study Design and Study Products • Section 6 Study Event Flow Chart, Day 1 Study Drug Administration at CRU - Footnotes “k” and “p” • Section 6 Study Event Flow Chart, Days 2 to 55 Study Drug Administration at Home – Footnotes “j” and “o” • Section 13.1 Overall Study Design and Plan • Section 13.4.1.2 Drug Administration During Treatment Period • Section 13.4.3.1 Maintenance of Randomization • Section 13.4.3.2 Procedures for Breaking the Blind Prior to Study Completion In addition, and “X” was also added in the “Randomization” row under Day 1 predose in Section 6 Study Events Flow Chart. **Fasting Conditions** As indicated throughout the protocol, subjects will be required to fast for at least 8 hours before and 4 hours after YPL-001/placebo morning administration on Days 1 and 56. For clarity, footnote “q” was added to Day 1 Study Drug Administration at CRU and footnote “k” was added to Day 56 Study Drug Administration at CRU in Section 6 Study Events Flow Chart. **Analytes to be Measured** As indicated throughout the protocol, blood samples will be collected for the analyses of verproside and picroside II in plasma. Hence, the row identified as “Blood for Verproside Phamacokinetics” on Day 56 of Section 6 Study Events Flow Chart, was corrected to read: “Blood for Verproside **& Picroside II PK**”. **End-of-Treatment – Early Termination Procedures** All procedures listed under End-of-Treatment/Early Termination column in Section 6 Study Events Flow Chart are also scheduled to be performed on Day 55 before the bronchoscopy procedures. Therefore, as it is not required to repeat these procedures for two consecutive days, End-of-Treatment procedures were removed on Day 56, however early termination (ET) procedures were listed under the new ET column. Hence, the following sections were corrected accordingly. • Section 6 Study Events Flow Chart • Section 13.2.4.2 End-of-Treatment or Early Termination (Day 56), (renamed Section 13.2.4.2 Early Termination). • Section 13.3.2 Inclusion Criteria – Criterion #16 • Section 13.3.4 Removal of Patients from the Study • Section 13.3.5.1.1 Prohibited Therapy • Section 13.3.5.1.2 Permitted Therapy

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	• Section 14.1.8.2 Monitoring • Section 14.5 Blood Volume for Study Assessments (Table 5: Blood Volume during Study) In addition, the following sentence was added to Section 13.2.4.2 End-of-Treatment or Early Termination (Day 56), (renamed Section 13.2.4.2 Early Termination): "Patients who want to terminate from the study and are not currently on-site will be contacted and asked to return to the CRU to perform the early termination procedures" **Investigator's Brochure Version** In Section 9.1 YPL-001, the Investigator's Brochure version was updated to reflect the reference section and the most recent version of the Investigator's Brochure. **Method of Blood Collection** Throughout the protocol, the option of using an angiocatheter was added. Hence, the following sections were corrected accordingly: • Section 11 Risk/Benefit • Section 14.3.3 Blood Biomarkers • Section 14.4.1 Blood Sampling and Processing • Section 14.5 Blood Volume for Study Assessments **Recording of Meal** To be consistent with clinical sites standard procedures, the last sentence of Section 13.2.4.1 Meal Schedule was corrected as follow: "Meals are not required to be completed by patients ~~and all meals and snacks eaten by patients will be recorded on the CRFs~~.' **Coffee, Tea and Alcohol Prohibition** As indicated in Section 13.3.5.2 Prohibitions, coffee tea, and red wine will be restricted for 7 days prior to Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample. Beer will be restricted for 14 days prior to Day 1 of the Treatment Period through collection of Day 56 last PK sample. Any other product containing xanthines or caffeine will be restricted 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample. Any other alcohol product will be restricted 48 hours prior to each CRU visit, 48 hours prior to dosing on Days 1 and 56 last PK sample. Hence, the xanthines/caffeine prohibition and the alcohol prohibition were corrected as follows for clarification: "Xanthines/caffeine **(other than coffee and tea)**: 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample." "Alcohol **(other than red wine and beer)**: 48 hours prior to each CRU

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	visit, 48 hours prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample." **e-Diary** Home dosing will be recorded using a yes/no answer in the e-diary. Therefore the last sentence of the second to last paragraph of Section 13.4.1.2 Drug Administration During Treatment Period was corrected as follows: **"**Patients will be given instructions on ~~recording of dosing times~~ **how to record their drug administration** in their e-diary on home-dosing days.' In addition, estimation of sputum quantity was added to the list of major symptoms of COPD exacerbation recorded daily by the patients on their e-diary, "color" and "consistency" was moved as example of sputum quality, and a statement indicating that the e-diary device will be return in case of early termination was also added. Hence, the following sections were corrected accordingly: • Section 5 Synopsis under Secondary Outcome Measures • Section 5 Synopsis under Summary of Study Design • Section 6 Study Events Flow Chart – Day 1, Footnote "j" • Section 6 Study Events Flow Chart – Days 2-55, Footnote "i" • Section 6 Study Events Flow Chart – Day 56, Footnotes "g" and "h" • Section 12.2 Study Endpoints • Section 13.1 Overall Study Design and Plan • Section 13.2.3 Run-In Period (Days 1 to 14 [± 2 days]) • Section 13.2.4 Treatment Period (Days 1 to 56) • Section 14.2.1 Electronic Diary • Section 14.2.3 Symptoms of Chronic Obstructive Pulmonary Disease Exacerbation **Treatment Compliance** Drug administration at home will be monitored by HGE Technologies Inc. via the e-diary. Therefore, the last sentence of Section 13.4.4. Treatment Compliance was corrected as follow: "Self-administration by patients at home will be monitored ~~by the CRU~~ via the e-diary and attempted phone calls will be performed to remind patients to take their medication, if they did not record their self-administration on the e-diary." **Oxygen Saturation** For consistency throughout the protocol, "oxygen levels, saturation (%)" was replaced with "oxygen saturation (%)." **Tiotropium Treatment** As indicated in Section 13.3.2 Inclusion Criteria and Section 13.3.5.1.2

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	Permitted Therapy, tiotropium will be withheld 24 hours prior to pulmonary function (spirometry) measurements. Hence, the 2nd paragraph of Section 14.3.1 Pulmonary Function (Spirometry), was corrected to read: "Short acting β2-agonist and anticholinergic bronchodilators (e.g., albuterol, ipratropium bromide) and long acting β2-agonist and anticholinergic bronchodilators (e.g., salmeterol, tiotropium) agents will be withheld approximately 4 and ~~12~~ **24** hours, respectively, before each pre-bronchodilator spirometry." **Spirometer Across Clinical Site** The 3rd paragraph of Section 14.3.1 Pulmonary Function (Spirometry) was corrected as follow: "Every effort will be made to perform all assessments for a given patient on the same instrument throughout the study~~ and all sites should be using the same brand and model of spirometer for this study~~." **Bronchoalveolar Lavage (BAL) Collection** It is planned that a maximum of 180 mL BAL will be performed during each planned bronchoscopy procedures. Therefore, to prevent confusion, the second sentence of Section 14.3.2.3, Bronchoalveolar Lavage (BAL) was corrected to read: "A **total of** 180 mL BAL**, using 6 x 30 mL aliquots of normal saline warmed to room temperature,** will be performed ~~in~~ **using** each subsegment of the right middle or lower lobe, as deemed appropriate by the Investigator~~, using 6 x 30 mL aliquots of normal saline warmed to room temperature~~." **Blood Volume for Clinical Safety Laboratory Tests, Pharmacodynamic (PD) Markers and Pharmacokinetic (PK) Samples:** Blood collection volume for PD markers, as indicated in Section 14.3.3 Blood Biomarkers and Section 14.5 Blood Volume for Study Assessments, only accounts for 1 tube. However, 3 tubes will be required to assess CRP (4 mL tube), fibrinogen (3.5 mL tube) and the rest of the PD biomarkers (6 mL tube). The blood volume per time point will be approximately 13.5 mL instead of 4.5 mL. As indicated above, End-of-Treatment listed on Day 56 were removed as the same tests are scheduled on Day 55 before the bronchoscopy procedures. Hence one sample was removed for a total of 3 on-study hematology and serum chemistry tests to be performed throughout the study. In addition, 4 mL of blood will be sufficient for the determination of verproside and picroside II concentration in plasma at each time point. Therefore the total blood volume was corrected to 310.5 mL for males and 317.5 mL for females. Section 14.3.3 Blood Biomarkers, Section 14.4.1 Blood Sampling and Processing, and Section 14.5 Blood

DATE/NAME	DESCRIPTION
	Volume for Study Assessments were corrected accordingly. Minor typographic and editorial corrections were made where applicable.
16-Feb-2015 by Caroline Engel	Final Protocol, Amendment 2 This protocol amendment is generated to clarify and adjust study procedures as listed below. **Number of Subjects:** The sample size was revised to 60 subjects as it is sufficient to meet the objectives of the study. In case of dropouts, discontinued patients may be replaced at the discretion of the Sponsor as indicated throughout the protocol. Therefore the following sections were corrected accordingly to indicate that at least 60 subjects are planned to be enrolled and randomized with 20 patients to receive one of the 3 treatments: • Section 5 Synopsis (the 1st sentence of the 2nd paragraph under Summary of Study Design and the 1st and 2nd sentences under Number of Patients). • The 1st sentence of the 2nd paragraph of Section 13.1 Overall Study Design and Plan. • The 1st and 3rd sentences of Section 13.3.1 Number of Patients. • The last sentence of Section 15.1.1 Sample Size Calculation. **Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) and COPD Assessment Test (CAT):** BDI/TDI and CAT questionnaires will not be used as a diagnostic tool to assess the patient's potential to meet all inclusion criteria and none of the exclusion criteria. Therefore these questionnaires are not required at screening. In addition, it is not required to perform them for 2 consecutive days to meet the study objectives and therefore, Day 55 assessments were removed. Section 6 Study Events Flow Chart was corrected accordingly. The first sentence in Section 14.3.4.1 Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) was also corrected to be consistent with Section 6. **Early Termination Procedures:** Weight, and oxygen levels, saturation (%), and heart rate assessed using a pulse oximeter were added to the procedures performed at the end of the Treatment Period on Day 56 or prior to early termination from the study to monitor subject's safety appropriately. A pulmonary function (spirometry) test was also added prior to early termination for safety monitoring. Section 6 Study Events Flow Chart was corrected accordingly.

DATE/NAME	DESCRIPTION
16-Feb-2015 by Caroline Engel	**Recording Concomitant Medication:** Concomitant medication will be recorded at each study visit by the clinical staff in to the electronic data capture system. Therefore, concomitant medications was removed from the list of events that will be recorded by the patients via their e-diary throughout the protocol. The following sections were corrected accordingly: • Footnotes in Section 6 Study Events Flow Chart. • The first sentence of the 4th paragraph of Section 13.2.3 Run-In Period (Days 1 to 14 [± 2 days]). • The 2nd sentence of the 2nd paragraph of Section 13.2.4 Treatment Period (Days 1 to 56). • The 2nd sentence of the first paragraph of Section 14.2.1 Electronic Diary. **Subject Numbering:** The first paragraph of Section 13.4.2 Method of Assigning Patients to Treatment Groups was modified to clarify that the screening number and randomization number are two separate identification number given to each subject at different stages of the study. **Adverse Events Reporting** Footnotes were added to clarify the rating severity definitions in Section 14.1.8.3 Reporting. Minor editorial and typographical corrections were made where applicable.
20-Nov-2014 by Ziv Machnes	Final Protocol, Amendment 1 This protocol amendment is generated to update the study population with regards to smoking frequency, to update the handling procedures for BAL samples, and to clarify other study procedures as listed below. **Study Population:** Section 13.3.2 - Inclusion Criteria, bullet 11 was updated to indicate that the study population will consist only of current and ex-smokers with a history of >10 pack years. As such, the indications for 'packs/year' were replaced with 'pack years' and the allowance for current smokers with <10 pack/years was removed. Wording was added to indicate an approximately equal number of current and ex-smokers will be enrolled, and that each treatment group will consist of an approximately equal number of smokers and ex-smokers. In addition, the stratification criteria for the randomization was updated to consist of either current or ex-smokers. The following sections were affected: • Section 5 – Synopsis (under Study Population and Number of Patients)

DATE/NAME	DESCRIPTION
20-Nov-2014 by Ziv Machnes	• Section 13.1 - Overall Study Design and Plan (second paragraph) • Section 13.3.1 – Number of Patients. • Section 13.4.2 - Method of Assigning Patients to Treatment Groups. **BAL Sample Handling:** Section 14.3.2.3 - Bronchoalveolar Lavage (BAL) was updated to indicate that sample handling, processing and storage procedures will be provided in a separate document. **Follow-up Procedures:** The wording in regards to follow-up procedures to be conducted on 14 days (± 2 day), after the last study drug administration, was updated to indicated a phone-call and not a visit, as indicated correctly in Section 6 – Study Event Flow Chart. Study event were updated accordingly. The following sections were affected: • Section 5 – Synopsis (under Duration of Participation for Patients, and Exploratory Outcome Measures [under Blood Assessments, Pulmonary Assessment, and Quality of Life Assessments]) • Section 13.3.5.2 – Prohibitions (under Alcohol) • Section 14.1.8.2 – Monitoring (first paragraph). **Study Duration:** The total duration of the study indicated in Section 5 – Synopsis (under Duration of Participation for Patients) was corrected to 12 weeks to correspond with the actual study duration as indicated throughout the protocol. **Inflammatory Markers in Blood Samples:** The list of cell types to be evaluated as part of the inflammatory markers in the blood was updated to include monocytes instead of macrophages, as macrophages are not expected to be present in blood. The following sections were affected: • Section 5 – Synopsis (under Study Objectives, fourth exploratory objective, and under Exploratory Outcome Measures [under Pharmacodynamic Assesments, Blood Assessments, first bullet]) • Section 12.1 - Study Objectives (fourth exploratory objective) • Section 12.2 - Study Endpoints (third exploratory endpoint) • Section 14.3.3 - Blood Biomarkers (first bullet) • Section 15.1.5.1 - Biomarkers (third bullet) **Neutrophil Evaluation in BAL Samples** Neutrophils were added to the list of cell types to be evaluated as a percentage of the total cell count in BAL samples. The following sections were affected: • Section 5 – Synopsis (under Study Objectives, second exploratory

DATE/NAME	DESCRIPTION
20-Nov-2014 by Ziv Machnes	objective and under Exploratory Outcome Measures [under Pharmacodynamic Assessments, Bronchoalveolar Lavage Assessments, second bullet]) • Section 12.1 - Study Objectives (second exploratory objective) • Section 12.2 - Study Endpoints (second exploratory endpoint) • Section 14.3.2.4 - Biomarkers (second bullet) • Section 15.1.5.1 – Biomarkers (second bullet) **Location of Study Drug Administration**: Wording was added in Section 6 – Study Events Flow Chart for Day 56, to clarify that the study drug will be administered at the CRU. **Meal Schedule**: The indication for fasting requirement in Section 13.2.4.1 – Meal Schedule, was corrected to indicate patients will fast overnight for at least 12 hours before bronchoscopy and BAL collection on Days -1 and 55 instead of Days -1 and 56, as correctly indicated in Section 6 – Study Events Flow Chart. **ECG Monitoring:** Following an update in Celerion's standard operating procedure, Section 14.1.5 – Electrocardiogram Monitoring was updated to include at least 5 minutes of rest prior to each ECG measurement (instead of at least 1 minute as previously indicated). **Hematology:** The tests included in the hematology panel Section 14.1.6.1 – Hematology were updated to indicate that the red blood cell (RBC) count will include a reticulocytes count, and that the white blood cell (WBC) count with differential will include monocytes but will not include reticulocytes. **Bronchoscopy and BAL:** Due to the sensitivity of YPL-001 components to UV light, a warning was added to protect all samples from exposure to UV light, as indicated for the PK blood samples. The following sections were affected: • Section 14.3.2.2 - Bronchial Brushings • Section 14.3.2.3 - Bronchoalveolar Lavage (BAL) **PK Population:** The indication for measurable concentration of verproside and picroside II in urine was removed from the definition of PK population in Section 15.1.2 - Patients to Analyze, as there is no urine PK sampling planned for this study. Minor typographic and editorial corrections were made where applicable.

DATE/NAME	DESCRIPTION
18-Sep-2014 by Caroline Engel	Final Protocol

2. SPONSOR – SIGNATORIES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

Sponsor:

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Byung Hwan, Ryoo
Signature

18/Sep/2015
Date

3. INVESTIGATORS SIGNATURES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

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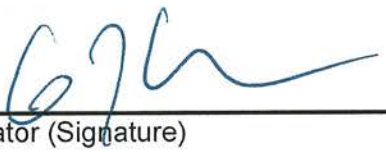

Investigator (Signature)

9/22/15

Date

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Date

3. INVESTIGATORS SIGNATURES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

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4. ADDITIONAL KEY CONTACTS FOR THE STUDY

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5. SYNOPSIS

Compound:	YPL-001
Clinical Indication:	Treatment of inflammatory diseases of the respiratory tract such chronic obstructive pulmonary disease (COPD)
Study Type:	Phase 2a, proof of concept
Study Objectives:	The **primary objective** of the study is to assess the safety and tolerability of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients. The **secondary objective** of the study is to assess the number and magnitude of daily respiratory symptoms of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients. The **exploratory objectives** of the study are to evaluate the following in moderate to severe COPD patients: 1. To assess bronchoalveolar lavage (BAL) epithelial brushings for YPL-001 component levels. 2. To compare BAL samples for total cell count (cells/mL) macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; neutrophil, macrophage, lymphocyte and eosinophil counts as absolute inflammatory cell numbers in YPL-001 groups versus placebo group. 3. To compare BAL samples for tumor necrosis factors alpha (TNF-α), interleukin (IL)-1β, IL-4, IL-5, IL-6, IL-8, IL-13, myeloperoxidase (MPO), neutrophil elastase, monocyte chemotactic protein (MCP)-1, and matrix metalloproteinase (MMP)-9 in YPL-001 groups versus placebo group. 4. To compare blood inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) and concentrations of C-reactive protein (CRP), fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9 in YPL-001 groups versus placebo group. 5. To compare spirometric functions (forced expiratory volume in one second [FEV_1], forced vital capacity [FVC], FEV_1/FVC, and inspiratory capacity [IC]) in YPL-001 groups versus placebo group. 6. To compare patient reported outcomes (Baseline Dyspnea Index [BDI]/Transition Dyspnea Index [TDI], COPD Assessment Test [CAT]) in YPL-001 groups versus placebo group. 7. To assess verproside and picroside II concentration in plasma and BAL and verproside and picroside II pharmacokinetics (PK) in plasma following multiple oral doses administration of two YPL-001 dose levels.

Summary of Study Design:	This is a Phase 2a, proof-of-concept, multicenter, randomized, double-blind, double-dummy, 3-treatment, parallel study, with low and high YPL-001 doses (80 mg and 160 mg twice daily [BID]) and a placebo control in moderate to severe COPD patients. At least 60 patients will be enrolled and randomized into 3 treatment groups (20 patients per group). Patients will participate only once. Safety and tolerability will be assessed throughout the study. Assessment of respiratory symptoms and symptom burden in YPL-001 and placebo treatments will be performed daily through patient self-report of peak expiratory flow (PEF), major and minor symptoms of COPD exacerbation, dyspnea, and activity in their electronic diary (e-diary). Spirometry measurement, bronchoalveolar lavage (BAL), and blood samples will be collected for the pharmacodynamic (PD) assessment of YPL-001 and placebo treatments. Serial blood samples will also be collected for PK assessment of verproside (the principal active ingredient of YPL-001) and picroside II. Other components of YPL-001 and its metabolites may also be analyzed in plasma. Following screening, eligible patients will discontinue non permitted respiratory drugs if already receiving them and enter a 14 ± 2 days Run-in Period during which patients will be given albuterol taken on an as required basis and daily tiotropium 18 µg (one capsule inhaled daily in the morning) to be administered at home. On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their daily symptoms throughout the Run-in Period. Patients will return to the clinical research unit (CRU) on the morning of Day -1 of the Treatment Period to confirm their eligibility and assess their health conditions. If they still meet all of the inclusion criteria and none of the exclusion criteria, they will undergo Day -1 scheduled study procedures. Patients will return to the CRU the next day (Day 1) to be randomized and receive one of the 3 treatments and undergo all scheduled study procedures. Patients will return on the morning of Days 15 (± 2 days), 29 (± 2 days), 43 (± 2 days), 55, and 56 of the Treatment Period for study drug administration and procedures. Prior to each release from the CRU, patients will receive a properly labeled YPL-001 kit (and/or any unused wallets from previously provided kits [when applicable]) and tiotropium/albuterol container with sufficient doses which will be self-administered by patients at home until the next morning visit at the CRU. Patients will continue recording their daily symptoms via the e-diary throughout the Treatment Period. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff. The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any adverse event (AE) has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary. Patients will be instructed to call the Investigator if breathing worsens or if they need to take more than 8 puffs per day of albuterol for more than 2 consecutive days. If the Investigator determines that the patient is too unstable to continue in the study, he/she will be discontinued. Rescue medication will be used for any patient with an exacerbation of COPD and

	will be administered in accordance with the study center standard of care.
Study Population:	Patients will be adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3) with a predominant bronchitic component, between 30 and 85 years of age (inclusive). An approximately equal number of current and ex-smokers will be enrolled.
Number of Patients:	The study is planned to enroll at least 60 patients. Patients will be divided in 3 treatment groups with 20 patients to receive one of the 3 treatments (i.e., low and high YPL-001 doses [80 mg and 160 mg BID] and a placebo control) as per the randomization schedule. Each treatment group will consist of an approximately equal number of current and ex-smokers.
Duration of Participation for Patients:	The planned length of participation in the study for each patient is approximately 12 weeks (from Day 1 of the Run-in Period through completion of the follow-up procedures on Day 70 [± 2 days]).
Duration of Study Conduct:	The study is planned to take place over approximately 12 to 24 months (from screening of the first patient through completion of all study procedures for the last patient). This time period may change in the event that the study is terminated early, additional time is required to review safety, or a decision is made to complete an unscheduled analysis for a group.
Study Products:	YPL-001 will be supplied as 80 mg tablets for oral administration. Placebo will be supplied as YPL-001 80 mg matching placebo tablets for oral administration. YPL-001 or placebo will be dispensed in accordance with the Randomization and Drug Dispensing Instructions provided in a separate document.
Dosage, Dosage Form, Route, and Dose Regimen:	Treatments are described as follows: Treatment A: Multiple oral YPL-001 80 mg doses (1 x 80 mg tablet + 1 x 1 YPL-001 80 mg matching placebo tablet) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56. Treatment B: Multiple oral YPL-001 160 mg doses (2 x 80 mg tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56. Treatment C: Multiple oral matching placebo (2 x 1 YPL-001 80 mg matching placebo tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56. In all treatments, one tiotropium (Spiriva® HandiHaler®) 18 µg capsule will also be administered QD every morning prior to study drugs administration. Albuterol will be administered on an as needed basis. Each dose of Treatments A, B, and C will be administered orally with approximately 240 mL of water.

Stopping Rules:	A decision to stop or suspend the study will be made jointly by the Sponsor and the Investigator following the review of all pertinent safety and tolerability. Together they will make one of the following determinations: 1. To continue with the study as planned. 2. To continue with the study and add additional safety evaluations. 3. To continue with the study by adjusting to a lower dose if 2 patients at any dose level meets any of the following criteria and the patient was determined to have received YPL-001 after unblinding: a. Has a drug–related, unexpected serious adverse event (SAE). b. Experiences drug-related grade ≥ 3 toxicity. 4. The study will be terminated if ≥ 3 patients at any dose level meet any of the following criteria and the patients were determined to have received YPL-001 after unblinding: a. Has a drug–related, unexpected SAE. b. Experience drug related grade ≥ 3 toxicity.
Primary Outcome Measures	Safety and tolerability will be monitored through physical examinations, vital signs, pulse oximetry, ECGs, clinical laboratory tests, and AEs.
Safety and Tolerability Analysis	The following analyses will be performed. Safety analyses will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data, when appropriate. **Medical History:** Medical history will be listed by patient. **Adverse Events:** AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion (e.g., 17.0 or higher) and data will be summarized by System organ class (SOC) and preferred term. The number of treatment-emergent AEs (TEAEs) will be reported. In addition, the number and percent of patients reporting each TEAE will be summarized separately for each treatment. A by-patient AE data listing, including verbatim term, preferred term, treatment, severity, outcome, and relationship to treatment, will be provided. **Physical Examination:** Changes in physical examinations will be described in the text of the final report and significant findings will be reported as AEs. **Clinical Laboratory Tests, Electrocardiograms, Vital Signs, and Pulse Oximetry Measurements:** All clinical laboratory tests, 12-lead ECGs, vital signs, and pulse oximetry measurements and their change from baseline, if applicable, will be summarized by treatment and time point of collection. A shift table describing out-of-normal range shifts will be provided for clinical laboratory results. A normal-abnormal shift table will be presented for ECGs.

Safety and Tolerability Analysis (continued):	**Concomitant Medications:** Concomitant medications will be listed by patient and coded using the most current World Health Organization (WHO) drug dictionary available at Celerion (e.g., 01-MAR-2014 or later).
Secondary Outcome Measures:	PEF, major (e.g., estimated sputum quality (e.g., color, consistency), and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (Duke Activity Status Index [DASI]) self-reported daily by the patients using an e-diary.
Symptom Monitoring Analysis:	Symptom free days and overall symptom burden will be evaluated and compared across treatment groups. Secondary outcome analysis will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative data and frequency counts will be compiled for classification of qualitative data, when appropriate. **Peak Expiratory Flow and Symptoms of COPD Exacerbation:** PEF measurements and symptoms of COPD exacerbation and their change from baseline will be summarized by treatment and time point of collection. **Dyspnea and Activity:** The Modified Borg Dyspnea Scale and DASI scores will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.
Exploratory Outcome Measures:	**Pharmacodynamic Assessments:** <u>Bronchoalveolar Lavage Assessments:</u> BAL samples will be collected at baseline and again at the completion of the study for PD assessments of biomarkers. Biomarker assessments include: 1. epithelial brushings for YPL-001 component levels; 2. total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells 3. total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers 4. concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9. <u>Blood Assessments:</u> Blood samples will be collected at screening, and throughout the study for PD assessments of biomarkers. Biomarker assessments include: 1. inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) 2. concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9. <u>Pulmonary Assessment:</u> Pulmonary function measurements (spirometry [FEV_1, FVC, FEV_1/FVC, and

Exploratory Outcome Measures (continued):	IC] will be performed at screening, and throughout the study. Quality of Life Assessments: Patient reported outcomes (e-diary, BDI/TDI, CAT) will be performed at baseline, and throughout the study. **Pharmacokinetic Assessments:** Bronchoalveolar Lavage Assessments: BAL samples will be collected at baseline and again at the completion of the study to determine verproside and picroside II concentrations in BAL. Other components of YPL-001 and its metabolites may also be analyzed. Plasma Assessments: Serial blood samples will be collected prior to the initial dosing and through 12 hours following dosing on Days 1 and 56 to determine verproside and picroside II concentrations in plasma. Predose samples will also be collected in the morning of Days 15 (± 2 days), 29 (± 2 days), 43 (± 2 days) and 56 for C_{trough} determination. Other components of YPL-001 and its metabolites may also be analyzed. The sampling schedule and/or collection intervals may be modified based on the results as the study progress.
Pharmacodynamic Analysis:	**Blood, Plasma, and Pulmonary biomarkers:** When applicable, the raw data and % change from baseline or placebo, as appropriate, for PD markers (BAL biomarkers, blood biomarkers, and pulmonary biomarker) will be summarized by time point and treatment using descriptive statistics (arithmetic means, standard deviations [SD], coefficients of variation [CV], sample size [N], minimum, maximum, and median). Figures will be created to display mean and individual level or activity as a function of time. **Quality of Life:** The quality of life parameters will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.
Pharmacokinetic Parameters and Analysis:	Noncompartmental PK parameters, including AUC_{0-t}, AUC_{0-inf}, AUC_{τ}, k_{el}, C_{max}, C_{max_ss}, C_{min_ss}, C_{trough}, t_{max}, t_{max_ss}, CL/F, CL_{ss}/F, V_z/F, V_{z_ss}/F, and $t_{1/2}$, as appropriate, will be calculated from plasma concentrations of verproside and picroside II from patients who received YPL-001 only. Additional PK parameters may be calculated if deemed appropriate. Plasma PK parameters may also be calculated for other components of YPL-001 and its metabolites. PK parameters will be summarized by treatment using descriptive statistics. Relative exposure of verproside and picroside II will be assessed between the two YPL-001 dose levels, and steady-state will be assessed by visual inspection in the active treatment groups. Verproside and picroside II concentration in BAL samples from patients who received YPL-001 only will be listed.

6. STUDY EVENTS FLOW CHART

Study Procedures[a]	Screen[b]	Run-in Period		Treatment Period																		
Days →		1	2-14 (±2)	-1	1																	
Hours →					Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12
Administrative Procedures																						
Informed Consent	X																					
Inclusion/Exclusion Criteria	X	X																				
Medical History	X																					
Randomization					X																	
Safety Evaluations																						
Physical Examination[c]	X			X[d]																		
Height	X																					
Weight	X			X[d]																		
Chest X-ray[e]	X																					
Berlin Questionnaire	X																					
12-Lead Electrocardiogram	X			X[f]																		
Vital Signs[g]	X			X[f]	X						X		X						X			
Pulse Oximetry	X			X[f]																		
Hem, Chem, and UA[h]	X			X[d]																		
Serum Pregnancy Test (♀ only)	X			X[d]																		
Serum FSH (postmenopausal ♀ only)	X																					
Urine Drug Screen	X			X[d]																		
Urine or Breathalyzer Alcohol Screen	X			X[d]																		
HIV/Hepatitis Screen	X																					
AE Inquiries																						
AE Monitoring										X												
ConMeds Monitoring	X									X												
Symptoms Monitoring																						
Diary Training		X																				
Diary Use[l]										X												
PEF, COPD exacerbation, dyspnea and activity[j]										X												
Study Drug Administration																						
Tiotropium Administration[p]		X	X	X	X																	
Study Drug Administration at CRU[k,q]						X																X

Study Procedures[a]	Screen[b]	Run-in Period		Treatment Period																		
Days →		1	2-14 (±2)	-1	1																	
Hours →					Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12
Pharmacodynamic																						
Pulmonary Function (Spirometry)[l]	X			X[d]																		
Pharmacodynamic																						
Bronchoscopy and BAL Biomarkers[m]				X																		
Blood Biomarkers	X				X						X											
BDI/TDI & CAT				X[d]																		
Pharmacokinetic																						
Blood for Verproside & Picroside II PK					X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]
Other Procedures																						
Visit & Return Visits[o]	X	X		X	X																	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.
b. Within 14 days of Day 1 (inclusive) of the Run-in Period.
c. A full physical examination will be performed at screening. Symptom-driven physical examinations will be performed at other scheduled times, and may be performed at other times at the Investigator's discretion.
d. To be performed prior to the bronchoscopy procedures.
e. To be performed at screening or within 3 months (inclusive) of screening.
f. ECGs, vital sign and pulse oximetry will be measured within 2 hours of bronchoscopy procedures. During the bronchoscopy procedures and BAL sample collection, patients will be continuously monitored for ECGs, vital signs (blood pressure, heart rate, respiration rate, and body temperature), and oxygen saturation.
g. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
h. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.
i. Patients will be provided with an e-diary device to record their self-administered doses, whether the dose was administered with food, and daily respiratory symptoms.
j. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).
k. Prior to release from the CRU, patients will receive a properly labeled kit with sufficient study drug for their assigned treatment which will be self-administered by patients at home until the next morning visit at the CRU. Patients must return the used and unused wallets at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.
l. Pulmonary function will be performed prior to and 20 to 30 minutes after inhalation of approximately 400 µg albuterol.
m. Bronchoscopy and BAL sample collection will be performed following a 12-hour fast.
n. To be performed prior to dosing.
o. Patients will be admitted to the CRU at the time indicated by the CRU.
p. Patients will receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. They must return the container (empty or not) at the next schedule visit.
q. On Day 1, patients will be required to fast overnight for at least 8 hours before and 4 hours after YPL-001/placebo morning administration.

STUDY EVENTS FLOW CHART *(CONTINUED)*

Study Procedures[a]	Treatment Period											
Days →	2-14	15 (± 2)		16-28	29 (± 2)		30-42	43 (± 2)		44-54	55	
Hours →		AM	PM		AM	PM		AM	PM		AM	PM
Safety Evaluations												
Physical Examination[b]					X[c]						X[d]	
Weight					X[c]						X[d]	
12-Lead Electrocardiogram					X[c]						X[e]	
Vital Signs[f]		X[c]			X[c]			X[c]			X[e]	
Pulse Oximetry											X[e]	
Hem, Chem, and UA[g]					X[c]						X[d]	
Serum Pregnancy Test (♀ only)		X[c]			X[c]			X[c]			X[d]	
Urine Drug Screen		X[c]			X[c]			X[c]			X[d]	
Urine or Breathalyzer Alcohol Screen		X[c]			X[c]			X[c]			X[d]	
AE Inquiries		X[c]			X[c]			X[c]			X[d]	
AE Monitoring	X											
ConMeds Monitoring	X											
Symptoms Monitoring												
Diary Use[n]	X											
PEF, COPD exacerbation, dyspnea and activity[i]	X											
Study Drug Administration												
Tiotropium Administration[o]	X											
Study Drug Administration at CRU		X			X			X			X	
Study Drug Administration at Home[j]	X		X	X		X	X		X	X		X
Pharmacodynamic												
Pulmonary Function (Spirometry)[k]		X[c]			X[c]			X[c]			X[n]	
Bronchoscopy and BAL Biomarkers[l]											X[c]	
Blood Biomarkers		X[c]			X[c]			X[c]				
BDI/TDI & CAT		X[d]			X[d]			X[d]				
Pharmacokinetic												
Blood for Verproside & Picroside II PK		X[c]			X[c]			X[c]				
Other Procedures												
Return Visits[m]		X			X			X			X	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.
b. Symptom-driven physical examinations will be performed at scheduled times, and may be performed at other times at the Investigator's discretion.
c. To be performed or completed prior to dosing.
d. To be performed or completed prior to bronchoscopy procedures and/or dosing.
e. ECGs, vital sign and pulse oximetry will be measured within 2 hours of bronchoscopy procedures. During the bronchoscopy procedures and BAL sample collection, patients will be continuously monitored for ECGs, vital signs (blood pressure, heart rate, respiration rate, and body temperature), and oxygen saturation.
f. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
g. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.
h. Patients will be provided with an e-diary device to record their self-administered doses, whether the dose was administered with food, and daily respiratory symptoms.
i. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).
j. Prior to release from the CRU on Days 15 (± 2 days), 29 (± 2 days), 43 (± 2 days), and 55 patients will receive a properly labeled kit and/or any unused wallets from previously provided kits (when applicable) with sufficient study drug for their assigned treatment which will be self-administered by patients at home until the next morning visit at the CRU. Patients must return the used and unused wallets at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.
k. Pulmonary function will be performed prior to and 20 to 30 minutes after inhalation of approximately 400 µg albuterol.
l. Bronchoscopy and BAL sample collection will be performed following a 12-hour fast.
m. Patients will be admitted to the CRU at the time indicated by the CRU.
n. To be completed prior to bronchoscopy procedures and dosing.
o. Patients will receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. They must return the container (empty or not) at the next schedule visit.

STUDY EVENTS FLOW CHART *(CONTINUED)*

Study Procedures[a]	Treatment Period																		ET[b]	FU[c]
Days →	56																			
Hours →	Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12		
Safety Evaluations																				
Physical Examination[d]																			X	
Weight																			X	
12-Lead Electrocardiogram																			X	
Vital Signs[e]	X						X		X						X			X	X	
Pulse Oximetry																			X	
Hem, Chem, and UA[f]																			X	
Serum Pregnancy Test (females only)																				
UrineDrug Screen	X																			
Urine or Breathalyzer Alcohol Screen	X																			
AE Inquiries	X																		X	
AE Monitoring	X																			X
Concomitant Medication Monitoring	X																			
Symptoms Monitoring																				
Diary Use[g]	X																		X	
PEF, COPD exacerbation, dyspnea and activity[h]	X																			
Study Drug Administration																				
Tiotropium Administration	X																			
Study Drug Administration at CRU[k]		X																		
Pharmacodynamic																				
Pulmonary Function (Spirometry)																			X	
Blood Biomarkers	X[i]						X													
BDI/TDI & CAT	X[i]																			
Pharmacokinetic																				
Blood for Verproside & Picroside II PK	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Other Procedures																				
Return Visits[j]	X																		X	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.

b. To be performed prior to early termination from the study.

c. The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

d. Symptom-driven physical examinations will be performed at scheduled times, and may be performed at other times at the Investigator's discretion.

e. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.

f. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.

g. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff.

h. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

i. To be performed at predose on Day 56 or upon early termination.

j. Patients will be admitted to the CRU at the time indicated by the CRU.

k. On Day 56, patients will be required to fast overnight for at least 8 hours before and 4 hours after YPL-001/placebo morning administration.

Abbreviations: ♀ = Female, AE = Adverse events, AM = Morning, BAL = bronchoalveolar lavage, BDI/TDI = Baseline Dyspnea Index/Transition Dyspnea Index Test, CAT = COPD Assessment Test, Chem = Serum chemistry, COPD = chronic obstructive pulmonary disease, CRU = Clinical research unit, ConMeds = Concomitant medication, DASI = Duke Activity Status Index, ECG = Electrocardiogram, e-diary = electronic diary, ET = Early termination, FSH = Follicle-stimulating hormone, Hem = Hematology, HIV = Human immunodeficiency virus, IL= interleukin, PEF = Peak expiratory flow, PK = Pharmacokinetics, PM = Evening, Preg = Serum pregnancy, Screen = Screening, UA = Urinalysis.

7. TABLE OF CONTENTS

8. ABBREVIATIONS

Only those uncommon abbreviations specific to this study are listed. Pharmacokinetic (PK) parameter abbreviations and definitions may be found in Section 15.1.6.1.

AE	Adverse event
AHR	Airway hyper-responsiveness
ALD	Approximate lethal dose
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
BALF	Bronchoalveolar lavage fluid
BDI	Baseline Dyspnea Index
BID	Twice daily
BLQ	Below the lower limit of quantification
BMI	Body mass index
bpm	Beat per minute
BUN	Blood urea nitrogen
°C	Degrees Celsius
CAT	COPD Assessment Test
Chem	Chemistry
CFR	Code of Federal Regulations
CK	Creatine kinase
CNS	Central nervous system
CO_2	Carbon dioxide
Coag	Coagulation
COPD	Chronic obstructive pulmonary disease
CRO	Contract Research Organization
CRP	C-reactive protein
CRU	Clinical research unit

CS	Clinically significant abnormality
CSC	Cigarette smoking condensate
CXCL	Chemokine (C-X-C motif) ligand
CV	Coefficient of variation
DASI	Duke Activity Status Index
dL	Deciliter
DRF	Dose range finding
e-diary	Electronic diary
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
ERS	European Respiratory Society
F	Female
°F	Degrees Fahrenheit
FDA	Unites States Foods and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FU	Follow-up
FVC	Forced vital capacity
g	gram
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HBsAg	hepatitis B surface antigen
HCO_3	Bicarbonate
HCV	hepatitis C antibodies
HED	Human equivalent dose
Hem	Hematology
HIV	Human immunodeficiency virus
hr	Hour
IC	Inspiratory capacity
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroid

IgE	Immunoglobulin E
IL	Interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
kg	Kilogram
kg/m^2	Kilogram per meter squared
LABA	long acting beta agonist
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
LOQ	Limit of quantitation
LPS	Lipopolysaccharide
LSM	Least-squares means
µg	Microgram
m^2	Square meter
M	Male
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCO	Myeloperoxidase
MCP	Monocyte chemotactic protein
MCV	Mean Corpuscular Volume
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
MIP	Monocyte inhibitory protein
mL	Milliliter
mmHg	Millimeter of mercury
MMP	Matrix metalloproteinase
msec	Millisecond
MTD	Maximum Tolerated Dose
N	Sample size
NCS	Not clinically significant

ng	Nanogram
No.	Number
NOAEL	No observed adverse effect levels
OTC	Over-the-counter
OVA	Ovalbumin
PD	Pharmacodynamic(s)
PEF	Peak expiratory flow
PK	Pharmacokinetic(s)
QA	Quality Assurance
QC	Quality Control
QT	Interval between the Q and T waves on the electrocardiogram tracing
QTcF	Corrected QT interval with Fridericia's formula
RBC	Red blood cell
RDW	Red cell distribution width
Resp	Respiration
ROS	Reactive oxygen species
SABA	Short-acting β2-agonist
SAD	Single ascending dose
SAE	Serious adverse event
SAMA	Short-acting anticholinergic agent
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SULT	Sulfotranferase
TBIL	Total bilirubin
TDI	Transition Dyspnea Index
TEAE	Treatment-emergent adverse event
Th	T helper
TNF-α	Tumor necrosis factors alpha
UA	Urinalysis
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal

US	United States
WBC	White blood cell
WHO	World Health Organization

9. INTRODUCTION AND BACKGROUND

This study is being conducted as the third in a series of studies for the clinical development of YPL-001. The trial will be conducted in compliance with the protocol, GCP, and applicable regulatory requirements. The patient population will be comprised of moderate to severe (GOLD Stage 2-3) COPD patients.

9.1 YPL-001

YPL-001 drug product is an oral dosage form of an herbal extract from the aerial parts of the plant Speedwell (*Pseudolysimachion rotundum* subsp. *Subintegrum*). *Pseudolysimachion* (*Veronica*) is a perennial herb which has been used as a traditional medicine in Korea and China for the treatment of inflammatory diseases of the respiratory tract such as asthma and COPD.

As a botanical drug product, the drug substance is a mixture of chemical species (iridoids [including verproside] and other related compounds) and biological activity is considered to be from the mixture and not from an individual component. It is unknown if the total activity from individual components is additive or synergistic. Five active constituents, classified as iridoids, have been identified in the herbal extract: verproside, picroside II, catalpolside, isovanilloyl catalpol, and 6-*O*-veratroylcatalpol. Recent experimentation has revealed that the principal active ingredient in *Pseudolysimachion* is verproside, a dihydroxylated catalpol derivative.

YPL-001, containing verproside and other active ingredients, is being developed as a potential oral treatment for long term inflammatory diseases of the respiratory tract such as asthma or bronchitic COPD. Current long term control medications include corticosteroids, cromolyn sodium, immunomodulators, long acting beta agonists, (LABAs), methylxanthines, and leukotriene modifiers. YPL-001 belongs most closely with the leukotriene modifier class of drug.

A brief overview of available information regarding YPL-001 follows below. Details can be found in the YPL-001 Investigator's Brochure of June 3, 2014. [1]

9.1.1 Preclinical Trials

9.1.1.1 Pharmacology

Five *in vivo* primary pharmacology studies have been completed.

In ovalbumin-sensitized mice, an animal model for asthma, YPL-001 reduced elevated immunoglobulin E (IgE), IL-4, IL-5, IL-13, airway hyper-responsiveness, and mucus hyper-secretion.

In the lipopolysaccharide (LPS)- and cigarette smoking condensate (CSC)-induced COPD mice model, verproside and roflumilast treatment inhibited the accumulation of neutrophils in Bronchoalveolar lavage fluid (BALF) as well as the increase of several proinflammatory cytokines and chemokines. Neutrophil infiltration induced by LPS and CSC treatments was associated with a significant increase in BALF levels of the chemoattractants, TNF-α, chemokine (C-X-C motif) ligand (CXCL)-1, and monocyte inhibitory protein (MIP)-2. These data also demonstrated that the effect of YPL-001 and verproside involves down-regulation of the influx of neutrophils and production of TNF-α,

CXCL-1, and MIP-2 molecules which play a major role in tissue remodeling.

YPL-001 significantly suppressed the increase of inflammatory cell counts, particularly neutrophils in BALF and also effectively suppressed elevated levels of TNF-α, CXCL-1 and MIP-2 with the reduction in airway inflammatory responses in CSC- and LPS-induced COPD mice.

YPL-001 also effectively suppressed the increased inflammatory cell count, particularly neutrophils in BALF and also significantly inhibited elevated levels of TNF-α, IL-1β and IL-6 with the reduction in reactive oxygen species (ROS) production and elastase activity in cigarette smoke- and LPS-induced COPD mice.

In the LPS- and cigarette smoke-induced COPD rats model, YPL-001 significantly inhibited the increase of inflammatory cell count, particularly neutrophils in BALF and also effectively suppressed elevated levels of TNF-α, IL-1β, IL-6, MIP-2 and CRP.

YPL-001 effectively inhibited development of both T helper (Th)2 and Th1/Th17 type asthma in these murine models. These effects resulted from inhibition of cytokine and chemokine production by infiltrated inflammatory cells and antigen specific T cells in lymph nodes. YPL-001 did not inhibit development of COPD which was induced by *E.coli* extracellular vesicles.

9.1.1.2 Pharmacokinetics

After oral administration of YPL-001 at 12.5, 25, and 50 mg/kg doses (5.225, 10.45, and 20.9 mg/kg as verproside) in rats, verproside was rapidly absorbed; verproside was detected at the first blood sampling time (5 min) and absorbed rapidly, with the t_{max} achieved at 0.46-0.61 hour for all three doses. The post-absorption phase of the mean plasma verproside concentration-time profiles showed a poly-exponential decay.

The area under the plasma concentration-time curve (AUC) and the maximum plasma concentration (C_{max}) of verproside were linearly increased as the oral dose of YPL-001 increased. Alternately, the dose normalized (based on 12.5 mg/kg) AUCs and C_{max} of verproside were comparable among different doses studied. The elimination half-lives ($t_{1/2}$), 2.14 – 3.91 hours, and other PK parameters of verproside for all three doses were also comparable. These findings indicate that the PK parameters of verproside were independent of doses.

The fraction of dose of verproside excreted unchanged in urine at 24 hours was less than 0.10%. Verproside was not detected in the 24 hours feces sample for all three doses studied. These results indicate that verproside is almost completely eliminated by the first pass metabolism due to O-methylation, glucuronidation, sulfation, and intestinal microflora-mediated metabolism. Verproside is metabolized to verproside glucuronides (M1 and M2), verproside sulfates (M3 and M4), O-methylverproside such as picroside II (M5) and isovanilloylcatalpol (M6), 3,4-dihydroxybenzoic acid (M11), 3-methyoxy-4-hydroxybenzoic acid (M15) and 3-hydroxy-4-methoxybenzoic acid (M16), which are further metabolized to their glucuronides and sulfates including M5 glucuronide (M7), M5 sulfate (M9), M6 glucuronide (M8), M6 sulfate (M10), M11 glucuronide (M12), M11 sulfates (M13 and M14), M15 glucuronides (M17 and M18), M15 sulfate (M20), M16 glucuronide (M19), and M16 sulfate (M21). The O-methylation of verproside to picroside II (M5) and isovanilloylcatalpol (M6) followed by glucuronidation and sulfation

were identified as the major metabolic pathway in bile and urine samples.

Picroside II, a major metabolite of verproside, was detected in plasma samples but most plasma concentrations in 12.5 and 25 mg/kg YPL-001 treated groups were below the lower limit of quantification (LLOQ, 2.5 ng/mL) compared to 50 mg/kg YPL-001 treated group. The picroside II-to-verproside AUC ratios in the 50 mg/kg YPL-001 treated group were 13.9-65.1%, suggesting that picroside II may be one of the major YPL-001 metabolites. Plasma concentrations of isovanilloylcatalpol, a metabolite of verproside and isomer of picroside II, were below LLOQ (2.5 ng/mL) after oral administration of all three YPL-001doses tested.

Verproside, catalposide, and picroside II were not considerably bound to human plasma proteins; the binding values were 36.3-55.0% at verproside concentrations of 0.1, 1.0, and 10.0 μg/mL, 31.2-49.5% at catalposide concentrations of 0.5, 1, and 10 μg/mL, and 34.0-41.2% at picroside II concentrations of 0.5, 1, and 10 μg/mL.

9.1.1.3 Toxicology

Two single dose toxicity studies with YPL-001 have been completed in rat and dog. In the rat study, polyuria was observed in the 5,000 mg/kg dosing group of each sex between 2-4 hours after YPL-001 administration. Discolored stool was observed dose-dependently in the all dosing groups of each sex at 1-3 days post administration. Soft stool, mucous stool and soiled perineal region were observed at 1 day after administration in the 2,500 and 5,000 mg/kg dosing group of each gender. There were no notable changes of body weight in any study group. There were no notable gross necropsy findings in any of the study groups. Based on the results above, when YLP-001 is administered orally to Sprague-Dawley rats, the approximate lethal dose (ALD) is higher than 5,000 mg/kg. In the dog study, There were no changes with respect to the toxicity of the test article in the clinical signs, body weight change and necropsy findings after a single dose. Vomiting and discoloration of stool was noted. The Maximum Tolerated Dose (MTD) was determined to be 2,000 mg/kg for males and 1,000 mg/kg for females.

Two dose range finding (DRF) studies with YPL-001 have been completed in rat and dog, followed by two pivotal, 4-week, GLP repeated-dose toxicology studies in the same species. In the rat DRF study, YPL-001 induced anemia and hemolysis at 667 mg/kg/d and at higher doses. In addition, enlargement of cecum was observed at 667 mg/kg/d and at higher doses. The NOEL for this study was 74 mg/kg/d in both genders. In the dog DRF study, decreases in red blood cell (RBC) values were present in males at the high dose level (1000 mg/kg/d). In females the TBIL values were elevated at the 1000 mg/kg/d dose levels. Females had enlarged spleens at 125, 250 and 1000 mg/kg dose levels without dose relationship (trend was toward significance). The MTD for this study was 1000 mg/kg/d.

Primary results from the pivotal, 4-week rat study included:

There were no abnormal clinical signs observed in any group during dosing or the recovery periods and no mortality was reported.

Hematology: Compared to controls, there were decreases in values of RBC, hematocrit, and hemoglobin at all dose levels of both genders in a dose-dependent fashion. The

values of hemoglobin distribution width, red cell distribution width (RDW) and reticulocyte at all dose levels of both genders were higher or significantly higher than those of vehicle control.

Clinical Biochemistry: There were significant increases in the values of TBIL at all dose levels of both genders when compared with that of vehicle control. After the recovery period, there were no noticeable changes related to the test article.

Organ Weights: Slight increase in absolute & relative weights of the spleen at 540 mg/kg/d in males and notable increase in absolute & relative weights of the spleen at all dose levels of females were observed. Weights of left and right kidneys in female at 540 mg/kg/d were significantly higher than that of vehicle control. After the recovery period, the absolute weights of the spleen and both kidneys in both genders at 540 mg/kg/d were significantly higher than that of vehicle control.

Necropsy Findings: At necropsy, 6 cases of dark reddish discoloration of spleen were observed at 540 mg/kg/d in both genders, and 1 case of enlargement of cecum was observed at 540 mg/kg/d in female. After the recovery period, one case of dark reddish discoloration of spleen was observed at 540 mg/kg/d in the female. The histopathology examination revealed increased hematopoiesis of spleen at the high dose in both genders.

No Observed Adverse Effect Levels (NOAEL): The NOAEL for this study was 180 mg/kg/d for both genders.

Primary results from the pivotal, 4-week dog study included:

YPL-001 colored stool with/without soft stool or diarrhea was persistently observed in both sexes at 1000 mg/kg/d during the dosing period. It was not observed during the recovery period. No mortality was reported.

Hematology: There were no treatment-related changes.

Clinical Biochemistry: The TBIL increased in a dose-dependent manner in both genders at 111, 333 and 1000 mg/kg/d, and it was not recovered completely after the 2-week recovery period.

Organ Weights: There were no treatment-related changes.

Necropsy Findings: Slight red discoloration of mucous membranes in the stomach or duodenum was observed in female treatment groups but not observed after the 2-week recovery period.

NOAEL: The NOAEL for this study was 1000 mg/kg/d for both genders.

9.1.2 Clinical Experience

To date, 2 studies have been conducted in healthy subjects, a randomized, double-blind, placebo-controlled, sequential single ascending dose (SAD) clinical study (AA98496) and a randomized, double-blind, placebo-controlled, sequential multiple ascending dose (MAD) clinical study (AA98495).

9.1.2.1 SAD study

All 5 cohorts of 8 subjects (6 active and 2 placebo), with one cohort crossing over to assess food effect, were dosed and completed. All dosed levels (i.e., 40, 80, 160, 240, and 320 mg) were well tolerated with no SAEs reported during the conduct of the study. All 9 AEs reported in 7 subjects were mild in severity and the most frequent AE reported, regardless of causality, was headache. Of the 7 AEs experienced by subjects receiving the active drug, the Investigator considered 2 of these to be possibly related (nausea, and vomiting), 2 unlikely related, and 3 unrelated. Of the 2 AEs experienced by subjects receiving placebo, the Investigator considered 1 of these to be possibly related (headache), and 1 unrelated.

Plasma samples were analyzed using a validated bioanalytical method. Verproside concentrations were lower than concentrations observed from the animal PK data. The limit of quantitation (LOQ) was approximately 20% of the C_{max} after a single 160 mg dose and approximately 10% of the C_{max} after a single 320 mg dose. Therefore, the half-life could not be well characterized since only a few PK concentrations were available for the estimation.

Verproside appeared to be rapidly absorbed following oral administration and independent on dose, as suggested by median t_{max} values of approximately 0.5 to 0.67 hours under fasting conditions. Verproside appeared to be cleared rapidly from plasma, with mean $t_{1/2}$ values under 1 hour; plasma verproside concentrations were below the lower limit of quantification (BLQ) for all subjects by 6 hours postdose. Table 1 below summaries the PK parameters of verproside following single-dose administrations of YPL-001 at each dose level:

Table 1 Summary of PK Parameters

Pharmacokinetic Parameters	Dose Level Mean ± SD					
	40 mg (N = 1)[a]	80 mg (N = 6)[b]	160 mg (fasting) (N = 6)[c]	160 mg (fed) (N = 6)[d]	240 mg (N = 6)[e]	320 mg (N = 6)[f]
C_{max} (ng/mL)	1.19	1.14 ± 0.328	2.90 ± 1.76	1.08 ± 0.287	4.78 ± 5.66	4.49 ± 1.44
t_{max} (hr)[g]	0.4969	0.6682 (0.5158, 1.0025)	0.5074 (0.3331, 0.6700)	1.2538 (0.9994, 2.0008)	0.5867 (0.3486, 1.5022)	0.5057 (0.3419, 1.5014)
AUC_{0-t} (ng·hr/mL)	0.7422	0.7520 ± 0.3818	2.5616 ± 1.7947	1.2822 ± 0.3599	5.4567 ± 5.0158	5.3612 ± 0.8664
AUC_{0-inf} (ng·hr/mL)	·	·	3.8048 ± 1.8238	·	8.2199 ± 5.3327	6.2162 ± 0.7776
$t_{1/2}$ (hr)	·	·	0.677 ± 0.263	·	0.919 ± 0.176	0.713 ± 0.100

[a] Individual values are presented for the 40 mg dose level
[b] N=5 for AUC_{0-t}
[c] N=3 for AUC_{0-inf} and $t_{1/2}$,
[d] N=4 for AUC_{0-t}
[e] N=3 for AUC_{0-inf}, and $t_{1/2}$,
[f] N=5 for AUC_{0-inf}, and $t_{1/2}$,
[g] t_{max} is presented as Median (Minimum, Maximum)
· = Value missing or not reportable

9.1.2.2 MAD Study

In total, 2 cohorts of 8 subjects and 1 cohort of 10 subjects received multiple YPL-001 doses of 80, 160, or 240 mg BID. Each cohort was constituted of 2 subjects receiving placebo and the remaining subjects receiving the active drug. All dose levels were well tolerated. There were no deaths or SAEs in this study. One (1) subject was discontinued due to the AE of chest pain. Overall, TEAEs were experienced by 38% of subjects in this study. The Investigator considered 1 AE (chest pain) to be possibly related to study drug and the remaining AEs unlikely or unrelated. There were no treatment-related trends in physical examination, laboratory, vital sign, or ECG assessments in this study.

Verproside appeared to be rapidly absorbed following multiple-dose oral administration, as suggested by median t_{max} values of approximately 0.5 - 0.9 hours and independent of dose. Following a multiple oral doses of YPL-001, verproside appeared to be cleared rapidly from plasma, with mean $t_{½}$ values under 1.6 hours, and plasma verproside concentrations were BLQ for most subjects by 12 hours postdose.

Picroside II appeared to be also rapidly absorbed following single- and multiple-dose oral administration, as suggested by median t_{max} values of approximately 0.6 to 0.9 hours and independent of dose. Following a single oral dose of YPL-001, picroside II appeared to be cleared rapidly from plasma, with mean $t_{½}$ values under 1 hour, CL/F values of 14000 – 18500 L/hour, and plasma picroside II concentrations BLQ by 10 - 12 hours postdose. Following multiple oral doses, mean $t_{½}$ values were under 2.5 hours, and plasma picroside II concentrations were BLQ for most subjects by 12 hours postdose.

For all 3 dose levels, minimal to modest accumulation of verproside and picroside II was observed following BID administration of YPL-001 for 2 weeks. The mean peak and total exposure of verproside and picroside II in plasma appeared to increase in a dose-dependent manner between 80 and 160 mg of YPL-001, but no increase in plasma bioavailability was observed between 160 and 240 mg dose levels. Table 2 and Table 3 below summaries the PK parameters of verproside and picroside II, respectively, following multiple-dose administrations of YPL-001 at each dose level:

Table 2 Summary of Verproside PK Parameters

Pharmacokinetic Parameters	YPL-001 Dose Level Mean ± SD		
	80 mg	**160 mg**	**240 mg**
AUC_t (pg*hr/mL)	4709 ± 4080 (N=6)	10860 ± 11424 (N=6)	9658 ± 9246 (N=5)
AUC_{0-t} (pg*hr/mL)	4596 ± 4127 (N=6)	10770 ± 11489 (N=6)	9566 ± 9298 (N=5)
C_{max_ss} (pg/mL)	2414 ± 1281 (N=6)	6737 ± 7342 (N=6)	5458 ± 4387 (N=5)
t_{max_ss} (hr)*	0.756 (0.252, 2.00) (N=6)	0.759 (0.329, 1.50) (N=6)	0.528 (0.272, 0.751) (N=5)
$t_{½}$ (hr)	1.47 ± 0.425 (N=6)	1.30 ± 0.406 (N=6)	1.57 ± 0.236 (N=5)

* = t_{max_ss} is presented as median (minimum, maximum)

Table 3 Summary of Picroside II PK Parameters

Pharmacokinetic Parameters	YPL-001 Dose Level Mean ± SD		
	80 mg	**160 mg**	**240 mg**
AUC_{τ} (pg*hr/mL)	2556 ± 599 (N=2)†	4287 ± 4369 (N=4)†	1985 ± 1024 (N=5)
AUC_{0t} (pg*hr/mL)	1124 ± 1044 (N=6)	3024 ± 3877 (N=6)	1804 ± 949 (N=5)
C_{max_ss} (pg/mL)	419 ± 240 (N=6)	1116 ± 1391 (N=6)	751 ± 490 (N=5)
t_{max_ss} (hr)*	0.756 (0.252, 2.00) (N=6)	0.759 (0.329, 1.50) (N=6)	0.748 (0.524, 0.751) (N=5)
$t_{½}$ (hr)	2.23 ± 0.254 (N=6)	1.84 ± 0.395 (N=6)	2.08 ± 0.793 (N=5)

* = t_{max_ss} is presented as median (minimum, maximum)
. = Value missing or not reportable

10. RATIONALE

10.1 Purpose of the Study

This study will be the initial exploration of multiple-dose administration of YPL-001 in COPD patients. The assessments of the safety, tolerability, COPD symptoms, PD, and PK of verproside and picroside II following administration of multiple doses of YPL-001 will guide decisions to further develop the drug and support the compound as a useful clinical candidate in the treatment of inflammatory diseases of the respiratory tract such as COPD and the data generated will support larger studies in patients with inflammatory diseases of the respiratory tract such COPD to demonstrate safety and evidence of efficacy and clinical benefit.

10.2 Dose Selection

This will be the first COPD patient study of YPL-001.

YPL-001 appeared well tolerated in a panel of standard animal toxicology studies. In the initial studies in humans, the initial dose of YPL-001 was justified conservatively according to the United States (US) Food and Drug Administration (FDA) guidance document “Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers”.[2]

Accordingly, the single and multiple dose escalation study (AA98496) initiated single doses at the 40 mg and 80 mg level, respectively. Dose escalations up to 320 mg and 240 mg in the SAD and MAD studies, respectively, were reached. All cohorts have been completed and all doses administered were well tolerated in human subjects and no clear pattern of toxicity is apparent.

Based on the review of safety, tolerability, and PK data from Cohorts 1 to 5 of the SAD study (AA98496) and Cohorts 1 to 3 of the MAD study, and the in vivo efficacy data in rat and mouse models, it is predicted that the therapeutic range should be between 1.2 mg/kg and 4.8 mg/kg which is equivalent to 84 mg to 336 mg daily in a 70 kg patient. Therefore, a low YPL-001 dose of 80 mg BID and the high YPL-001 dose of 160 mg BID were selected for this proof-of-concept study.

The total strength (23.75 mg) of identified compounds in YPL-001 as a whole in the 40 mg starting dose administered in the first-time-in-human dose escalation study (AA98496) corresponded to approximately 35% of the dosages that have been used in the traditional medicine setting in China (68.65 mg). In this present proof-of-concept study the total strength (47.50 mg) of identified compounds in the initial starting dose of 80 mg is still lower than the dosages that have been used in the traditional medicine setting in China, as shown in Table 4, corresponding to 70% of the traditional Chinese medicine.

Table 4: Traditional Chinese Medicine Use Versus Proposed Clinical Starting Dose

Identified Compounds in YPL-001	1.40 g (Single Dose) Traditional Chinese Medicine[a] (mg)	2.80 g/day (Divided Dose) Traditional Chinese Medicine[a] (mg)	80 mg (Single Dose) for MAD Study[b] (mg)
Verproside	47.94	95.88	30.64
Veratric acid	2.10	4.20	1.08
Catalpolside	3.77	7.54	4.08
Picroside II	3.43	6.86	3.36
Isovanilloyl catalpol	3.53	7.06	4.72
6-*O*-veratroyl catalpol	7.88	15.76	3.62
Total	68.65	137.30	47.50

[a] Traditional medicine dosage from Chinese Medical Great Dictionary; Zhong Yao Da Ci Dian.
[b] Proposed dosage of YPL-001 in MAD study

11. RISK/BENEFIT

YPL-001 is being developed as a potential oral treatment for long term control of persistent asthma and COPD. YPL-001 belongs most closely with the leukotriene modifier class of drug and has the potential to inhibit the accumulation of neutrophils the increase of several proinflammatory cytokines and chemokines which play a major role in tissue remodeling. The development of a product to improve the treatment of asthma and COPD will be of benefit to the wider community/patients with respiratory disease.

The safety monitoring practices employed by this protocol (i.e., physical examination, vital signs, pulse oximetry, 12-lead ECG, hematology, serum chemistry, urinalysis, AE monitoring, and AE questioning) are deemed adequate to protect the patients' safety and should detect all expected TEAEs. The procedures employed in this study to assess efficacy are primarily non-invasive and present no undue risk to the patient.

The approximate volume of blood planned for collection from each patient over the course of the study (see Section 14.5), presents no undue risk to the patients nor does the possibility of collection (for wasting to ensure clean sample) of additional blood in the event an angiocatheter is utilized and the possibility of additional blood collection for recheck of safety labs if deemed necessary by the Investigator.

12. STUDY OBJECTIVES AND ENDPOINTS

12.1 Study Objectives

The primary objective of the study is to assess the safety and tolerability of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients.

The secondary objective of the study is to assess the number and magnitude of daily respiratory symptoms of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients.

The exploratory objectives of the study are to evaluate the following in moderate to severe COPD patients:

1. To assess BAL epithelial brushings for YPL-001 component levels.
2. To compare BAL samples for total cell count (cells/mL) macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; neutrophil, macrophage, lymphocyte, and eosinophil counts as absolute inflammatory cell numbers in YPL-001 groups versus placebo group.
3. To compare BAL samples for TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9 in YPL-001 groups versus placebo group.
4. To compare blood inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) and concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9 in YPL-001 groups versus placebo group.
5. To compare spirometric functions (FEV_1, FVC, FEV_1/FVC, and IC) in YPL-001 groups versus placebo group.
6. To compare patient reported outcomes (BDI/TDI, CAT) in YPL-001 groups versus placebo group.
7. To assess verproside and picroside II concentration in plasma and BAL and verproside and picroside II PK in plasma following multiple oral doses administration of two YPL-001 dose levels.

12.2 Study Endpoints

The primary endpoint is the number and severity of TEAEs following multiple oral doses of YPL-001 or placebo.

The secondary endpoint is the number of symptom free days and overall symptom burden following multiple oral doses of YPL-001 or placebo, assessed by measuring:

- daily PEF;
- major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation;

- dyspnea (using the Modified Borg Dyspnea Scale); and
- activity (using the DASI).

The exploratory endpoints are:

1. YPL-001 component levels in epithelial brushings;
2. BAL biomarkers following multiple oral doses of YPL-001 or placebo, measuring:
   - total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells
   - total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers
   - concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9.
3. Blood biomarkers following multiple oral doses of YPL-001 or placebo, measuring:
   - inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils, and lymphocytes)
   - concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9.
4. Pulmonary function results (spirometry) following multiple oral doses of YPL-001 or placebo.
5. Quality of life scores using the BDI/TDI, CAT questionnaires.
6. Concentrations and PK of verproside and picroside II in plasma following multiple oral doses of YPL-001.
7. Concentrations of verproside and picroside II in BAL following multiple oral doses of YPL-001.

13. INVESTIGATIONAL PLAN

13.1 Overall Study Design and Plan

This is a Phase 2a, proof-of-concept, multicenter, randomized, double-blind, double-dummy, 3-treatment, parallel study, with low and high YPL-001 doses (80 mg and 160 mg BID) and a placebo control, in moderate to severe COPD patients.

At least 60 patients will be enrolled and randomized into 3 treatment groups (20 patients per group). Patients will participate only once. An approximately equal number of current and ex-smokers will be enrolled in the study.

Safety and tolerability will be assessed throughout the study. Assessment of respiratory symptoms and symptom burden in YPL-001 and placebo treatments will be performed daily through patient self-report of PEF, major and minor symptoms of COPD exacerbation, dyspnea, and activity in their e-diary. Spirometry measurement, BAL, and blood samples will be collected for the PD assessment of YPL-001 and placebo treatments. Serial blood samples will also be collected for PK assessment of verproside (the principal active ingredient of YPL-001) and picroside II. Other components of YPL-001 and its metabolites may also be analyzed in plasma.

Following screening, eligible patients will discontinue non permitted respiratory drugs if already receiving them and enter a 14 ± 2 days Run-in Period during which patients will be given albuterol taken on an as required basis and daily tiotropium 18 µg (one capsule inhaled daily in the morning) to be administered at home. On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their daily symptoms throughout the Run-in Period.

Patients will return to the CRU on the morning of Day -1 of the Treatment Period to confirm their eligibility and assess their health conditions. If they still meet all of the inclusion criteria and none of the exclusion criteria, they will undergo Day -1 scheduled study procedures. Patients will return to the CRU the next day (Day 1) to be randomized and receive one of the 3 treatments and undergo all scheduled study procedures. Patients will return on the morning of Days 15 (± 2 days), 29 (± 2 days), 43 (± 2 days), 55, and 56 of the Treatment Period for study drug administration and procedures. Prior to each release from the CRU, patients will receive a properly labeled kit and/or any unused wallets from previously provided kits (when applicable) with sufficient doses which will be self-administered by patients at home until the next morning visit at the CRU. Patients will continue recording their daily symptoms via the e-diary throughout the Treatment Period. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff.

The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

Patients will be instructed to call the Investigator if breathing worsens or if they need to take more than 8 puffs per day of albuterol for more than 2 consecutive days. If the Investigator determines that the patient is too unstable to continue in the study, he/she

will be discontinued. Rescue medication will be used for any patient with an exacerbation of COPD and will be administered in accordance with the study center standard of care.

Discontinued patients may be replaced at the discretion of the Sponsor.

13.2 Study Conduct

Please see the Study Events Flow Chart for a summary of the schedule of study participation and procedures in Section 6.

13.2.1 Screening

Screening will begin within 14 days of Day 1 (inclusive) of the Run-in Period. Informed consent will be obtained at screening (see Section 16.1.3) and prior to any study procedures being performed. Patients will have to meet all eligibility criteria before being enrolled in the study (see Section 13.3). Patients will be informed of the study restrictions (see Section 13.3.5).

The following will be recorded at screening: medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI, and history of tobacco use (including number of pack-year and cigarette smoked per day).

Screening procedures are listed in Section 6.

13.2.2 Patient Confinement

Patients will be admitted to the CRU on the morning of each scheduled visit at a time designated by the CRU as delineated in the Study Events Flow Chart (Section 6). Patients will remain in the clinic through completion of all scheduled study procedures.

13.2.3 Run-In Period (Days 1 to 14 [± 2 days])

Eligible patients will be admitted to the CRU on the morning of Day 1 of the Run-in Period at a time designated by the CRU. Patients will discontinue all restricted concomitant medications as indicated in Section 13.3.5.1 and undergo the Run-in procedures as listed in Section 6.

During the Run-in Period, patients will self-administer tiotropium (Spiriva® HandiHaler®) daily for 14 ± 2 days before Day 1 of the Treatment Period. Patients will be instructed to inhale 1 capsule of tiotropium (Spiriva® HandiHaler®) every morning. Patients will also receive albuterol for as needed use. Patient will keep this rescue albuterol throughout the Run-in Period.

Prior to release from the CRU, patients will receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. They must return the container (empty or not) at the next schedule visit, which is scheduled after 14 ± 2 days.

Each patient will also be issued and trained on the use of the e-diary to record their self-administered doses and their daily respiratory symptoms. Prior to each morning dose, patients will record at home their daily PEF, major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat,

nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

13.2.4 Treatment Period (Days 1 to 56)

Patients who completed the Run-in Period and still meet all the inclusion criteria and none of the exclusion criteria will be randomized to receive one of the assigned treatments (80 mg or 160 mg YPL-001 BID, or placebo BID) on Day 1 through Day 56 (see Section 13.4.1 and Section 13.4.2).

Safety and tolerability will be monitored throughout the Treatment Period as listed in Section 6. Patients will continue to record their self-administered doses and their daily respiratory symptoms on their e-diary. Prior to each morning dose, patients will record at home their daily PEF, major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

BAL samples for YPL-001 concentrations and PD assessments will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

Spirometry and quality of life questionnaires for PD assessments will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

Blood samples for PD and PK assessment will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

13.2.4.1 Meal Schedule

Patients will be required to fast overnight for at least 12 hours before bronchoscopy and BAL collection on Days -1 and 55. On Days 1 and 56, patients will be required to fast overnight for at least 8 hours before and for at least 4 hours after the morning dose. On all other days, patients will be asked to fast for at least 2 hours before and 2 hours after each morning dose. Patients will also be asked to fast for at least 2 hours before and after each evening dose.

Patients will also be required to fast for at least 8 hours before the scheduled serum chemistry tests at the time points delineated in the Study Events Flow Chart (Section 6).

During in-clinic dosing, water (except that administered with dosing) will not be permitted from 1 hour before until 1 hour after each dosing. Water will be allowed as desired at all other times. On all other days, patients will be informed to follow the same restrictions.

On Days 1 and 56, patients will fast from all food and drink except water between meals and snacks. Foods and beverages containing alcohol, xanthines, caffeine, vegetables from the mustard green family, mustard, tea (especially speedwell tea), or grapefruit/Seville oranges will not be served in the CRU. Across all CRUs, menus should be similar in content. The same menu and meal (except for snacks) schedule will be administered uniformly for all patients confined within the same CRU, across all treatment groups. Meals are not required to be completed by patients.

13.2.4.2 Early Termination

Early termination evaluations will be performed on patients prior to early termination. Patients who want to terminate from the study and are not currently on-site will be contacted and asked to return to the CRU to perform the early termination procedures.

The early termination procedures are listed in Section 6.

13.2.5 Follow-up Call (14 ± 2 days)

The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

13.2.6 Scheduled End of Study

The end of the study is scheduled after completion of the evaluations in the 3 treatment groups or after dose-limiting clinical safety endpoints have been reached to preclude continuation of the study. The clinical conduct of the study is intended to last approximately 12 to 24 months.

This time period may change in the event that the study is terminated early, additional time is required to review safety, or a decision is made to complete an unscheduled analysis for a group.

13.3 Selection of Study Population

13.3.1 Number of Patients

The study is planned to enroll at least 60 patients. An approximately equal number of current and ex-smokers will be enrolled. Patients will be divided in 3 treatment groups with 20 patients to receive one of the 3 treatments (i.e., low and high YPL-001 doses [80 mg and 160 mg BID] and a placebo control) as per the randomization schedule. Each treatment group will consist of an approximately equal number of current and ex-smokers.

13.3.2 Inclusion Criteria

Patient candidates must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Adult males and/or females, 30 to 85 years of age (inclusive).
2. History of COPD for at least 12 months prior to screening.
3. Diagnosed with COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines with symptoms compatible with COPD for at least 12 months prior to screening.

4. Classified as moderate to severe COPD based on the current severity classification GOLD Stage 2-3 disease in terms of post-bronchodilator spirometry at screening:
   - Post-bronchodilator FEV_1/FVC ratio of <70%
   - Post-bronchodilator FEV_1 ≥30 % and <80 % of predicted normal values
5. Weigh at least 52 kg for males and 45 kg for females and within the normal range according to accepted normal values of the Body Mass Index (BMI) chart 18.5-40.0 kg/m^2 inclusive.
6. In the judgment of the Investigator, the patient is medically stable with no change in symptoms, medication, or with clinical laboratory results that in the Investigator's opinion are compatible with the diagnosis of either COPD or a complication thereof and are judged acceptable for inclusion with predominantly bronchitic symptoms at screening.
7. Must be on a stable medical regimen for COPD ≥ 30 days prior to screening.
8. In the Investigator's opinion patients should be able to withhold tiotropium 24 hours prior to Day 1 of the Run-in Period, if already receiving it and prior to each scheduled CRU visit.
9. Must have oxygen saturation on room air > 93%.
10. Hemoglobin must be equal to or above the lower limit of normal at screening and check-in.
11. Current or ex-smoker with a history of >10 pack years. Ten pack years are defined as: 20 cigarettes a day for 10 years; 10 cigarettes a day for 20 years; or 40 cigarettes a day for 5 years (i.e., [number of cigarettes smoked per day × number of years smoked]/20). Patients, who undergo smoking cessation therapy, must be completed 3 months prior to screening visit and smoking status should not change between the patient's screening visit and patient's last study visit.
12. For a female of childbearing potential: either be sexually inactive (abstinent) for 14 days prior to the first dose and throughout the study or be using one of the following acceptable birth control methods:
    a. non-hormone releasing intrauterine device in place for at least 3 months prior to the first dose.
    b. surgical sterilization of the partner (vasectomy for 4 months minimum).
    c. physical barrier method (e.g., condom, diaphragm) with spermicide for at least 14 days prior to the first dose and throughout the study.
13. A female patient who claims to be sexually inactive, but becomes sexually active during the course of the study must agree to use a physical barrier method (e.g., condom, diaphragm) with spermicide from the time of the start of sexual activity through to the completion of the study.

14. For a female of non-childbearing potential: must have undergone one of the following sterilization procedures at least 6 months prior to the first dose:

    a. hysteroscopic sterilization;

    b. bilateral tubal ligation or bilateral salpingectomy;

    c. hysterectomy;

    d. bilateral oophorectomy;

    or be postmenopausal with amenorrhea for at least 1 year prior to the first dose and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status as per Investigator judgment.

15. Non-vasectomized males must agree to be sexually abstinent or to use a condom with spermicide when engaging in sexual activity from the first dose through completion of the last scheduled study procedures on Day 56 or upon early termination. Patients will be advised to use a condom with spermicide for 90 days following the last administration of the study drug, and to not donate sperm during this same period of time. In the event that the sexual partner is surgically sterile, use of a condom with spermicide is not necessary. No restrictions are required for vasectomized males provided their vasectomy has been performed 120 days or more prior to study start. Males who have been vasectomized less than 120 days prior to study start must follow the same restrictions as non-vasectomized males.

16. Understands study procedures and provides written informed consent for the trial.

17. Be able to comply with the protocol, such as all the study restrictions, and the assessments therein.

13.3.3 Exclusion Criteria

Patients will be excluded from the study if there is evidence of any of the following criteria at screening or check-in, as appropriate.

1. History of life-threatening COPD including respiratory arrest, intensive care unit admission and/or requiring intubation.
2. History of more than 2 hospitalizations for COPD within 12 months prior to screening.
3. Presentation of an acute exacerbation of COPD that will be associated with increase sputum volume or change in sputum color within 4 weeks before Day 1 of the Run-in Period.
4. Evidence of cor pulmonale, or clinically significant pulmonary hypertension.
5. Continuous use of more than 2L/day of oxygen.
6. History or presence of other respiratory disorders, such as asthma, α-1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis or other chronic pulmonary diseases.
7. A chest X-ray at screening (or within 3 months prior to screening) showing abnormalities, which in the opinion of the Investigator are clinically significant and unrelated to COPD.

8. A history of chronic disease including, but not limited to, unstable or uncontrolled hypertension (or been diagnosed with hypertension in the 6 months before screening), severe sleep apnea (assessed using the Berlin Questionnaire [refer to Section 14.1.8]), cardiovascular, endocrine, neurological, hepatic, gastrointestinal, renal, hematological, urological, immunological or ophthalmic diseases that the Investigator believes are clinically significant e.g., unstable and could impact patient safety by participation in the study.
9. History or presence of:
    - significant cardiac arrhythmia;
    - prostatic hyperplasia;
    - bladder-neck obstruction;
    - urinary retention;
    - narrow-angle glaucoma.
10. Evidence of clinically relevant abnormal baseline hematology, serum chemistry, or urinalysis. Patients with an AST > 2 x ULN, ALT > 2 x ULN, bilirubin > 2 x ULN or creatinine > 2 x ULN (confirmation of results may be done once).
11. Evidence of hepatic impairment with a Child-Pugh class A score or higher.
12. Lung resection or lung reduction surgery within 12 months.
13. Positive alcohol (using urine dipstick or breathalyzer) and/or urine drug testing at screening or at each CRU visit, unless the positive drug screen is due to prescription drug use and is approved by the PI and the medical monitor.
14. Positive testing for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C antibodies (HCV).
15. History or presence of alcoholism or drug abuse within the 2 years prior to Day 1 of the Treatment Period.
16. Hypersensitivity or idiosyncratic reaction to compounds related to YPL-001, including Speedwell tea and herbal remedies.
17. Requires one (or more) routine therapies for COPD during the indicated restricted time period as listed in Section 13.3.5.1.1.
18. Use of any drugs or substances known to be significant inhibitors (strong or moderate) of UDP-glucuronosyltransferase (UGT) (such as 17-beta-estradiol glucuronide, flavonoids [citrus fruit], silybin [herb supplement milk thistle]) and/or sulfotransferases (SULT) (refer to Appendix 1), within 12 hours prior to Day 1 of the Run-in Period. Additional sources may be consulted by the PI or medical monitor to confirm lack of PK/PD interaction with study drug.
19. Blood donation or significant blood loss within 56 days prior to Day 1 of the Treatment Period.
20. Plasma donation within 7 days prior to Day 1 of the Treatment Period.

21. Participation in another clinical trial within 30 days prior to Day 1 of the Run-in Period.
22. Females who are pregnant or lactating.
23. Surgery within the past 3 months prior to Day 1 of the Treatment Period determined by the Investigator to be clinically relevant.
24. Active or history of any disease or condition that would, in the opinion of the Investigator and/or medical monitor, place the patient at an unacceptable risk to participate in this study.

13.3.4 Removal of Patients from the Study

Patient participation in this trial may be discontinued for any of the following reasons:

1. Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol.
2. Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient.
3. The patient interrupts trial study drug administration for more than 7 consecutive days of dosing or missed a total of 17 doses (15%) throughout the Treatment Period.
4. Patient's decision to withdraw.
5. Requirement for prohibited concomitant medication.
6. Patient failure to comply with protocol requirements or study related procedures.
7. Termination of the study by the Investigator, Sponsor, FDA, Celerion, or other regulatory authorities.

The clinical report will include reason(s) for patient withdrawals as well as details relevant to the patient withdrawal. If a patient is withdrawn from the trial prior to study completion, the patient will undergo all procedures scheduled for study completion (early termination evaluations) as the situation allows (see Section 13.2.4.2). Any patient withdrawn due to an AE (whether serious or non-serious) or clinically significant abnormal laboratory test values will be evaluated by the Investigator and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

Patients withdrawn may be replaced at the Sponsor’s discretion.

13.3.5 Study Restrictions

13.3.5.1 Concomitant Therapy

All medications taken during the 30 days prior to the first dose will be recorded and reviewed by the Investigator.

Any medication taken by patients during the course of the study will be recorded. Concomitant medication will be coded using the most current WHO drug dictionary available at Celerion (e.g., 01-MAR-2014 or later). If drug therapy other than that specified by the protocol is taken, a joint decision will be made by the Investigator and Sponsor to continue or discontinue the patient.

13.3.5.1.1 Prohibited Therapy

The following medications are not permitted within the time delineated below and during the study (from Day 1 of the Run-in Period to the completion of the last scheduled study procedures on Day 56 or upon early termination). Intake of these medications during the Run-in Period constitutes a non-eligibility criterion and the patients will not be randomized into the study. If any of these medications are taken during the Treatment Period, the need for this patient to be withdrawn from the study will be carefully evaluated by the Investigator and the Sponsor on the basis of the potential impact on efficacy or safety evaluation and in the patient's best interest:

1. Any medications administered for the treatment of worsening of COPD within 4 weeks prior to Day 1 of the Run-in Period:
   - nebulized, inhaled, oral, IV, IM corticosteroids;
   - oral or parenteral β2 agonists;
   - Antibiotics.
2. Inhaled corticosteroids (ICS), LABA, and/or inhaled ICS/LABA fixed combinations within 12 hours prior to Day 1 of the Run-in Period;
3. Inhaled long acting anticholinergic agents other than tiotropium within 2 weeks prior to Day 1 of the Run-in Period;
4. Inhaled short-acting β2-agonists (SABA) other than albuterol (e.g., terbutaline, fenoterol) within 12 hours prior to Day 1 of the Run-in Period;
5. Inhaled short-acting anticholinergic agents (SAMA) (e.g., ipratropium) within 12 hours prior to Day 1 of the Run-in Period;
6. PDE inhibitors (including roflumilast) within 2 weeks prior to Day 1 of the Run-in Period.
7. Leukotriene modifiers and xanthines derivatives within 2 weeks prior to Day 1 of the Run-in Period.
8. Drugs or substances known to be significant inhibitors (strong or moderate) of UGT and/or SULT, within 12 hours prior to Day 1 of the Run-in Period and through collection of the final PK sample.
9. Acetaminophen will be prohibited 24 hours prior to Day 1 of the Treatment Period and through collection of the final PK sample.
10. Vitamin supplements and herbal products (especially Speedwell) will be prohibited 7 days prior Day 1 of the Treatment Period and through collection of the final PK sample.

13.3.5.1.2 Permitted Therapy

Throughout the study Period (from Day 1 of the Run-in Period to the completion of the last scheduled study procedures on Day 56 or upon early termination) patients will be permitted to take the following medications in addition to the study drugs:

1. Albuterol, as required (except approximately 4 hours before schedule pulmonary function test);
2. Tiotropium (Spiriva® HandiHaler®) 18 µg once a day (except approximately 24 hours before schedule pulmonary function test);
3. Ibuprofen, as required, up to 1200 mg per day for intercurrent illness or AEs. Ibuprofen should not be taken for 2 hours before or after each dosing.
4. In the case of a concomitant disease, appropriate treatment will be permitted if it does not interfere with the study evaluation parameters and does not qualify under the section "Prohibited Therapy" (see Section 13.3.5.1.1)

13.3.5.2 Prohibitions

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/caffeine (other than coffee and tea): 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Alcohol (other than red wine and beer): 48 hours prior to each CRU visit, 48 hours prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts), and mustard: 14 days prior to Day 1 of the Treatment Period through collection of Day 56 last PK sample.
- Fruit Juice: 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Tea (especially Speedwell tea), coffee, and red wine: 7 days prior to Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Grapefruit/Seville orange and beer: 14 days prior to Day 1 of the Treatment Period through collection of Day 56 last PK sample.

13.3.5.3 Activity

Patients will remain ambulatory or seated upright for 1 hour following each study medication administration.

Patients will be advised to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

13.4 Treatments

13.4.1 Treatments administered

13.4.1.1 Drug Administration During Run-in Period

Tiotropium (Spiriva® HandiHaler®) will be supplied as 18 µg capsules for inhalation.

Albuterol will be supplied as 100 µg albuterol base (1 actuation = 100 µg albuterol base) for oral inhalation. Albuterol may be administered via a nebulizer or a metered-dose inhaler.

Multiple oral inhalation of tiotropium (Spiriva® HandiHaler®) 18 µg capsule will be administered QD every morning for 14 ± 2 days during the Run-in Period. Albuterol will be administered on an as needed basis.

13.4.1.2 Drug Administration During Treatment Period

YPL-001 will be supplied as 80 mg tablets for oral administration.

Placebo will be supplied as YPL-001 80 mg matching placebo tablets for oral administration.

Treatments A, B, and C are described as follows:

Treatment A: Multiple oral YPL-001 80 mg doses (1 x 80 mg tablet + 1 x 1 YPL-001 80 mg matching placebo tablet) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56.

Treatment B: Multiple oral YPL-001 160 mg doses (2 x 80 mg tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56.

Treatment C: Multiple oral matching placebo (2 x 1 YPL-001 80 mg matching placebo tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56.

Each dose of Treatments A, B and C will be administered with approximately 240 mL of water.

In all treatments, one tiotropium (Spiriva® HandiHaler®) 18 µg capsule will also be administered QD every morning prior to study drugs administration. Albuterol will be administered on an as needed basis.

YPL-001 or placebo will be dispensed in accordance with the Randomization and Drug Dispensing Instructions provided in a separate document.

Prior to release from the CRU on Days 1, 15 (± 2 days), and 29 (± 2 days), of the Treatment Period, patients will receive a properly labeled new kit, which contains 4 wallets of 2 blister cards, with the appropriate doses which will be self-administered by

patients at home. Any unused wallets from previously provided kits will also be dispensed to patients on Days 15 (± 2 days) and 29 (± 2 days). Prior to release from the CRU on Days 43 (± 2 days), and 55, patients will received unused wallets from previously provided kits with the appropriate doses which will be self-administered by patients at home. Patients will also receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. Patients will record their self-administered doses in their e-diary, and whether the dose was administered with food, and must return the YPL-001 used and unused wallets and the tiotropium and albuterol container (empty or not) at the next schedule visit at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.

Patients will be instructed not to crush, split or chew the study drug.

The exact clock time of dosing will be recorded on on-site dosing days. Patients will be given instructions on how to record their drug administration in their e-diary on home-dosing days.

Each dose will be administered under fasting conditions as described in Section 13.2.4.1.

13.4.1.3 Stopping Rules

A decision to stop or suspend the study will be made jointly by the Sponsor and the Investigator following the review of all pertinent safety and tolerability. Together they will make one of the following determinations:

1. To continue with the study as planned.
2. To continue with the study and add additional safety evaluations.
3. To continue with the study by adjusting to a lower dose if 2 patients at any dose level meets any of the following criteria and the patient was determined to have received YPL-001 after unblinding:
   a. Has a drug–related, unexpected SAE.
   b. Experiences drug-related grade ≥ 3 toxicity.
4. The study will be terminated if ≥ 3 patients at any dose level meet any of the following criteria and the patients were determined to have received YPL-001 after unblinding:
   a. Has a drug–related, unexpected SAE.
   b. Experience drug related grade ≥ 3 toxicity.

PK data will not be required for the dose-escalation decision.

When applicable, a written statement fully documenting the reasons for study termination will be provided to the Institutional Review Board (IRB).

13.4.2 Method of Assigning Patients to Treatment Groups

Each patient will be assigned a unique screening identification number upon screening. Patients who complete the study screening assessments, complete the Run-in Period, and meet all the eligibility criteria will be assigned a unique randomization identification number, different from the screening number, and receive the corresponding product, according to a randomization scheme generated at Celerion. Each treatment group will consist of an approximately equal number of current and ex-smokers.

Patients will receive one of the 3 treatments (Treatments A, B, or C) on one occasion.

If replacement patients are used, the replacement patient number will be 100 more than the original (e.g., Patient No. 0101 will replace Patient No. 0001).

13.4.3 Blinding

This is a double-blind, double-dummy, randomized study.

13.4.3.1 Maintenance of Randomization

A computerized randomization scheme will be created by a Celerion unblinded statistician (who is not otherwise involved in the study) and shall be considered blinded (per the following).

The randomization will not be made available to the Sponsor, patients, or members of the staff responsible for the monitoring and evaluation of safety assessments.

The bioanalytical department will also be blinded to the randomization scheme.

13.4.3.2 Procedures for Breaking the Blind Prior to Study Completion

The site Pharmacist/Study Coordinator will receive two sets of randomization code envelopes, one set for “Current Smokers” and another for “Ex-Smokers”. Each individual envelope is marked on the outside with one of the randomization numbers and contains the treatment for that patient. These envelopes must be kept in a secure locked location.

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the patient.

In the event of a medical emergency, it is requested that the Investigator make every effort to contact the medical monitor or designee prior to breaking the blind. If breaking the blind is required because of a medical emergency, the treatment identity would be revealed by the qualified designee, for that patient only. In the event that the emergency is one, in which it appears that the other patients may be at imminent risk, the blind may be broken for all patients dosed at that dose level. The unblinding should be noted in the patient’s electronic case report form (eCRF).

In all cases where the code is broken, the Investigator should record the date, reason for code breaking and his/her name for signature on the envelope.

At the end of the study, the envelopes will be reviewed by the Sponsor.

13.4.3.3 Revealing of Randomization

In the absence of a medical emergency, the blinded randomization for this entire trial will not be revealed until the following conditions are fulfilled:

1. All data are entered in the database, edits checks are performed, queries closed, CRFs signed by the Investigator, and the database is officially locked.
2. All PK/PD samples have been analyzed and quality checked by the responsible analytical associate.

13.4.4 Treatment Compliance

During in-clinic dosing, a qualified designate will be responsible for monitoring the administration of timed oral doses. When appropriate, a mouth check will be performed by the qualified designate to ensure that the patients have swallowed the study medication. Once a patient has finished the water, the qualified designate will use a flashlight and a tongue depressor to check the side of the mouth, the sides of the upper and lower gums and the area under the tongue. Patients' hands will also be verified to ensure that the medication was ingested.

Self-administration by patients at home will be monitored via the e-diary and attempted phone calls will be performed to remind patients to take their medication, if they did not record their self-administration on the e-diary.

14. STUDY PROCEDURES

14.1 Safety Assessments

This study primarily assesses the safety and tolerability of YPL-001. Safety will be determined by evaluating physical examinations, vital signs, pulse oximetry, ECGs, clinical laboratory parameters, and AEs.

If deemed necessary, additional safety measurements will be performed at the discretion of the Investigator.

Study procedures should be completed as close to the prescribed/scheduled time as possible. The Quality of Life questionnaire should be performed prior to any other procedures. When the following procedures are scheduled at the same time, they will be performed in the following order:

1. Vital signs and pulse oximetry
2. ECG
3. Pulmonary function measurement
4. Bronchoscopy and BAL collection

All other procedures can be performed without specific order.

14.1.1 Body Height and Weight

Body height (centimeters) and body weight (kilograms) will be measured as outlined in the Study Events Flow Chart (Section 6).

14.1.2 Physical Examination

All full physical examinations will include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose and throat, respiratory system, cardiovascular system, gastrointestinal system, neurological condition, blood and lymphatic systems, and the musculoskeletal system.

A licensed physician will examine each patient as outlined in the Study Events Flow Chart (Section 6).

Medical history will be recorded at screening.

Physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator.

14.1.3 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate will be measured as outlined in the Study Events Flow Chart (Section 6).

Vital signs may be taken at any other times, if deemed necessary. Blood pressure and heart rate measurements will be performed with patients in a seated position for at least 1 minute, except when they are supine or semi-reclined because of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the Investigator.

When performed prior to the morning dose, blood pressure and heart rate will be measured within 2 hours prior to dosing. When scheduled postdose, vital signs readings will be performed within approximately 10 minutes of the scheduled time point. When performing the bronchoscopy, vital signs (body temperature, respiratory rate, blood pressure, and heart rate) will be monitored continuously until the end of the procedure.

14.1.4 Pulse Oximetry

Oxygen saturation (%), and heart rate will be assessed using a pulse oximeter. All readings will be performed with a pulse oximeter (oxygen saturation [%], and heart rate) as outlined in the Study Events Flow Chart in Section 6.

When performed prior to the morning dose, pulse oximetry monitoring will be measured within 2 hours prior to dosing. Readings may be taken at other times, if deemed necessary by the Investigator. When performing the bronchoscopy, oxygen saturation will be monitored continuously until the end of the procedure.

Any clinically relevant oxygen saturation reading below 93% will be documented as an AE, as per Investigator discretion.

14.1.5 Electrocardiogram Monitoring

When performed prior to the morning dose, ECG will be measured within 2 hours prior to dosing. When performing the bronchoscopy, ECG will be monitored continuously until the end of the procedure.

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6). Patients will be required to lie quietly in a supine position for at least 5 minute prior to ECG measurements. Single 12-lead ECGs may be performed at various unscheduled time points, if deemed necessary by the Investigator.

Single 12-lead ECGs will be interpreted and signed and dated by the Investigator. The ECGs will be classified as normal, having a non-clinically significant abnormality (NCS), or having a clinically significant abnormality (CS). In addition, ECG parameters of ventricular rate, PQ or PR interval, QRS duration, and QT interval (corrected according to Bazett's formula [QTcB] and uncorrected) will be noted on the CRF.

14.1.6 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 6). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator. The clinical laboratory tests include the following:

14.1.6.1 Hematology

- Hemoglobin
- Hematocrit
- RBC count (including a reticulocytes count)
- Platelet count
- Mean Corpuscular Hemoglobin (MCH)
- Mean Corpuscular Volume (MCV)
- Mean Corpuscular Hemoglobin Concentration (MCHC)
- RDW
- White blood cell (WBC) count with differential (including eosinophil, neutrophil, basophil, lymphocytes, and monocytes)

14.1.6.2 Serum Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.

- BUN
- Creatinine*
- Bilirubin (total and direct)
- Uric acid
- Albumin
- Alkaline phosphatase (ALP)
- Creatine kinase (CK)
- Lactate dehydrogenase (LDH)
- Estimated glomerular filtration rate
- Alpha-1 Antitrypsin**
- AST
- ALT
- Amylase
- Lipase
- Glucose (fasting)
- Carbon dioxide (CO_2)/Bicarbonate (HCO_3)
- Sodium
- Potassium
- Chloride

* Creatinine clearance will be calculated using Cockcroft-Gault formula at screening.

** To be performed at screening only.

14.1.6.3 Serology

- HIV
- HBsAg
- HCV

14.1.6.4 Human Chorionic Gonadotropin (Serum Pregnancy Test)

The test will be performed for females only.

14.1.6.5 Follicle-Stimulating Hormone

The test will be performed in postmenopausal females only.

14.1.6.6 Urinalysis

- pH
- Specific gravity
- Protein
- Glucose
- Ketones
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Leukocyte Esterase

If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination will be performed.

14.1.6.7 Urine/Breathalyzer Alcohol Screen

Alcohol levels will be tested using urine dipsticks or breathalyzers.

14.1.6.8 Urine Drug Screen

- Cannabinoids
- Cocaine
- Amphetamines
- Barbiturates
- Benzodiazepines
- Opiates

14.1.7 Chest X-Ray

A baseline chest x-ray will be performed at the screening visit. If the patient has had an x-ray within the last 3 months prior to the screening visit, and the CRU has access to the report and images, this can be used as the baseline chest x-ray and does not need to be repeated.

14.1.8 Berlin Questionnaire

The Berlin Questionnaire is a validated screening questionnaire used to quickly identify the risk (low to high) of sleep disordered breathing. The questionnaire consists of three categories and risk is based on the responses to individual items and overall scores in the symptom categories. Assessments will be performed according to the Study Events Flow Chart (Section 6). The questionnaire will be provided as a separate document and a copy of the questionnaire to be used will be kept in the study binder.

14.1.9 Adverse Events

14.1.9.1 Adverse Event Definition

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.[3]

14.1.9.2 Monitoring

The patients will be instructed to inform the Investigator or clinic staff of any AEs and intercurrent illnesses experienced during the trial. Additionally, a specific inquiry regarding AEs will be conducted prior to each dosing at the CRU, after the last scheduled study procedures on Day 56 (or upon early withdrawal), and at the follow-up phone call. The inquiry will be made in a non-specific manner using open-ended questions so as not to bias the response (e.g., How have you been feeling since your last visit?).

All symptoms will be evaluated by the Investigator.

Any patient who has a clinically significant AE (whether serious or non-serious) or clinically significant abnormal laboratory test value will be evaluated by the Investigator, or other monitoring physician, and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

Treatment of SAEs will be performed by a physician, either at the CRU or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal or unknown (lost to follow-up).

14.1.9.3 Reporting

AEs will be coded using the most current MedDRA® available at Celerion (e.g., 17.0 or higher). The Sponsor will inform the Celerion Global Project Manager which version is to be used prior to initiation of the study.

The Investigator will review each event and assess its relationship to drug treatment (unrelated, unlikely, possible, probable, definite). The severity of each sign or symptom reported will be graded based on the NIH NCI CTCAE toxicity grading scale 5-point severity scale (Grade 1, 2, 3, 4 and 5) [4] and the date and time of onset, time relationship to drug dosing, duration, and outcome (resolved, improved, unchanged, worse, fatal, or unknown/lost to follow-up) of each event will be noted.

The relationship of each AE will be assessed using the following definitions:

Unrelated	▪ Event occurring before dosing. ▪ Event or intercurrent illness due wholly to factors other than drug treatment.
Unlikely	▪ Poor temporal relationship with drug treatment. ▪ Event easily explained by patient's clinical state or other factors.
Possible	▪ Reasonable temporal relationship with drug treatment. ▪ Event could be explained by patient's clinical state or other factors.

Probable	▪ Reasonable temporal relationship with drug treatment. ▪ Likely to be known reaction to agent or chemical group, or predicted by known pharmacology. ▪ Event cannot easily be explained by patient's clinical state or other factors.
Definite	▪ Distinct temporal relationship with drug treatment. ▪ Known reaction to agent or chemical group, or predicted by known pharmacology. ▪ Event cannot be explained by patient's clinical state or other factors.

The following definitions for rating severity will be used:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**. Note**:** An experience may be severe but may not be serious, e.g., severe headache).
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A semi-colon indicates 'or' within the description of the grade; ADL = Activities of Daily Living

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

14.1.9.4 Serious Adverse Events

If any AEs are serious, as defined by the Food and Drug Administration (FDA) Code of Federal Regulations (CFR), Chapter 21, special procedures will be followed. All SAEs will be reported to the Medical Monitor via fax or e-mail within one working day of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012[3]. The institutional review board (IRB) will be notified of the Alert Reports as per FDA regulations.

If an SAE occurs to a patient on this study, the Medical Monitor is to be contacted (see Section 4).

A SAE is any AE or suspected adverse reaction that in the view of either the Investigator or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

14.2 Symptom Assessments

14.2.1 Electronic Diary

On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their self-administered doses, whether the dose was administered with food, and daily respiratory symptoms throughout the Run-in and Treatment Periods. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff.

Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

14.2.2 Peak Expiratory Flow

PEF assessments will be made daily prior to each dose from Day 1 of the Run-in Period to Day 56 of the Treatment Period. Three measurements will be made at each time point using a hand held PEF meter. Readings not performed in the CRU will be recorded in the patient e-diary. All PEF assessments should be performed before administration of a bronchodilator where possible.

14.2.3 Symptoms of Chronic Obstructive Pulmonary Disease Exacerbation

Patient will be asked to record the major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation via the e-diary before each dosing.

14.2.4 Dyspnea (Modified Borg Dyspnea Scale)

Severity level of patient's dyspnea will be assessed via the modified Borg dyspnea scale programmed within the e-diary. The modified Borg dyspnea scale is a self-administered categorical scale with a score from 0 to 10, where 0 (as a measure of dyspnea) corresponds to the sensation of normal breathing (absence of dyspnea) and 10 corresponds to the patient's maximum possible sensation of dyspnea.

14.2.5 Activity (Duke Activity Status Index)

Patient's functional capacity and activity status will be assessed via the DASI programmed within the e-diary. DASI is a self-administered 12-item questionnaire that assesses daily activities such as personal care, ambulation, household tasks, sexual function and recreation with respective metabolic costs. Each item has a specific weight based on the metabolic cost. The final score ranges between 0 and 58.2 points. The higher the score, the better the functional capacity.

14.3 Pharmacodynamic Assessments

14.3.1 Pulmonary Function (Spirometry)

Spirometry measures will be taken at the time points delineated in the Study Events Flow Chart (Section 6) using a standard calibrated spirometer to determine the parameters detailed below.

- FEV_1;
- FVC (forced vital capacity);
- FEV_1/FVC;
- IC.

Short acting β2-agonist and anticholinergic bronchodilators (e.g., albuterol, ipratropium bromide) and long acting β2-agonist and anticholinergic bronchodilators (e.g., salmeterol, tiotropium) agents will be withheld approximately 4 and 24 hours, respectively, before each pre-bronchodilator spirometry.

Every effort will be made to perform all assessments for a given patient on the same instrument throughout the study.

At screening, baseline pre-bronchodilator spirometry will be performed (prior to albuterol administration) for a minimum of 3 times and a maximum of 8 times in order to obtain 3 manoeuvers with FEV_1 values within 150 mL of each other, using the manoeuver with the highest value of FEV_1 and FVC as the basis for comparison.

Patients shall receive 4 inhalations of albuterol (100 µg/inhalation) for a total dose of

400 µg via metered-dose inhaler using a spacer. Within approximately 20 to 30 minutes after albuterol administration, the baseline post-bronchodilator spirometry will be performed.

Assessment of FEV_1 stability will take place:

1. Prior to Day 1 dosing of the Treatment Period (Day -1 measurement): Predose FEV_1 is defined as the time point prior to Day 1 dosing in the Treatment Period and will be performed pre- and post-bronchodilatator administration. Predose FEV_1 will be compared to the corresponding baseline measurement. If the best FEV_1 measurement at predose on Day -1 of the Treatment Period has declined by greater than 20% from the best FEV_1 at screening, the visit may be rescheduled up to 3 times, at the discretion of the Investigator.

2. Following Day 1 dosing: At all other spirometry time point, measurements will be performed once. If the value shows a difference of greater than 150 mL decline than the best FEV_1 value collected predose on Day -1, up to 3 measures will be performed.

   Consideration should be given, if a patient experiences any change in post Day 1 dose FEV_1 from the Day 1 predose FEV_1 value (measured following dosing with albuterol) equal to or greater than 20 % and should alert the Investigator to consider whether individual patients should continue to dose. The pulmonary function manoeuver(s) used to make this assessment must be valid and meet acceptable quality spirometry standards.

The Investigator may also use his or her discretion as to the completion of dosing for any period in which an FEV_1 decline and/or respiratory symptoms occur(s).

14.3.2 Bronchoscopy and Bronchoalveolar Lavage (BAL) Biomarkers

Patients will be fasted for 12 hours before the bronchoscopy procedures. If required, blood pressure medications can be taken with small sip of water based on preapproval of local Investigator.

14.3.2.1 Bronchoscopy

The bronchoscopy with bronchial brushings will be performed at the time points delineated in the Study Events Flow Chart (Section 6) by a licensed physician experienced in conducting the procedure according to guidelines published on the use of bronchoscopy for research on airway diseases such as COPD.[5,6]

Albuterol will be administered 20 minutes prior to the beginning of the bronchoscopy. An intravenous line will also be established to administer conscious sedation, and to administer emergency medications if the need were to arise. During the procedure, oxygen saturation (S_PO_2), blood pressure, and heart rate and rhythm (continuous electrocardiogram) will be monitored. Oxygen 2-4 L via nasal cannula will be administered during bronchoscopy and oxygen saturation will be maintained at ≥95%. Conscious sedation will be achieved with incremental doses of 1–4 mg midazolam and

50-100 µg fentanyl. Local upper and lower airway topical anesthesia will be achieved with 1% or 2% lidocaine. The dose of lidocaine administered during the procedure will not exceed a total of 450 mg. The bronchoscope will usually be inserted preferably through the nares into trachea. The bronchoscope will be wedged into 2 subsegments of the right middle or lower lobe, as deemed appropriate by the Investigator. Emergency treatments for cardiopulmonary arrest and pneumothorax will be immediately available in the bronchoscopy room. The patient will remain in the recovery suite for observation for a minimum of 2 hours after the procedure.

14.3.2.2 Bronchial Brushings

Prior to BAL, a cytology brush is inserted into the bronchoscope channel and brushings are collected twice from each of 4 quadrants of visible subsegments of the right middle or lower lobe, as deemed appropriate by the Investigator, under direct visualization. The cellular material is washed off in saline following each brushing. The brushing is performed a total of 8 times. The liquid is centrifuged and the cell pellet is stored at -70°C.

Samples must be protected from UV light during collection, processing, and storage.

14.3.2.3 Bronchoalveolar Lavage (BAL)

BAL in the right middle or lower lobe, as deemed appropriate by the Investigator, will be performed at the time points delineated in the Study Events Flow Chart (Section 6) by a licensed physician experienced in conducting the procedure. A total of 180 mL BAL, using 6 x 30 mL aliquots of normal saline warmed to room temperature, will be performed using each subsegment of the right middle or lower lobe, as deemed appropriate by the Investigator. BAL fluid will be aspirated following each 30 mL instillation. The lavage material, which averages 25% return in COPD patients, typically yields 1-10 x 10^6 macrophages. The centrifuged cell pellet and supernatant will be kept cooled until processed or stored as indicated in the laboratory manual to be provided as a separate document.

Samples must be protected from UV light during collection, processing, and storage.

14.3.2.4 Biomarkers

BAL samples will be analyzed for:

- YPL-001 component levels in epithelial brushings;
- total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells
- total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers
- concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9.

14.3.3 Blood Biomarkers

Blood samples will be collected via direct venipuncture or an angiocatheter at the time points delineated in the Study Events Flow Chart (Section 6) for PD assessments of biomarkers. Biomarker assessments include:

- inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils, and lymphocytes)
- concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9.

Blood will be drawn into 3 tubes. A manual for blood sampling, collection, processing, and sample shipment will be provided in a separate document.

14.3.4 Quality of Life Questionnaires

14.3.4.1 Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI)

Dyspnea at baseline (Day -1 of the Treatment Period) will be assessed with the BDI. This instrument has 3 domains (functional impairment, magnitude of task, and magnitude of effort) with the values added for a combined focal score. Functional impairment determines the impact of breathlessness on the ability to carry out activities; magnitude of task determines the type of task that causes breathlessness, magnitude of effort establishes the level of effort that results in breathlessness. The BDI scores range from 0 (very severe impairment) to 4 (no impairment) for each domain with the baseline focal score consisting of the sum of each domain (0 to 12).

Dyspnea throughout the study will be performed at the time points delineated in the Study Events Flow Chart (Section 6). The change from baseline is measured by the TDI score which ranges from -3 (major deterioration) to +3 (major improvement) for each domain with the TDI focal score consisting in the sum of each domain (-9 to +9).

The same Investigator or designee will interview specifically the patients during the study.

A copy of the questionnaire to be used will be kept in the study binder.

14.3.4.2 COPD Assessment Test (CAT)

CAT is a short and simple questionnaire of 8 items completed by patients to be performed at the time points delineated in the Study Events Flow Chart (Section 6). Scores for each of the 8 items are summed to give a single, final score ranging from 0 (no impact on daily activities) to 40 (very high impact on daily activity). This is a measure of the overall impact of a patient's condition on their life. Scores for the individual items within the questionnaire will provide insight into the relative influence that the different components of COPD have on its overall impact on a patient's life.[7,8]

A copy of the questionnaire to be used will be kept in the study binder.

14.4 Pharmacokinetic Assessments

The sampling schedule and/or collection intervals delineated in the Study Events Flow Chart (Section 6) may be modified based on the results from previously dosed patients.

14.4.1 Blood Sampling and Processing

Samples must be protected from UV light during collection, processing, and storage.

Samples will be collected via direct venipuncture or an angiocatheter at the time points delineated in the Study Events Flow Chart (Section 6).

Blood will be drawn into 4 mL pre-chilled evacuated tubes containing K_2EDTA. A manual for blood sampling, collection, processing, and sample shipment will be provided in a separate document.

14.5 Blood Volume for Study Assessments

Table 5: Blood Volume during Study

Sample Type	Number of Time Points	Volume per Time Point*	Sample Volume Over Course of Study
Screening laboratory safety tests (including hematology, serum chemistry, serology), FSH (for postmenopausal female patients only) and serum pregnancy (for female patients only).	1	~ 17 mL	~ 17 mL
On-study serum chemistry and serum pregnancy (for female patients only) when scheduled at the same time	3	~ 8.5 mL	~ 25.5 mL
Additional on-study serum pregnancy (for female patients only)	2	~ 3.5 mL	~ 7 mL
On-study hematology	3	~ 4 mL	~ 12 mL
Blood samples for PD biomarkers (except CRP and fibrinogen)	8	~ 6 mL	~ 48 mL
Blood samples for PD biomarker - CRP	8	~ 4	~ 32
Blood samples for PD biomarker - Fibrinogen	8	~ 3.5	~ 28
Blood samples for PK of verproside and picroside II	37	~ 4 mL	~ 148 mL
Total Blood Volume for males →			~ 310.5 mL**
Total Blood Volume for females →			~ 317.5 mL**

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

** If an angiocatheter is used, up to 5 mL of blood will be used to flush the catheter prior to each collection of PK and/or PD blood samples. Hence the total blood volume collected may increase by approximately 205 mL.

15. DATA ANALYSIS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCPs.

15.1 Statistical Analysis

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a SAP. The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP.

15.1.1 Sample Size Calculation

According to the exploratory nature of this study no formal statistical hypotheses will be tested. However, a sample size of 60 evaluable patients is deemed to be sufficient to assess the safety and tolerability and to provide an indication of the potential effect of YPL-001 on COPD exacerbation symptoms, selected biomarkers and pulmonary function parameters.

15.1.2 Patients to Analyze

Safety population: the safety population data set will include all available data for patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo. Safety data for all discontinued patients will be included in this set for the time points for which their data are available.

Symptom monitoring population: the symptom monitoring population data set will include all available data for patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo. Symptom monitoring data for all discontinued patients will be included in this set for the time points for which their data are available.

PK population:

- The PK full data set will include all patients receiving at least one dose of YPL-001 and having at least one measurable plasma concentration of verproside and picroside II.
- The PK per-protocol data set will include all patients receiving all scheduled doses of YPL-001 and having sufficient samples collected to determine PK parameters from plasma concentrations of verproside and picroside II on Days 1 and/or 56.

PD population:

- The PD full data set will include all patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo and provide at least 1 post-baseline PD measurement.
- The PD per-protocol data set will include all patients receiving all scheduled doses of

the investigational product (i.e., YPL-001) or placebo and having measurable PD data.

PK/PD population: All patients who receive at least one dose of YPL-001 and having any measurable concentration of verproside and picroside II and measurable PD data will be included in the PK/PD relationship assessment, as applicable.

15.1.3 Safety Analysis

The following analyses will be performed. Safety analyses will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data, when appropriate.

Medical History:

Medical history will be listed by patient.

Adverse Events:

AEs will be coded using the most current MedDRA® available at Celerion (e.g., 17.0 or higher) and data will be summarized by SOC and preferred term. The number of TEAEs will be reported. In addition, the number and percent of patients reporting each TEAE will be summarized separately for each treatment.

A by-patient AE data listing, including verbatim term, preferred term, treatment, severity, outcome, and relationship to treatment, will be provided.

Physical Examination:

Changes in physical examinations will be described in the text of the final report and significant findings will be reported as AEs.

Clinical Laboratory Tests, Electrocardiograms, Vital Signs and Pulse Oximetry:

All clinical laboratory tests, 12-lead ECGs, vital signs, and pulse oximetry measurements and their change from baseline, if applicable, will be summarized by treatment and time point of collection.

A shift table describing out-of-normal range shifts will be provided for clinical laboratory results.

A normal-abnormal shift table will be presented for ECGs.

Peak Expiratory Flow:

PEF measurements and its change from baseline, will be summarized by treatment and time point of collection.

Concomitant Medications:

Concomitant medications will be listed by patient and coded using the most current WHO drug dictionary available at Celerion (e.g., 01-MAR-2014 or later).

15.1.4 Symptom Monitoring Analysis

Symptom free days and overall symptom burden will be evaluated and compared across treatment groups. Secondary outcome analysis will be based on treatment actually

received by patients. Descriptive statistics will be calculated for quantitative data and frequency counts will be compiled for classification of qualitative data, when appropriate.

Peak Expiratory Flow and Symptoms of COPD Exacerbation:

PEF measurements and symptoms of COPD exacerbation and their change from baseline will be summarized by treatment and time point of collection.

Dyspnea and Activity:

The Modified Borg Dyspnea Scale and DASI scores will be listed and presented descriptively.

Additional analysis may be performed if deemed appropriate.

15.1.5 Pharmacodynamic Analysis

15.1.5.1 Biomarkers

When applicable, the following PD biomarkers will be summarized by treatment group using descriptive statistics (arithmetic means, SD, CV, N, minimum, maximum, and median). Figures will be created to display mean and individual level or activity as a function of time, as appropriate:

- Pulmonary biomarker (i.e., Pulmonary Function measurements [Spirometry]): pre- and post-bronchodilator change in activity by time point will be calculated relative to the pre- and post-bronchodilator baseline activity;
- BAL biomarkers (i.e., total cell count [cells/mL] of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; total cell count [cells/mL] of neutrophils, macrophages, lymphocytes and eosinophils as absolute inflammatory cell numbers; and concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9): raw and % change from baseline levels; and
- Blood biomarkers (i.e., inflammatory markers [total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes] and concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9): raw and % change from baseline levels.

PK/PD relationship may be explored graphically using scatter plots and an appropriate regression model.

15.1.5.2 Quality of Life

The quality of life parameters reported from the BDI/TDI and CAT questionnaires will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.

15.1.6 Pharmacokinetic Analysis

15.1.6.1 Pharmacokinetic Parameters

15.1.6.1.1 Plasma

PK parameters will be computed from the individual plasma verproside and picroside II concentrations using a noncompartmental approach. Appropriate validated PK software (e.g., WinNonlin Professional) will be used. PK parameters for other components of YPL-001 and its metabolites may also be computed, as appropriate.

The following PK parameters will be computed following Day 1 morning dose:

AUC_{0-12}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to 12 hours.
AUC_{0-t}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (C_t). This parameter will be reported only if plasma concentrations fall below the lower limit of quantitation before the last time point prior to the evening drug administration on Day 1 for at least one patient. Otherwise, only AUC_{0-12} will be reported.
AUC_{0-inf}	Area under the drug concentration-time curve from time zero to infinity, $AUC_{0-inf} = AUC_{0-t} + C_t/k_{el}$, where k_{el} is the terminal elimination rate constant. †
C_{max}	Maximum observed drug concentration.
t_{max}	Time of the maximum drug concentration (obtained without interpolation).
k_{el}	Apparent terminal elimination rate constant, calculated by linear regression of the terminal linear portion of the log concentration vs. time curve. †
$t_{1/2}$	Apparent elimination half-life, calculated as $\ln(2)/k_{el}$. †
CL/F	Oral clearance [$Dose/AUC_{0-inf}$]. †
V_Z/F	Apparent volume of distribution at the terminal phase, calculated as $Dose/(k_{el} * AUC_{0-inf})$.†

† All k_{el} and related PK parameters (AUC_{0-inf}, $t_{1/2}$, CL/F, and V_z/F) will be reported only if the half-life of verproside or picroside II can be appropriately estimated from a 12-hour sampling period following dosing.

The following PK parameters will be computed following Day 56 morning dose:

AUC_{τ}	The area under the plasma concentration versus time curve over the final dosing interval, as calculated by the log-linear trapezoidal method (e.g., 0-12 hours).
AUC_{0-t}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (C_t).
C_{max_ss}	Maximum observed drug concentration at steady-state.
$C_{min,ss}$	Minimum observed/measured non-zero concentration at steady-state.
C_{trough}	Concentration at the end of a dosing interval.
C_{avg}	Ratio of AUC_{τ} to the dosing interval, τ.
%Fluc	Percent fluctuation will be calculated as follows: $\frac{C_{\max\_ss} - C_{\min\_ss}}{C_{avg}} x\ 100$
Swing	Percent swing will be calculated as follows: $\frac{C_{\max\_ss} - C_{\min\_ss}}{C_{\min\_ss}} \text{ x } 100$
t_{max_ss}	Time to reach the maximum drug concentration (obtained without interpolation) at steady-state.
CL_{ss}/F	Total body clearance estimated at steady-state after oral administration, calculated as Dose/AUC_{τ}.
V_{z_ss}/F	Apparent volume of distribution at steady-state, calculated as $(CL_{ss}/F)/k_{el}$.*

* All k_{el} and related PK parameters ($t_{1/2}$ or V_{z_ss}/F) will not be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

If metabolite data are available, metabolite to parent ratios may be calculated for AUC_{0-t}, AUC_{τ}, and C_{max_ss}.

15.1.6.1.2 Bronchoalveolar Lavage

Levels of YPL-001 components in epithelial brushing will be listed.

15.1.6.2 Statistical Methods for Pharmacokinetic Analyses

PK parameters will be summarized by treatment group using descriptive statistics (arithmetic means, SD, CV, N, minimum, maximum, and median). In addition, geometric means will be calculated for AUC_{τ} and C_{max_ss}, as appropriate. Figures will be created to display mean and individual verproside and picroside II concentration-time curves. Additional PK analyses may be performed if deemed appropriate.

No value for k_{el}, $t_{1/2}$, and V_{z_ss}/F, as appropriate, will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

An estimate of the relative systemic exposure of AUC_{τ} and C_{max_ss} will be performed by dose normalized ratio analysis expressing the geometric mean ratio and 90% CI of the geometric mean ratio.

Steady-state will be assessed by visual inspection of predose plasma C_{trough} values on Days 15 (± 2 days), 29 (± 2 days), 43 (± 2 days), and 56 following multiple oral dose administration of YPL-001.

Additional analyses will be performed as deemed necessary upon review of the data.

15.1.7 Assessment of Efficacy

Efficacy will not be assessed in this study.

16. STUDY ADMINISTRATION

16.1 Ethics

16.1.1 Institutional Review Board

This protocol will be reviewed by an IRB and the study will not start until the Board has approved the protocol or a modification thereof. The Board is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The board is ICH compliant.

16.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, GCP, 21 CFR Parts 50, 56, and 312, the ethical princliples set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

16.1.3 Patient Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the patients in non-technical terms. Patients will be required to read, sign and date an informed consent form summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Patients will be given a copy of their informed consent form.

16.2 Termination of the Study

The Sponsor reserves the right to discontinue this study and the Investigator reserves the right to terminate their participation at any time.

16.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion relevant to the quality of this study. Designated personnel of Celerion will be responsible for maintaining quality assurance (QA) and quality control (QC) to ensure that the trial is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and Good Laboratory Practice requirements as well as applicable regulatory requirements.

The Clinical Study Report will be audited by the QA department and the quality assurance audit certificate will be included in the study report.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to statistical database lock.

Patient compliance will be monitored throughout the study via procedures such as questioning at check-in to review inclusion and exclusion criteria, urine drug screen at

check-in, mouth check following dosing, and confinement for all conduct procedures with clinical research staff on site at all times.

16.4 Direct Access to Source Data/Documents

The Investigator must maintain, at all times, the primary records (i.e., source documents) of each patient's data. Examples of source documents are laboratory reports, drug inventory, study drug label records, and eCRFs that are used as the source.

Celerion will ensure that the sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6] 5.1.2 & 6.10). In the event that other trial-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

16.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of YPL-001 80 mg tablets, and matching placebo tablets to allow completion of this study. The lot numbers and expiration dates (where available) of the drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the drugs supplied. At the conclusion of the study, any unused drugs (including placebo) will either be retained by the CRU, or returned to the Sponsor, depending on the specific requirements of the regulatory bodies to whom the study report will be submitted. If no supplies remain, this fact will be indicated in the Drug Accountability section of the final report.

16.6 Data Handling and Record Keeping

Celerion standard eCRFs will be used. Each eCRF is reviewed and signed off by the Investigator.

All raw data generated in connection with this study, together with the original copy of the final report, will be retained at each CRU in a designated storage facility, until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

16.7 Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be discussed between Sponsor and the Investigator. All revisions and/or amendments to the protocol in writing must be approved by the Sponsor, the Investigator, and the IRB before implementation.

16.8 Finance and Insurance

Finance and insurance will be addressed in a separate document.

16.9 Publication Policy

All unpublished information given to Celerion by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor's written consent to publish the article.

17. REFERENCES

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[6] Jarjour NN, Peters SP, Djukanović R, and Calhoun WJ. Investigative use of bronchoscopy in asthma. Am J Respir Crit Care Med. 1998;157(3 Pt 1):692-697.

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[8] The COPD Assessment Test healthcare professional user guide: expert guidance on frequently asked questions (issue 3: February 2012). Jones PW, Jenkins C, Bauerle O (on behalf of the CAT Development Steering Group).

18. APPENDIXES

18.1 Appendix 1 - SULT Drug Interaction Table

The following list provides medications that are substrates and inhibitors of sulfotransferase. Adapted from Zhang H, Cui D, Wang B, Han YH, et al. Pharmacokinetic drug interactions involving 17alpha-ethinylestradiol: a new look at an old drug. Clin Pharmacokinet. 2007;46(2):133-57; Coughtrie MW, Johnston LE. Interactions between dietary chemicals and human sulfotransferases-molecular mechanisms and clinical significance. Drug Metab Dispos. 2001;29(4 Pt 2):522-528; King RS, Ghosh AA, and Wu J Inhibition of human phenol and estrogen sulfotransferase by certain non-steroidal anti-inflammatory agents. Curr Drug Metab. 2006;7(7):745–753; Nagai M, et al. Inhibitory effects of herbal extracts on the activity of human sulfotransferase isoform sulfotransferase 1A3 (SULT1A3). Biol Pharm Bull. 2009;32(1):105-109; and Harris, R. M.; Waring, R. H. Sulfotransferase inhibition: potential impact of diet and environmental chemicals on steroid metabolism and drug. Current Drug Metabolism 2008;9(4):269-275.

Inhibitors
17-beta-estradiol glucuronide
Vitamin C
Brown rice
Beer
Meclofenamate
Nimesulide
Salicylic acid
Acetylsalicylic acid
Naproxen
Banaba extract
Rafuma extract
Grape seed extract
Peanut seed coat extract
Gingko extract
Biloba leaf extract
St. John’s wort
Gymnema
Milk thistle

Celerion Project No.: AA98497

Sponsor Project No.: YPL-001-YJP-130403

IND No.: 114903

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

1. PROTOCOL REVISION HISTORY

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	Final Protocol, Amendment 3 This protocol amendment is generated to clarify and adjust study procedures as listed below. The changes to the protocol are presented with new text in **bold** font and deleted text in ~~strikethrough~~ font. **Serious Adverse Event Contact Information** Drug Safety Solution's Medical Monitor will be contacted in case of serious adverse events. Hence the information under Sponsor Contact for Serious Adverse Events (Medical Monitor) in Section 4 Additional Key Contacts for the Study was corrected as follows: ~~Primary Contact:~~ ~~Yongnam Lee, Ph.D.~~ ~~Principal Scientist,~~ ~~Yungjin Pharm. CO., LTD.~~ ~~#451-20 Cheonho-3 dong, Gangdong-gu, Seoul, 134-721, Republic of Korea~~ ~~Tel.: +82-(31) 546-6980 ext. 220~~ ~~Fax: +82-(31) 546-6983~~ ~~E-mail: nami0209@yungjin.co.kr~~ ~~Mobile: +82-(10) 6311-4228~~ ~~Secondary Contact:~~ ~~Kangrae Ha, B.Sc.~~ ~~E-mail: hakr@yungjin.co.kr~~ **Dr. Kathy Smith** **Drug Safety Solution** **Tel.: +1 919 264-5626** **E-mail: ksmith@drugsafety.biz** Section 14.1.8.4 Serious Adverse Events and Section 13.4.3.2 Procedures for Breaking the Blind Prior to Study Completion was also corrected accordingly. **Certified Clinical Laboratory:** Brigham and Women's Hospital and UAB Lung Health Center clinical laboratories contact information were added to Section 4 Additional Key Contacts for the Study. **Clinical Indication:** As indicated in the objectives of the study, the study will examine the pharmacodynamic (PD) effect of YPL-001 in patients with chronic obstructive pulmonary disease (COPD) only. Therefore, to prevent potential confusion and to capture the intended indication of the study

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	specifically "asthma" was removed from the Clinical Indication in Section 5 synopsis and Section 10.1 Purpose of the Study. **Study Population:** As indicated throughout the protocol, patients will be will be adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3). Hence to be consistent with the GOLD Stage standards, the first sentence under Study Population from Section 5, Synopsis was corrected as follow: "Patients will be adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3) with a predominant bronchitic component ~~and a history of frequent (>2/year) COPD exacerbations,~~ between 40 and 80 years of age (inclusive)." **Randomization and Drug Dispensing** Instruction for randomization and drug dispensing are provided in a separate document. To be consistent with this document, which states that two sets of randomization code envelopes will be provided to site pharmacist/study coordinators and patients will received appropriately labeled kits and/or any unused wallets from previously provided kits (when applicable) for YPL-001 home dosing in addition to the containers for tiotropium/albuterol home dosing, the following section were modified accordingly: • Section 5 Synopsis under Summary of Study Design and Study Products • Section 6 Study Event Flow Chart, Day 1 Study Drug Administration at CRU - Footnotes "k" and "p" • Section 6 Study Event Flow Chart, Days 2 to 55 Study Drug Administration at Home – Footnotes "j" and "o" • Section 13.1 Overall Study Design and Plan • Section 13.4.1.2 Drug Administration During Treatment Period • Section 13.4.3.1 Maintenance of Randomization • Section 13.4.3.2 Procedures for Breaking the Blind Prior to Study Completion In addition, and "X" was also added in the "Randomization" row under Day 1 predose in Section 6 Study Events Flow Chart. **Fasting Conditions** As indicated throughout the protocol, subjects will be required to fast for at least 8 hours before and 4 hours after YPL-001/placebo morning administration on Days 1 and 56. For clarity, footnote "q" was added to Day 1 Study Drug Administration at CRU and footnote "k" was added to Day 56 Study Drug Administration at CRU in Section 6 Study Events

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	Flow Chart. **Analytes to be Measured** As indicated throughout the protocol, blood samples will be collected for the analyses of verproside and picroside II in plasma. Hence, the row identified as "Blood for Verproside Phamacokinetics" on Day 56 of Section 6 Study Events Flow Chart, was corrected to read: "Blood for Verproside **& Picroside II PK**". **End-of-Treatment – Early Termination Procedures** All procedures listed under End-of-Treatment/Early Termination column in Section 6 Study Events Flow Chart are also scheduled to be performed on Day 55 before the bronchoscopy procedures. Therefore, as it is not required to repeat these procedures for two consecutive days, End-of-Treatment procedures were removed on Day 56, however early termination (ET) procedures were listed under the new ET column. Hence, the following sections were corrected accordingly. • Section 6 Study Events Flow Chart • Section 13.2.4.2 End-of-Treatment or Early Termination (Day 56), (renamed Section 13.2.4.2 Early Termination). • Section 13.3.2 Inclusion Criteria – Criterion #16 • Section 13.3.4 Removal of Patients from the Study • Section 13.3.5.1.1 Prohibited Therapy • Section 13.3.5.1.2 Permitted Therapy • Section 14.1.8.2 Monitoring • Section 14.5 Blood Volume for Study Assessments (Table 5: Blood Volume during Study) In addition, the following sentence was added to Section 13.2.4.2 End-of-Treatment or Early Termination (Day 56), (renamed Section 13.2.4.2 Early Termination): "Patients who want to terminate from the study and are not currently on-site will be contacted and asked to return to the CRU to perform the early termination procedures" **Investigator's Brochure Version** In Section 9.1 YPL-001, the Investigator's Brochure version was updated to reflect the reference section and the most recent version of the Investigator's Brochure. **Method of Blood Collection** Throughout the protocol, the option of using an angiocatheter was added. Hence, the following sections were corrected accordingly: • Section 11 Risk/Benefit

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	• Section 14.3.3 Blood Biomarkers • Section 14.4.1 Blood Sampling and Processing • Section 14.5 Blood Volume for Study Assessments **Recording of Meal** To be consistent with clinical sites standard procedures, the last sentence of Section 13.2.4.1 Meal Schedule was corrected as follow: "Meals are not required to be completed by patients ~~and all meals and snacks eaten by patients will be recorded on the CRFs~~.' **Coffee, Tea and Alcohol Prohibition** As indicated in Section 13.3.5.2 Prohibitions, coffee tea, and red wine will be restricted for 7 days prior to Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample. Beer will be restricted for 14 days prior to Day 1 of the Treatment Period through collection of Day 56 last PK sample. Any other product containing xanthines or caffeine will be restricted 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample. Any other alcohol product will be restricted 48 hours prior to each CRU visit, 48 hours prior to dosing on Days 1 and 56 last PK sample. Hence, the xanthines/caffeine prohibition and the alcohol prohibition were corrected as follows for clarification: "Xanthines/caffeine **(other than coffee and tea)**: 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample." "Alcohol **(other than red wine and beer)**: 48 hours prior to each CRU visit, 48 hours prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample." **e-Diary** Home dosing will be recorded using a yes/no answer in the e-diary. Therefore the last sentence of the second to last paragraph of Section 13.4.1.2 Drug Administration During Treatment Period was corrected as follows: ***"***Patients will be given instructions on ~~recording of dosing times~~ **how to record their drug administration** in their e-diary on home-dosing days.' In addition, estimation of sputum quantity was added to the list of major symptoms of COPD exacerbation recorded daily by the patients on their e-diary, "color" and "consistency" was moved as example of sputum quality, and a statement indicating that the e-diary device will be return in case of early termination was also added. Hence, the following sections were corrected accordingly: • Section 5 Synopsis under Secondary Outcome Measures • Section 5 Synopsis under Summary of Study Design • Section 6 Study Events Flow Chart – Day 1, Footnote "j"

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	• Section 6 Study Events Flow Chart – Days 2-55, Footnote "i" • Section 6 Study Events Flow Chart – Day 56, Footnotes "g" and "h" • Section 12.2 Study Endpoints • Section 13.1 Overall Study Design and Plan • Section 13.2.3 Run-In Period (Days 1 to 14 [± 2 days]) • Section 13.2.4 Treatment Period (Days 1 to 56) • Section 14.2.1 Electronic Diary • Section 14.2.3 Symptoms of Chronic Obstructive Pulmonary Disease Exacerbation **Treatment Compliance** Drug administration at home will be monitored by HGE Technologies Inc. via the e-diary. Therefore, the last sentence of Section 13.4.4. Treatment Compliance was corrected as follow: "Self-administration by patients at home will be monitored ~~by the CRU~~ via the e-diary and attempted phone calls will be performed to remind patients to take their medication, if they did not record their self-administration on the e-diary." **Oxygen Saturation** For consistency throughout the protocol, "oxygen levels, saturation (%)" was replaced with "oxygen saturation (%)." **Tiotropium Treatment** As indicated in Section 13.3.2 Inclusion Criteria and Section 13.3.5.1.2 Permitted Therapy, tiotropium will be withheld 24 hours prior to pulmonary function (spirometry) measurements. Hence, the 2nd paragraph of Section 14.3.1 Pulmonary Function (Spirometry), was corrected to read: "Short acting β2-agonist and anticholinergic bronchodilators (e.g., albuterol, ipratropium bromide) and long acting β2-agonist and anticholinergic bronchodilators (e.g., salmeterol, tiotropium) agents will be withheld approximately 4 and ~~12~~ **24** hours, respectively, before each pre-bronchodilator spirometry." **Spirometer Across Clinical Site** The 3rd paragraph of Section 14.3.1 Pulmonary Function (Spirometry) was corrected as follow: "Every effort will be made to perform all assessments for a given patient on the same instrument throughout the study~~ and all sites should be using the same brand and model of spirometer for this study~~." **Bronchoalveolar Lavage (BAL) Collection** It is planned that a maximum of 180 mL BAL will be performed during each planned bronchoscopy procedures. Therefore, to prevent confusion,

DATE/NAME	DESCRIPTION
23-Apr-2015 by Caroline Engel	the second sentence of Section 14.3.2.3, Bronchoalveolar Lavage (BAL) was corrected to read: "A **total of** 180 mL BAL**, using 6 x 30 mL aliquots of normal saline warmed to room temperature,** will be performed ~~in~~ **using** each subsegment of the right middle or lower lobe, as deemed appropriate by the Investigator~~, using 6 x 30 mL aliquots of normal saline warmed to room temperature~~." **Blood Volume for Clinical Safety Laboratory Tests, Pharmacodynamic (PD) Markers and Pharmacokinetic (PK) Samples:** Blood collection volume for PD markers, as indicated in Section 14.3.3 Blood Biomarkers and Section 14.5 Blood Volume for Study Assessments, only accounts for 1 tube. However, 3 tubes will be required to assess CRP (4 mL tube), fibrinogen (3.5 mL tube) and the rest of the PD biomarkers (6 mL tube). The blood volume per time point will be approximately 13.5 mL instead of 4.5 mL. As indicated above, End-of-Treatment listed on Day 56 were removed as the same tests are scheduled on Day 55 before the bronchoscopy procedures. Hence one sample was removed for a total of 3 on-study hematology and serum chemistry tests to be performed throughout the study. In addition, 4 mL of blood will be sufficient for the determination of verproside and picroside II concentration in plasma at each time point. Therefore the total blood volume was corrected to 310.5 mL for males and 317.5 mL for females. Section 14.3.3 Blood Biomarkers, Section 14.4.1 Blood Sampling and Processing, and Section 14.5 Blood Volume for Study Assessments were corrected accordingly. Minor typographic and editorial corrections were made where applicable.
16-Feb-2015 by Caroline Engel	Final Protocol, Amendment 2 This protocol amendment is generated to clarify and adjust study procedures as listed below. **Number of Subjects:** The sample size was revised to 60 subjects as it is sufficient to meet the objectives of the study. In case of dropouts, discontinued patients may be replaced at the discretion of the Sponsor as indicated throughout the protocol. Therefore the following sections were corrected accordingly to indicate that at least 60 subjects are planned to be enrolled and randomized with 20 patients to receive one of the 3 treatments: • Section 5 Synopsis (the 1st sentence of the 2nd paragraph under Summary of Study Design and the 1st and 2nd sentences under Number of Patients). • The 1st sentence of the 2nd paragraph of Section 13.1 Overall Study Design and Plan.

DATE/NAME	DESCRIPTION
16-Feb-2015 by Caroline Engel	• The 1st and 3rd sentences of Section 13.3.1 Number of Patients. • The last sentence of Section 15.1.1 Sample Size Calculation. **Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) and COPD Assessment Test (CAT):** BDI/TDI and CAT questionnaires will not be used as a diagnostic tool to assess the patient's potential to meet all inclusion criteria and none of the exclusion criteria. Therefore these questionnaires are not required at screening. In addition, it is not required to perform them for 2 consecutive days to meet the study objectives and therefore, Day 55 assessments were removed. Section 6 Study Events Flow Chart was corrected accordingly. The first sentence in Section 14.3.4.1 Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) was also corrected to be consistent with Section 6. **Early Termination Procedures:** Weight, and oxygen levels, saturation (%), and heart rate assessed using a pulse oximeter were added to the procedures performed at the end of the Treatment Period on Day 56 or prior to early termination from the study to monitor subject's safety appropriately. A pulmonary function (spirometry) test was also added prior to early termination for safety monitoring. Section 6 Study Events Flow Chart was corrected accordingly. **Recording Concomitant Medication:** Concomitant medication will be recorded at each study visit by the clinical staff in to the electronic data capture system. Therefore, concomitant medications was removed from the list of events that will be recorded by the patients via their e-diary throughout the protocol. The following sections were corrected accordingly: • Footnotes in Section 6 Study Events Flow Chart. • The first sentence of the 4th paragraph of Section 13.2.3 Run-In Period (Days 1 to 14 [± 2 days]). • The 2nd sentence of the 2nd paragraph of Section 13.2.4 Treatment Period (Days 1 to 56). • The 2nd sentence of the first paragraph of Section 14.2.1 Electronic Diary. **Subject Numbering:** The first paragraph of Section 13.4.2 Method of Assigning Patients to Treatment Groups was modified to clarify that the screening number and randomization number are two separate identification number given to each subject at different stages of the study.

DATE/NAME	DESCRIPTION
16-Feb-2015 by Caroline Engel	**Adverse Events Reporting** Footnotes were added to clarify the rating severity definitions in Section 14.1.8.3 Reporting. Minor editorial and typographical corrections were made where applicable.
20-Nov-2014 by Ziv Machnes	Final Protocol, Amendment 1 This protocol amendment is generated to update the study population with regards to smoking frequency, to update the handling procedures for BAL samples, and to clarify other study procedures as listed below. **Study Population:** Section 13.3.2 - Inclusion Criteria, bullet 11 was updated to indicate that the study population will consist only of current and ex-smokers with a history of >10 pack years. As such, the indications for 'packs/year' were replaced with 'pack years' and the allowance for current smokers with <10 pack/years was removed. Wording was added to indicate an approximately equal number of current and ex-smokers will be enrolled, and that each treatment group will consist of an approximately equal number of smokers and ex-smokers. In addition, the stratification criteria for the randomization was updated to consist of either current or ex-smokers. The following sections were affected: • Section 5 – Synopsis (under Study Population and Number of Patients) • Section 13.1 - Overall Study Design and Plan (second paragraph) • Section 13.3.1 – Number of Patients. • Section 13.4.2 - Method of Assigning Patients to Treatment Groups. **BAL Sample Handling:** Section 14.3.2.3 - Bronchoalveolar Lavage (BAL) was updated to indicate that sample handling, processing and storage procedures will be provided in a separate document. **Follow-up Procedures:** The wording in regards to follow-up procedures to be conducted on 14 days (± 2 day), after the last study drug administration, was updated to indicated a phone-call and not a visit, as indicated correctly in Section 6 – Study Event Flow Chart. Study event were updated accordingly. The following sections were affected: • Section 5 – Synopsis (under Duration of Participation for Patients, and Exploratory Outcome Measures [under Blood Assessments, Pulmonary Assessment, and Quality of Life Assessments])

DATE/NAME	DESCRIPTION
20-Nov-2014 by Ziv Machnes	• Section 13.3.5.2 – Prohibitions (under Alcohol) • Section 14.1.8.2 – Monitoring (first paragraph). **Study Duration:** The total duration of the study indicated in Section 5 – Synopsis (under Duration of Participation for Patients) was corrected to 12 weeks to correspond with the actual study duration as indicated throughout the protocol. **Inflammatory Markers in Blood Samples:** The list of cell types to be evaluated as part of the inflammatory markers in the blood was updated to include monocytes instead of macrophages, as macrophages are not expected to be present in blood. The following sections were affected: • Section 5 – Synopsis (under Study Objectives, fourth exploratory objective, and under Exploratory Outcome Measures [under Pharmacodynamic Assesments, Blood Assessments, first bullet]) • Section 12.1 - Study Objectives (fourth exploratory objective) • Section 12.2 - Study Endpoints (third exploratory endpoint) • Section 14.3.3 - Blood Biomarkers (first bullet) • Section 15.1.5.1 - Biomarkers (third bullet) **Neutrophil Evaluation in BAL Samples** Neutrophils were added to the list of cell types to be evaluated as a percentage of the total cell count in BAL samples. The following sections were affected: • Section 5 – Synopsis (under Study Objectives, second exploratory objective and under Exploratory Outcome Measures [under Pharmacodynamic Assessments, Bronchoalveolar Lavage Assessments, second bullet]) • Section 12.1 - Study Objectives (second exploratory objective) • Section 12.2 - Study Endpoints (second exploratory endpoint) • Section 14.3.2.4 - Biomarkers (second bullet) • Section 15.1.5.1 – Biomarkers (second bullet) **Location of Study Drug Administration**: Wording was added in Section 6 – Study Events Flow Chart for Day 56, to clarify that the study drug will be administered at the CRU. **Meal Schedule**: The indication for fasting requirement in Section 13.2.4.1 – Meal Schedule, was corrected to indicate patients will fast overnight for at least 12 hours before bronchoscopy and BAL collection on Days -1 and 55

DATE/NAME	DESCRIPTION
20-Nov-2014 by Ziv Machnes	instead of Days -1 and 56, as correctly indicated in Section 6 – Study Events Flow Chart. **ECG Monitoring:** Following an update in Celerion's standard operating procedure, Section 14.1.5 – Electrocardiogram Monitoring was updated to include at least 5 minutes of rest prior to each ECG measurement (instead of at least 1 minute as previously indicated). **Hematology:** The tests included in the hematology panel Section 14.1.6.1 – Hematology were updated to indicate that the red blood cell (RBC) count will include a reticulocytes count, and that the white blood cell (WBC) count with differential will include monocytes but will not include reticulocytes. **Bronchoscopy and BAL:** Due to the sensitivity of YPL-001 components to UV light, a warning was added to protect all samples from exposure to UV light, as indicated for the PK blood samples. The following sections were affected: • Section 14.3.2.2 - Bronchial Brushings • Section 14.3.2.3 - Bronchoalveolar Lavage (BAL) **PK Population:** The indication for measurable concentration of verproside and picroside II in urine was removed from the definition of PK population in Section 15.1.2 - Patients to Analyze, as there is no urine PK sampling planned for this study. Minor typographic and editorial corrections were made where applicable.
18-Sep-2014 by Caroline Engel	Final Protocol

2. SPONSOR – SIGNATORIES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

Sponsor:

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Sponsor Representative:

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Ryoo Byung Hwan — Signature

23/April/2015 — Date

3. INVESTIGATORS SIGNATURES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

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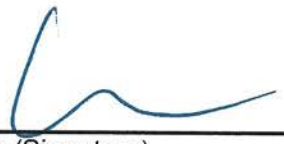

Investigator (Signature)

5/11/15
Date

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Investigator (Signature)

Date

INVESTIGATORS SIGNATURES (*CONTINUED*)

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

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Investigator (Signature)

5/1/2015
Date

4. ADDITIONAL KEY CONTACTS FOR THE STUDY

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5. SYNOPSIS

Compound:	YPL-001
Clinical Indication:	Treatment of inflammatory diseases of the respiratory tract such chronic obstructive pulmonary disease (COPD)
Study Type:	Phase 2a, proof of concept
Study Objectives:	The **primary objective** of the study is to assess the safety and tolerability of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients. The **secondary objective** of the study is to assess the number and magnitude of daily respiratory symptoms of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients. The **exploratory objectives** of the study are to evaluate the following in moderate to severe COPD patients: 1. To assess bronchoalveolar lavage (BAL) epithelial brushings for YPL-001 component levels. 2. To compare BAL samples for total cell count (cells/mL) macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; neutrophil, macrophage, lymphocyte and eosinophil counts as absolute inflammatory cell numbers in YPL-001 groups versus placebo group. 3. To compare BAL samples for tumor necrosis factors alpha (TNF-α), interleukin (IL)-1β, IL-4, IL-5, IL-6, IL-8, IL-13, myeloperoxidase (MPO), neutrophil elastase, monocyte chemotactic protein (MCP)-1, and matrix metalloproteinase (MMP)-9 in YPL-001 groups versus placebo group. 4. To compare blood inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) and concentrations of C-reactive protein (CRP), fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9 in YPL-001 groups versus placebo group. 5. To compare spirometric functions (forced expiratory volume in one second [FEV_1], forced vital capacity [FVC], FEV_1/FVC, and inspiratory capacity [IC]) in YPL-001 groups versus placebo group. 6. To compare patient reported outcomes (Baseline Dyspnea Index [BDI]/Transition Dyspnea Index [TDI], COPD Assessment Test [CAT]) in YPL-001 groups versus placebo group. 7. To assess verproside and picroside II concentration in plasma and BAL and verproside and picroside II pharmacokinetics (PK) in plasma following multiple oral doses administration of two YPL-001 dose levels.

Summary of Study Design:	This is a Phase 2a, proof-of-concept, multicenter, randomized, double-blind, double-dummy, 3-treatment, parallel study, with low and high YPL-001 doses (80 mg and 160 mg twice daily [BID]) and a placebo control in moderate to severe COPD patients. At least 60 patients will be enrolled and randomized into 3 treatment groups (20 patients per group). Patients will participate only once. Safety and tolerability will be assessed throughout the study. Assessment of respiratory symptoms and symptom burden in YPL-001 and placebo treatments will be performed daily through patient self-report of peak expiratory flow (PEF), major and minor symptoms of COPD exacerbation, dyspnea, and activity in their electronic diary (e-diary). Spirometry measurement, bronchoalveolar lavage (BAL), and blood samples will be collected for the pharmacodynamic (PD) assessment of YPL-001 and placebo treatments. Serial blood samples will also be collected for PK assessment of verproside (the principal active ingredient of YPL-001) and picroside II. Other components of YPL-001 and its metabolites may also be analyzed in plasma. Following screening, eligible patients will discontinue non permitted respiratory drugs if already receiving them and enter a 14 ± 2 days Run-in Period during which patients will be given albuterol taken on an as required basis and daily tiotropium 18 µg (one capsule inhaled daily in the morning) to be administered at home. On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their daily symptoms throughout the Run-in Period. Patients will return to the clinical research unit (CRU) on the morning of Day -1 of the Treatment Period to confirm their eligibility and assess their health conditions. If they still meet all of the inclusion criteria and none of the exclusion criteria, they will undergo Day -1 scheduled study procedures. Patients will return to the CRU the next day (Day 1) to be randomized and receive one of the 3 treatments and undergo all scheduled study procedures. Patients will return on the morning of Days 15, 29, 43, 55, and 56 of the Treatment Period for study drug administration and procedures. Prior to each release from the CRU, patients will receive a properly labeled YPL-001 kit (and/or any unused wallets from previously provided kits [when applicable]) and tiotropium/albuterol container with sufficient doses which will be self-administered by patients at home until the next morning visit at the CRU. Patients will continue recording their daily symptoms via the e-diary throughout the Treatment Period. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff. The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any adverse event (AE) has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary. Patients will be instructed to call the Investigator if breathing worsens or if they need to take more than 8 puffs per day of albuterol for more than 2 consecutive days. If the Investigator determines that the patient is too unstable to continue in the study, he/she will be discontinued. Rescue medication will be used for any patient with an exacerbation of COPD and will be administered in accordance with the study center standard of care.

Study Population:	Patients will be adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3) with a predominant bronchitic component, between 40 and 80 years of age (inclusive). An approximately equal number of current and ex-smokers will be enrolled.
Number of Patients:	The study is planned to enroll at least 60 patients. Patients will be divided in 3 treatment groups with 20 patients to receive one of the 3 treatments (i.e., low and high YPL-001 doses [80 mg and 160 mg BID] and a placebo control) as per the randomization schedule. Each treatment group will consist of an approximately equal number of current and ex-smokers.
Duration of Participation for Patients:	The planned length of participation in the study for each patient is approximately 12 weeks (from Day 1 of the Run-in Period through completion of the follow-up procedures on Day 70 [± 2 days]).
Duration of Study Conduct:	The study is planned to take place over approximately 12 to 24 months (from screening of the first patient through completion of all study procedures for the last patient). This time period may change in the event that the study is terminated early, additional time is required to review safety, or a decision is made to complete an unscheduled analysis for a group.
Study Products:	YPL-001 will be supplied as 80 mg tablets for oral administration. Placebo will be supplied as YPL-001 80 mg matching placebo tablets for oral administration. YPL-001 or placebo will be dispensed in accordance with the Randomization and Drug Dispensing Instructions provided in a separate document.
Dosage, Dosage Form, Route, and Dose Regimen:	Treatments are described as follows: Treatment A: Multiple oral YPL-001 80 mg doses (1 x 80 mg tablet + 1 x 1 YPL-001 80 mg matching placebo tablet) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56. Treatment B: Multiple oral YPL-001 160 mg doses (2 x 80 mg tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56. Treatment C: Multiple oral matching placebo (2 x 1 YPL-001 80 mg matching placebo tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56. In all treatments, one tiotropium (Spiriva® HandiHaler®) 18 µg capsule will also be administered QD every morning prior to study drugs administration. Albuterol will be administered on an as needed basis. Each dose of Treatments A, B, and C will be administered orally with approximately 240 mL of water.

Stopping Rules:	A decision to stop or suspend the study will be made jointly by the Sponsor and the Investigator following the review of all pertinent safety and tolerability. Together they will make one of the following determinations: 1. To continue with the study as planned. 2. To continue with the study and add additional safety evaluations. 3. To continue with the study by adjusting to a lower dose if 2 patients at any dose level meets any of the following criteria and the patient was determined to have received YPL-001 after unblinding: a. Has a drug–related, unexpected serious adverse event (SAE). b. Experiences drug-related grade ≥ 3 toxicity. 4. The study will be terminated if ≥ 3 patients at any dose level meet any of the following criteria and the patients were determined to have received YPL-001 after unblinding: a. Has a drug–related, unexpected SAE. b. Experience drug related grade ≥ 3 toxicity.
Primary Outcome Measures	Safety and tolerability will be monitored through physical examinations, vital signs, pulse oximetry, ECGs, clinical laboratory tests, and AEs.
Safety and Tolerability Analysis	The following analyses will be performed. Safety analyses will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data, when appropriate. **Medical History:** Medical history will be listed by patient. **Adverse Events:** AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion (e.g., 17.0 or higher) and data will be summarized by System organ class (SOC) and preferred term. The number of treatment-emergent AEs (TEAEs) will be reported. In addition, the number and percent of patients reporting each TEAE will be summarized separately for each treatment. A by-patient AE data listing, including verbatim term, preferred term, treatment, severity, outcome, and relationship to treatment, will be provided. **Physical Examination:** Changes in physical examinations will be described in the text of the final report and significant findings will be reported as AEs. **Clinical Laboratory Tests, Electrocardiograms, Vital Signs, and Pulse Oximetry Measurements:** All clinical laboratory tests, 12-lead ECGs, vital signs, and pulse oximetry measurements and their change from baseline, if applicable, will be summarized by treatment and time point of collection. A shift table describing out-of-normal range shifts will be provided for clinical laboratory results. A normal-abnormal shift table will be presented for ECGs.

Safety and Tolerability Analysis (continued):	**Concomitant Medications:** Concomitant medications will be listed by patient and coded using the most current World Health Organization (WHO) drug dictionary available at Celerion (e.g., 01-MAR-2014 or later).
Secondary Outcome Measures:	PEF, major (e.g., estimated sputum quality (e.g., color, consistency), and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (Duke Activity Status Index [DASI]) self-reported daily by the patients using an e-diary.
Symptom Monitoring Analysis:	Symptom free days and overall symptom burden will be evaluated and compared across treatment groups. Secondary outcome analysis will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative data and frequency counts will be compiled for classification of qualitative data, when appropriate. **Peak Expiratory Flow and Symptoms of COPD Exacerbation:** PEF measurements and symptoms of COPD exacerbation and their change from baseline will be summarized by treatment and time point of collection. **Dyspnea and Activity:** The Modified Borg Dyspnea Scale and DASI scores will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.
Exploratory Outcome Measures:	**Pharmacodynamic Assessments:** <u>Bronchoalveolar Lavage Assessments:</u> BAL samples will be collected at baseline and again at the completion of the study for PD assessments of biomarkers. Biomarker assessments include: 1. epithelial brushings for YPL-001 component levels; 2. total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells 3. total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers 4. concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9. <u>Blood Assessments:</u> Blood samples will be collected at screening, and throughout the study for PD assessments of biomarkers. Biomarker assessments include: 1. inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) 2. concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9. <u>Pulmonary Assessment:</u> Pulmonary function measurements (spirometry [FEV_1, FVC, FEV_1/FVC, and

Exploratory Outcome Measures (continued):	IC] will be performed at screening, and throughout the study. Quality of Life Assessments: Patient reported outcomes (e-diary, BDI/TDI, CAT) will be performed at baseline, and throughout the study. **Pharmacokinetic Assessments:** Bronchoalveolar Lavage Assessments: BAL samples will be collected at baseline and again at the completion of the study to determine verproside and picroside II concentrations in BAL. Other components of YPL-001 and its metabolites may also be analyzed. Plasma Assessments: Serial blood samples will be collected prior to the initial dosing and through 12 hours following dosing on Days 1 and 56 to determine verproside and picroside II concentrations in plasma. Predose samples will also be collected in the morning of Days 15, 29, 43 and 56 for C_{trough} determination. Other components of YPL-001 and its metabolites may also be analyzed. The sampling schedule and/or collection intervals may be modified based on the results as the study progress.
Pharmacodynamic Analysis:	**Blood, Plasma, and Pulmonary biomarkers:** When applicable, the raw data and % change from baseline or placebo, as appropriate, for PD markers (BAL biomarkers, blood biomarkers, and pulmonary biomarker) will be summarized by time point and treatment using descriptive statistics (arithmetic means, standard deviations [SD], coefficients of variation [CV], sample size [N], minimum, maximum, and median). Figures will be created to display mean and individual level or activity as a function of time. **Quality of Life:** The quality of life parameters will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.
Pharmacokinetic Parameters and Analysis:	Noncompartmental PK parameters, including AUC_{0-t}, AUC_{0-inf}, AUC_{τ}, k_{el}, C_{max}, C_{max_ss}, C_{min_ss}, C_{trough}, t_{max}, t_{max_ss}, CL/F, CL_{ss}/F, V_z/F, V_{z_ss}/F, and $t_{1/2}$, as appropriate, will be calculated from plasma concentrations of verproside and picroside II from patients who received YPL-001 only. Additional PK parameters may be calculated if deemed appropriate. Plasma PK parameters may also be calculated for other components of YPL-001 and its metabolites. PK parameters will be summarized by treatment using descriptive statistics. Relative exposure of verproside and picroside II will be assessed between the two YPL-001 dose levels, and steady-state will be assessed by visual inspection in the active treatment groups. Verproside and picroside II concentration in BAL samples from patients who received YPL-001 only will be listed.

6. STUDY EVENTS FLOW CHART

Study Procedures[a]	Screen[b]	Run-in Period		Treatment Period																			
Days →		1	2-14 (±2)	-1	1																		
Hours →					Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12
Administrative Procedures																							
Informed Consent	X																						
Inclusion/Exclusion Criteria	X	X																					
Medical History	X																						
Randomization					X																		
Safety Evaluations																							
Physical Examination[c]	X			X[d]																			
Height	X																						
Weight	X			X[d]																			
Chest X-ray[e]	X																						
12-Lead Electrocardiogram	X			X[f]																			
Vital Signs[g]	X			X[f]	X						X		X						X				
Pulse Oximetry	X			X[f]																			
Hem, Chem, and UA[h]	X			X[d]																			
Serum Pregnancy Test (♀ only)	X			X[d]																			
Serum FSH (postmenopausal ♀ only)	X																						
Urine Alcohol & Drug Screen	X			X[d]																			
HIV/Hepatitis Screen	X																						
AE Inquiries																							
AE Monitoring										X													
ConMeds Monitoring	X									X													
Symptoms Monitoring																							
Diary Training		X																					
Diary Use[i]										X													
PEF, COPD exacerbation, dyspnea and activity[j]										X													
Study Drug Administration																							
Tiotropium Administration[p]		X	X	X	X																		
Study Drug Administration at CRU[k,q]						X																	X
Pharmacodynamic																							
Pulmonary Function (Spirometry)[l]	X			X[d]																			

Study Procedures[a]	Screen[b]	Run-in Period		Treatment Period																		
Days →		1	2-14 (±2)	-1	1																	
Hours →					Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12
Pharmacodynamic																						
Bronchoscopy and BAL Biomarkers[m]				X																		
Blood Biomarkers	X				X						X											
BDI/TDI & CAT				X[d]																		
Pharmacokinetic																						
Blood for Verproside & Picroside II PK					X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]
Other Procedures																						
Visit & Return Visits[o]	X	X		X	X																	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.
b. Within 14 days of Day 1 (inclusive) of the Run-in Period.
c. A full physical examination will be performed at screening. Symptom-driven physical examinations will be performed at other scheduled times, and may be performed at other times at the Investigator's discretion.
d. To be performed prior to the bronchoscopy procedures.
e. To be performed at screening or within 3 months (inclusive) of screening.
f. ECGs, vital sign and pulse oximetry will be measured within 2 hours of bronchoscopy procedures. During the bronchoscopy procedures and BAL sample collection, patients will be continuously monitored for ECGs, vital signs (blood pressure, heart rate, respiration rate, and body temperature), and oxygen saturation.
g. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
h. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.
i. Patients will be provided with an e-diary device to record their self-administered doses, whether the dose was administered with food, and daily respiratory symptoms.
j. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).
k. Prior to release from the CRU, patients will receive a properly labeled kit with sufficient study drug for their assigned treatment which will be self-administered by patients at home until the next morning visit at the CRU. Patients must return the used and unused wallets at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.
l. Pulmonary function will be performed prior to and 20 to 30 minutes after inhalation of approximately 400 µg albuterol.
m. Bronchoscopy and BAL sample collection will be performed following a 12-hour fast.
n. To be performed prior to dosing.
o. Patients will be admitted to the CRU at the time indicated by the CRU.
p. Patients will receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. They must return the container (empty or not) at the next schedule visit.
q. On Day 1, patients will be required to fast overnight for at least 8 hours before and 4 hours after YPL-001/placebo morning administration.

STUDY EVENTS FLOW CHART *(CONTINUED)*

Study Procedures[a]	Treatment Period											
Days →	2-14	15		16-28	29		30-42	43		44-54	55	
Hours →		AM	PM		AM	PM		AM	PM		AM	PM
Safety Evaluations												
Physical Examination[b]					X[c]						X[d]	
Weight					X[c]						X[d]	
12-Lead Electrocardiogram					X[c]						X[e]	
Vital Signs[f]		X[c]			X[c]			X[c]			X[e]	
Pulse Oximetry											X[e]	
Hem, Chem, and UA[g]					X[c]						X[d]	
Serum Pregnancy Test (♀ only)		X[c]			X[c]			X[c]			X[d]	
Urine Alcohol & Drug Screen		X[c]			X[c]			X[c]			X[d]	
AE Inquiries		X[c]			X[c]			X[c]			X[d]	
AE Monitoring	X											
ConMeds Monitoring	X											
Symptoms Monitoring												
Diary Use[h]	X											
PEF, COPD exacerbation, dyspnea and activity[i]	X											
Study Drug Administration												
Tiotropium Administration[o]	X											
Study Drug Administration at CRU		X			X			X			X	
Study Drug Administration at Home[j]	X		X	X		X	X		X	X		X
Pharmacodynamic												
Pulmonary Function (Spirometry)[k]		X[c]			X[c]			X[c]			X[n]	
Bronchoscopy and BAL Biomarkers[l]											X[c]	
Blood Biomarkers		X[c]			X[c]			X[c]				
BDI/TDI & CAT		X[d]			X[d]			X[d]				
Pharmacokinetic												
Blood for Verproside & Picroside II PK		X[c]			X[c]			X[c]				
Other Procedures												
Return Visits[m]		X			X			X			X	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.
b. Symptom-driven physical examinations will be performed at scheduled times, and may be performed at other times at the Investigator's discretion.
c. To be performed or completed prior to dosing.
d. To be performed or completed prior to bronchoscopy procedures and/or dosing.
e. ECGs, vital sign and pulse oximetry will be measured within 2 hours of bronchoscopy procedures. During the bronchoscopy procedures and BAL sample collection, patients will be continuously monitored for ECGs, vital signs (blood pressure, heart rate, respiration rate, and body temperature), and oxygen saturation.
f. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
g. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.
h. Patients will be provided with an e-diary device to record their self-administered doses, whether the dose was administered with food, and daily respiratory symptoms.
i. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).
j. Prior to release from the CRU on Days 15, 29, 43, and 55 patients will receive a properly labeled kit and/or any unused wallets from previously provided kits (when applicable) with sufficient study drug for their assigned treatment which will be self-administered by patients at home until the next morning visit at the CRU. Patients must return the used and unused wallets at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.
k. Pulmonary function will be performed prior to and 20 to 30 minutes after inhalation of approximately 400 µg albuterol.
l. Bronchoscopy and BAL sample collection will be performed following a 12-hour fast.
m. Patients will be admitted to the CRU at the time indicated by the CRU.
n. To be completed prior to bronchoscopy procedures and dosing.
o. Patients will receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. They must return the container (empty or not) at the next schedule visit.

STUDY EVENTS FLOW CHART *(CONTINUED)*

Study Procedures[a]	Treatment Period																		ET[b]	FU[c]
Days →	56																			
Hours →	Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12		
Safety Evaluations																				
Physical Examination[d]																			X	
Weight																			X	
12-Lead Electrocardiogram																			X	
Vital Signs[e]	X						X		X						X			X	X	
Pulse Oximetry																			X	
Hem, Chem, and UA[f]																			X	
Serum Pregnancy Test (females only)																				
Urine Alcohol & Drug Screen	X																			
AE Inquiries	X																		X	
AE Monitoring	X																			X
Concomitant Medication Monitoring	X																			
Symptoms Monitoring																				
Diary Use[g]	X																		X	
PEF, COPD exacerbation, dyspnea and activity[h]	X																			
Study Drug Administration																				
Tiotropium Administration	X																			
Study Drug Administration at CRU[k]		X																		
Pharmacodynamic																				
Pulmonary Function (Spirometry)																			X	
Blood Biomarkers	X[i]						X													
BDI/TDI & CAT	X[i]																			
Pharmacokinetic																				
Blood for Verproside & Picroside II PK	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Other Procedures																				
Return Visits[j]	X																		X	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.

b. To be performed prior to early termination from the study.

c. The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

d. Symptom-driven physical examinations will be performed at scheduled times, and may be performed at other times at the Investigator's discretion.

e. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.

f. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.

g. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff.

h. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

i. To be performed at predose on Day 56 or upon early termination.

j. Patients will be admitted to the CRU at the time indicated by the CRU.

k. On Day 56, patients will be required to fast overnight for at least 8 hours before and 4 hours after YPL-001/placebo morning administration.

Abbreviations: ♀ = Female, AE = Adverse events, AM = Morning, BAL = bronchoalveolar lavage, BDI/TDI = Baseline Dyspnea Index/Transition Dyspnea Index Test, CAT = COPD Assessment Test, Chem = Serum chemistry, COPD = chronic obstructive pulmonary disease, CRU = Clinical research unit, ConMeds = Concomitant medication, DASI = Duke Activity Status Index, ECG = Electrocardiogram, e-diary = electronic diary, ET = Early termination, FSH = Follicle-stimulating hormone, Hem = Hematology, HIV = Human immunodeficiency virus, IL= interleukin, PEF = Peak expiratory flow, PK = Pharmacokinetics, PM = Evening, Preg = Serum pregnancy, Screen = Screening, UA = Urinalysis.

7. TABLE OF CONTENTS

8. ABBREVIATIONS

Only those uncommon abbreviations specific to this study are listed. Pharmacokinetic (PK) parameter abbreviations and definitions may be found in Section 15.1.6.1.

AE	Adverse event
AHR	Airway hyper-responsiveness
ALD	Approximate lethal dose
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
BALF	Bronchoalveolar lavage fluid
BDI	Baseline Dyspnea Index
BID	Twice daily
BLQ	Below the lower limit of quantification
BMI	Body mass index
bpm	Beat per minute
BUN	Blood urea nitrogen
°C	Degrees Celsius
CAT	COPD Assessment Test
Chem	Chemistry
CFR	Code of Federal Regulations
CK	Creatine kinase
CNS	Central nervous system
CO_2	Carbon dioxide
Coag	Coagulation
COPD	Chronic obstructive pulmonary disease
CRO	Contract Research Organization
CRP	C-reactive protein
CRU	Clinical research unit

CS	Clinically significant abnormality
CSC	Cigarette smoking condensate
CXCL	Chemokine (C-X-C motif) ligand
CV	Coefficient of variation
DASI	Duke Activity Status Index
dL	Deciliter
DRF	Dose range finding
e-diary	Electronic diary
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
ERS	European Respiratory Society
F	Female
°F	Degrees Fahrenheit
FDA	Unites States Foods and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FU	Follow-up
FVC	Forced vital capacity
g	gram
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HBsAg	hepatitis B surface antigen
HCO_3	Bicarbonate
HCV	hepatitis C antibodies
HED	Human equivalent dose
Hem	Hematology
HIV	Human immunodeficiency virus
hr	Hour
IC	Inspiratory capacity
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroid

IgE	Immunoglobulin E
IL	Interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
kg	Kilogram
kg/m^2	Kilogram per meter squared
LABA	long acting beta agonist
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
LOQ	Limit of quantitation
LPS	Lipopolysaccharide
LSM	Least-squares means
µg	Microgram
m^2	Square meter
M	Male
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCO	Myeloperoxidase
MCP	Monocyte chemotactic protein
MCV	Mean Corpuscular Volume
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
MIP	Monocyte inhibitory protein
mL	Milliliter
mmHg	Millimeter of mercury
MMP	Matrix metalloproteinase
msec	Millisecond
MTD	Maximum Tolerated Dose
N	Sample size
NCS	Not clinically significant

ng	Nanogram
No.	Number
NOAEL	No observed adverse effect levels
OTC	Over-the-counter
OVA	Ovalbumin
PD	Pharmacodynamic(s)
PEF	Peak expiratory flow
PK	Pharmacokinetic(s)
QA	Quality Assurance
QC	Quality Control
QT	Interval between the Q and T waves on the electrocardiogram tracing
QTcF	Corrected QT interval with Fridericia's formula
RBC	Red blood cell
RDW	Red cell distribution width
Resp	Respiration
ROS	Reactive oxygen species
SABA	Short-acting β2-agonist
SAD	Single ascending dose
SAE	Serious adverse event
SAMA	Short-acting anticholinergic agent
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SULT	Sulfotranferase
TBIL	Total bilirubin
TDI	Transition Dyspnea Index
TEAE	Treatment-emergent adverse event
Th	T helper
TNF-α	Tumor necrosis factors alpha
UA	Urinalysis
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal

US	United States
WBC	White blood cell
WHO	World Health Organization

9. INTRODUCTION AND BACKGROUND

This study is being conducted as the third in a series of studies for the clinical development of YPL-001. The trial will be conducted in compliance with the protocol, GCP, and applicable regulatory requirements. The patient population will be comprised of moderate to severe (GOLD Stage 2-3) COPD patients.

9.1 YPL-001

YPL-001 drug product is an oral dosage form of an herbal extract from the aerial parts of the plant Speedwell (*Pseudolysimachion rotundum* subsp. *Subintegrum*). *Pseudolysimachion* (*Veronica*) is a perennial herb which has been used as a traditional medicine in Korea and China for the treatment of inflammatory diseases of the respiratory tract such as asthma and COPD.

As a botanical drug product, the drug substance is a mixture of chemical species (iridoids [including verproside] and other related compounds) and biological activity is considered to be from the mixture and not from an individual component. It is unknown if the total activity from individual components is additive or synergistic. Five active constituents, classified as iridoids, have been identified in the herbal extract: verproside, picroside II, catalpolside, isovanilloyl catalpol, and 6-*O*-veratroylcatalpol. Recent experimentation has revealed that the principal active ingredient in *Pseudolysimachion* is verproside, a dihydroxylated catalpol derivative.

YPL-001, containing verproside and other active ingredients, is being developed as a potential oral treatment for long term inflammatory diseases of the respiratory tract such as asthma or bronchitic COPD. Current long term control medications include corticosteroids, cromolyn sodium, immunomodulators, long acting beta agonists, (LABAs), methylxanthines, and leukotriene modifiers. YPL-001 belongs most closely with the leukotriene modifier class of drug.

A brief overview of available information regarding YPL-001 follows below. Details can be found in the YPL-001 Investigator's Brochure of June 3, 2014. [1]

9.1.1 Preclinical Trials

9.1.1.1 Pharmacology

Five *in vivo* primary pharmacology studies have been completed.

In ovalbumin-sensitized mice, an animal model for asthma, YPL-001 reduced elevated immunoglobulin E (IgE), IL-4, IL-5, IL-13, airway hyper-responsiveness, and mucus hyper-secretion.

In the lipopolysaccharide (LPS)- and cigarette smoking condensate (CSC)-induced COPD mice model, verproside and roflumilast treatment inhibited the accumulation of neutrophils in Bronchoalveolar lavage fluid (BALF) as well as the increase of several proinflammatory cytokines and chemokines. Neutrophil infiltration induced by LPS and CSC treatments was associated with a significant increase in BALF levels of the chemoattractants, TNF-α, chemokine (C-X-C motif) ligand (CXCL)-1, and monocyte inhibitory protein (MIP)-2. These data also demonstrated that the effect of YPL-001 and verproside involves down-regulation of the influx of neutrophils and production of TNF-α,

CXCL-1, and MIP-2 molecules which play a major role in tissue remodeling.

YPL-001 significantly suppressed the increase of inflammatory cell counts, particularly neutrophils in BALF and also effectively suppressed elevated levels of TNF-α, CXCL-1 and MIP-2 with the reduction in airway inflammatory responses in CSC- and LPS-induced COPD mice.

YPL-001 also effectively suppressed the increased inflammatory cell count, particularly neutrophils in BALF and also significantly inhibited elevated levels of TNF-α, IL-1β and IL-6 with the reduction in reactive oxygen species (ROS) production and elastase activity in cigarette smoke- and LPS-induced COPD mice.

In the LPS- and cigarette smoke-induced COPD rats model, YPL-001 significantly inhibited the increase of inflammatory cell count, particularly neutrophils in BALF and also effectively suppressed elevated levels of TNF-α, IL-1β, IL-6, MIP-2 and CRP.

YPL-001 effectively inhibited development of both T helper (Th)2 and Th1/Th17 type asthma in these murine models. These effects resulted from inhibition of cytokine and chemokine production by infiltrated inflammatory cells and antigen specific T cells in lymph nodes. YPL-001 did not inhibit development of COPD which was induced by *E.coli* extracellular vesicles.

9.1.1.2 Pharmacokinetics

After oral administration of YPL-001 at 12.5, 25, and 50 mg/kg doses (5.225, 10.45, and 20.9 mg/kg as verproside) in rats, verproside was rapidly absorbed; verproside was detected at the first blood sampling time (5 min) and absorbed rapidly, with the t_{max} achieved at 0.46-0.61 hour for all three doses. The post-absorption phase of the mean plasma verproside concentration-time profiles showed a poly-exponential decay.

The area under the plasma concentration-time curve (AUC) and the maximum plasma concentration (C_{max}) of verproside were linearly increased as the oral dose of YPL-001 increased. Alternately, the dose normalized (based on 12.5 mg/kg) AUCs and C_{max} of verproside were comparable among different doses studied. The elimination half-lives ($t_{1/2}$), 2.14 – 3.91 hours, and other PK parameters of verproside for all three doses were also comparable. These findings indicate that the PK parameters of verproside were independent of doses.

The fraction of dose of verproside excreted unchanged in urine at 24 hours was less than 0.10%. Verproside was not detected in the 24 hours feces sample for all three doses studied. These results indicate that verproside is almost completely eliminated by the first pass metabolism due to O-methylation, glucuronidation, sulfation, and intestinal microflora-mediated metabolism. Verproside is metabolized to verproside glucuronides (M1 and M2), verproside sulfates (M3 and M4), O-methylverproside such as picroside II (M5) and isovanilloylcatalpol (M6), 3,4-dihydroxybenzoic acid (M11), 3-methyoxy-4-hydroxybenzoic acid (M15) and 3-hydroxy-4-methoxybenzoic acid (M16), which are further metabolized to their glucuronides and sulfates including M5 glucuronide (M7), M5 sulfate (M9), M6 glucuronide (M8), M6 sulfate (M10), M11 glucuronide (M12), M11 sulfates (M13 and M14), M15 glucuronides (M17 and M18), M15 sulfate (M20), M16 glucuronide (M19), and M16 sulfate (M21). The O-methylation of verproside to picroside II (M5) and isovanilloylcatalpol (M6) followed by glucuronidation and sulfation

were identified as the major metabolic pathway in bile and urine samples.

Picroside II, a major metabolite of verproside, was detected in plasma samples but most plasma concentrations in 12.5 and 25 mg/kg YPL-001 treated groups were below the lower limit of quantification (LLOQ, 2.5 ng/mL) compared to 50 mg/kg YPL-001 treated group. The picroside II-to-verproside AUC ratios in the 50 mg/kg YPL-001 treated group were 13.9-65.1%, suggesting that picroside II may be one of the major YPL-001 metabolites. Plasma concentrations of isovanilloylcatalpol, a metabolite of verproside and isomer of picroside II, were below LLOQ (2.5 ng/mL) after oral administration of all three YPL-001doses tested.

Verproside, catalposide, and picroside II were not considerably bound to human plasma proteins; the binding values were 36.3-55.0% at verproside concentrations of 0.1, 1.0, and 10.0 μg/mL, 31.2-49.5% at catalposide concentrations of 0.5, 1, and 10 μg/mL, and 34.0-41.2% at picroside II concentrations of 0.5, 1, and 10 μg/mL.

9.1.1.3 Toxicology

Two single dose toxicity studies with YPL-001 have been completed in rat and dog. In the rat study, polyuria was observed in the 5,000 mg/kg dosing group of each sex between 2-4 hours after YPL-001 administration. Discolored stool was observed dose-dependently in the all dosing groups of each sex at 1-3 days post administration. Soft stool, mucous stool and soiled perineal region were observed at 1 day after administration in the 2,500 and 5,000 mg/kg dosing group of each gender. There were no notable changes of body weight in any study group. There were no notable gross necropsy findings in any of the study groups. Based on the results above, when YLP-001 is administered orally to Sprague-Dawley rats, the approximate lethal dose (ALD) is higher than 5,000 mg/kg. In the dog study, There were no changes with respect to the toxicity of the test article in the clinical signs, body weight change and necropsy findings after a single dose. Vomiting and discoloration of stool was noted. The Maximum Tolerated Dose (MTD) was determined to be 2,000 mg/kg for males and 1,000 mg/kg for females.

Two dose range finding (DRF) studies with YPL-001 have been completed in rat and dog, followed by two pivotal, 4-week, GLP repeated-dose toxicology studies in the same species. In the rat DRF study, YPL-001 induced anemia and hemolysis at 667 mg/kg/d and at higher doses. In addition, enlargement of cecum was observed at 667 mg/kg/d and at higher doses. The NOEL for this study was 74 mg/kg/d in both genders. In the dog DRF study, decreases in red blood cell (RBC) values were present in males at the high dose level (1000 mg/kg/d). In females the TBIL values were elevated at the 1000 mg/kg/d dose levels. Females had enlarged spleens at 125, 250 and 1000 mg/kg dose levels without dose relationship (trend was toward significance). The MTD for this study was 1000 mg/kg/d.

Primary results from the pivotal, 4-week rat study included:

There were no abnormal clinical signs observed in any group during dosing or the recovery periods and no mortality was reported.

Hematology: Compared to controls, there were decreases in values of RBC, hematocrit, and hemoglobin at all dose levels of both genders in a dose-dependent fashion. The

values of hemoglobin distribution width, red cell distribution width (RDW) and reticulocyte at all dose levels of both genders were higher or significantly higher than those of vehicle control.

Clinical Biochemistry: There were significant increases in the values of TBIL at all dose levels of both genders when compared with that of vehicle control. After the recovery period, there were no noticeable changes related to the test article.

Organ Weights: Slight increase in absolute & relative weights of the spleen at 540 mg/kg/d in males and notable increase in absolute & relative weights of the spleen at all dose levels of females were observed. Weights of left and right kidneys in female at 540 mg/kg/d were significantly higher than that of vehicle control. After the recovery period, the absolute weights of the spleen and both kidneys in both genders at 540 mg/kg/d were significantly higher than that of vehicle control.

Necropsy Findings: At necropsy, 6 cases of dark reddish discoloration of spleen were observed at 540 mg/kg/d in both genders, and 1 case of enlargement of cecum was observed at 540 mg/kg/d in female. After the recovery period, one case of dark reddish discoloration of spleen was observed at 540 mg/kg/d in the female. The histopathology examination revealed increased hematopoiesis of spleen at the high dose in both genders.

No Observed Adverse Effect Levels (NOAEL): The NOAEL for this study was 180 mg/kg/d for both genders.

Primary results from the pivotal, 4-week dog study included:

YPL-001 colored stool with/without soft stool or diarrhea was persistently observed in both sexes at 1000 mg/kg/d during the dosing period. It was not observed during the recovery period. No mortality was reported.

Hematology: There were no treatment-related changes.

Clinical Biochemistry: The TBIL increased in a dose-dependent manner in both genders at 111, 333 and 1000 mg/kg/d, and it was not recovered completely after the 2-week recovery period.

Organ Weights: There were no treatment-related changes.

Necropsy Findings: Slight red discoloration of mucous membranes in the stomach or duodenum was observed in female treatment groups but not observed after the 2-week recovery period.

NOAEL: The NOAEL for this study was 1000 mg/kg/d for both genders.

9.1.2 Clinical Experience

To date, 2 studies have been conducted in healthy subjects, a randomized, double-blind, placebo-controlled, sequential single ascending dose (SAD) clinical study (AA98496) and a randomized, double-blind, placebo-controlled, sequential multiple ascending dose (MAD) clinical study (AA98495).

9.1.2.1 SAD study

All 5 cohorts of 8 subjects (6 active and 2 placebo), with one cohort crossing over to assess food effect, were dosed and completed. All dosed levels (i.e., 40, 80, 160, 240, and 320 mg) were well tolerated with no SAEs reported during the conduct of the study. All 9 AEs reported in 7 subjects were mild in severity and the most frequent AE reported, regardless of causality, was headache. Of the 7 AEs experienced by subjects receiving the active drug, the Investigator considered 2 of these to be possibly related (nausea, and vomiting), 2 unlikely related, and 3 unrelated. Of the 2 AEs experienced by subjects receiving placebo, the Investigator considered 1 of these to be possibly related (headache), and 1 unrelated.

Plasma samples were analyzed using a validated bioanalytical method. Verproside concentrations were lower than concentrations observed from the animal PK data. The limit of quantitation (LOQ) was approximately 20% of the C_{max} after a single 160 mg dose and approximately 10% of the C_{max} after a single 320 mg dose. Therefore, the half-life could not be well characterized since only a few PK concentrations were available for the estimation.

Verproside appeared to be rapidly absorbed following oral administration and independent on dose, as suggested by median t_{max} values of approximately 0.5 to 0.67 hours under fasting conditions. Verproside appeared to be cleared rapidly from plasma, with mean $t_{1/2}$ values under 1 hour; plasma verproside concentrations were below the lower limit of quantification (BLQ) for all subjects by 6 hours postdose. Table 1 below summaries the PK parameters of verproside following single-dose administrations of YPL-001 at each dose level:

Table 1 Summary of PK Parameters

Pharmacokinetic Parameters	Dose Level Mean ± SD					
	40 mg (N = 1)[a]	80 mg (N = 6)[b]	160 mg (fasting) (N = 6)[c]	160 mg (fed) (N = 6)[d]	240 mg (N = 6)[e]	320 mg (N = 6)[f]
C_{max} (ng/mL)	1.19	1.14 ± 0.328	2.90 ± 1.76	1.08 ± 0.287	4.78 ± 5.66	4.49 ± 1.44
t_{max} (hr)[g]	0.4969	0.6682 (0.5158, 1.0025)	0.5074 (0.3331, 0.6700)	1.2538 (0.9994, 2.0008)	0.5867 (0.3486, 1.5022)	0.5057 (0.3419, 1.5014)
AUC_{0-t} (ng·hr/mL)	0.7422	0.7520 ± 0.3818	2.5616 ± 1.7947	1.2822 ± 0.3599	5.4567 ± 5.0158	5.3612 ± 0.8664
AUC_{0-inf} (ng·hr/mL)	·	·	3.8048 ± 1.8238	·	8.2199 ± 5.3327	6.2162 ± 0.7776
$t_{1/2}$ (hr)	·	·	0.677 ± 0.263	·	0.919 ± 0.176	0.713 ± 0.100

[a] Individual values are presented for the 40 mg dose level
[b] N=5 for AUC_{0-t}
[c] N=3 for AUC_{0-inf} and $t_{1/2}$,
[d] N=4 for AUC_{0-t}
[e] N=3 for AUC_{0-inf}, and $t_{1/2}$,
[f] N=5 for AUC_{0-inf}, and $t_{1/2}$,
[g] t_{max} is presented as Median (Minimum, Maximum)
· = Value missing or not reportable

9.1.2.2 MAD Study

In total, 2 cohorts of 8 subjects and 1 cohort of 10 subjects received multiple YPL-001 doses of 80, 160, or 240 mg BID. Each cohort was constituted of 2 subjects receiving placebo and the remaining subjects receiving the active drug. All dose levels were well tolerated. There were no deaths or SAEs in this study. One (1) subject was discontinued due to the AE of chest pain. Overall, TEAEs were experienced by 38% of subjects in this study. The Investigator considered 1 AE (chest pain) to be possibly related to study drug and the remaining AEs unlikely or unrelated. There were no treatment-related trends in physical examination, laboratory, vital sign, or ECG assessments in this study.

Verproside appeared to be rapidly absorbed following multiple-dose oral administration, as suggested by median t_{max} values of approximately 0.5 - 0.9 hours and independent of dose. Following a multiple oral doses of YPL-001, verproside appeared to be cleared rapidly from plasma, with mean $t_{½}$ values under 1.6 hours, and plasma verproside concentrations were BLQ for most subjects by 12 hours postdose.

Picroside II appeared to be also rapidly absorbed following single- and multiple-dose oral administration, as suggested by median t_{max} values of approximately 0.6 to 0.9 hours and independent of dose. Following a single oral dose of YPL-001, picroside II appeared to be cleared rapidly from plasma, with mean $t_{½}$ values under 1 hour, CL/F values of 14000 – 18500 L/hour, and plasma picroside II concentrations BLQ by 10 - 12 hours postdose. Following multiple oral doses, mean $t_{½}$ values were under 2.5 hours, and plasma picroside II concentrations were BLQ for most subjects by 12 hours postdose.

For all 3 dose levels, minimal to modest accumulation of verproside and picroside II was observed following BID administration of YPL-001 for 2 weeks. The mean peak and total exposure of verproside and picroside II in plasma appeared to increase in a dose-dependent manner between 80 and 160 mg of YPL-001, but no increase in plasma bioavailability was observed between 160 and 240 mg dose levels. Table 2 and Table 3 below summaries the PK parameters of verproside and picroside II, respectively, following multiple-dose administrations of YPL-001 at each dose level:

Table 2 Summary of Verproside PK Parameters

Pharmacokinetic Parameters	YPL-001 Dose Level Mean ± SD		
	80 mg	**160 mg**	**240 mg**
AUC_t (pg*hr/mL)	4709 ± 4080 (N=6)	10860 ± 11424 (N=6)	9658 ± 9246 (N=5)
AUC_{0-t} (pg*hr/mL)	4596 ± 4127 (N=6)	10770 ± 11489 (N=6)	9566 ± 9298 (N=5)
C_{max_ss} (pg/mL)	2414 ± 1281 (N=6)	6737 ± 7342 (N=6)	5458 ± 4387 (N=5)
t_{max_ss} (hr)*	0.756 (0.252, 2.00) (N=6)	0.759 (0.329, 1.50) (N=6)	0.528 (0.272, 0.751) (N=5)
$t_{½}$ (hr)	1.47 ± 0.425 (N=6)	1.30 ± 0.406 (N=6)	1.57 ± 0.236 (N=5)

* = t_{max_ss} is presented as median (minimum, maximum)

Table 3 Summary of Picroside II PK Parameters

Pharmacokinetic Parameters	YPL-001 Dose Level Mean ± SD		
	80 mg	**160 mg**	**240 mg**
AUC_{τ} (pg*hr/mL)	2556 ± 599 (N=2)†	4287 ± 4369 (N=4)†	1985 ± 1024 (N=5)
AUC_{0t} (pg*hr/mL)	1124 ± 1044 (N=6)	3024 ± 3877 (N=6)	1804 ± 949 (N=5)
C_{max_ss} (pg/mL)	419 ± 240 (N=6)	1116 ± 1391 (N=6)	751 ± 490 (N=5)
t_{max_ss} (hr)*	0.756 (0.252, 2.00) (N=6)	0.759 (0.329, 1.50) (N=6)	0.748 (0.524, 0.751) (N=5)
$t_{½}$ (hr)	2.23 ± 0.254 (N=6)	1.84 ± 0.395 (N=6)	2.08 ± 0.793 (N=5)

* = t_{max_ss} is presented as median (minimum, maximum)
. = Value missing or not reportable

10. RATIONALE

10.1 Purpose of the Study

This study will be the initial exploration of multiple-dose administration of YPL-001 in COPD patients. The assessments of the safety, tolerability, COPD symptoms, PD, and PK of verproside and picroside II following administration of multiple doses of YPL-001 will guide decisions to further develop the drug and support the compound as a useful clinical candidate in the treatment of inflammatory diseases of the respiratory tract such as COPD and the data generated will support larger studies in patients with inflammatory diseases of the respiratory tract such COPD to demonstrate safety and evidence of efficacy and clinical benefit.

10.2 Dose Selection

This will be the first COPD patient study of YPL-001.

YPL-001 appeared well tolerated in a panel of standard animal toxicology studies. In the initial studies in humans, the initial dose of YPL-001 was justified conservatively according to the United States (US) Food and Drug Administration (FDA) guidance document “Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers”.[2]

Accordingly, the single and multiple dose escalation study (AA98496) initiated single doses at the 40 mg and 80 mg level, respectively. Dose escalations up to 320 mg and 240 mg in the SAD and MAD studies, respectively, were reached. All cohorts have been completed and all doses administered were well tolerated in human subjects and no clear pattern of toxicity is apparent.

Based on the review of safety, tolerability, and PK data from Cohorts 1 to 5 of the SAD study (AA98496) and Cohorts 1 to 3 of the MAD study, and the in vivo efficacy data in rat and mouse models, it is predicted that the therapeutic range should be between 1.2 mg/kg and 4.8 mg/kg which is equivalent to 84 mg to 336 mg daily in a 70 kg patient. Therefore, a low YPL-001 dose of 80 mg BID and the high YPL-001 dose of 160 mg BID were selected for this proof-of-concept study.

The total strength (23.75 mg) of identified compounds in YPL-001 as a whole in the 40 mg starting dose administered in the first-time-in-human dose escalation study (AA98496) corresponded to approximately 35% of the dosages that have been used in the traditional medicine setting in China (68.65 mg). In this present proof-of-concept study the total strength (47.50 mg) of identified compounds in the initial starting dose of 80 mg is still lower than the dosages that have been used in the traditional medicine setting in China, as shown in Table 4, corresponding to 70% of the traditional Chinese medicine.

Table 4: Traditional Chinese Medicine Use Versus Proposed Clinical Starting Dose

Identified Compounds in YPL-001	1.40 g (Single Dose) Traditional Chinese Medicine[a] (mg)	2.80 g/day (Divided Dose) Traditional Chinese Medicine[a] (mg)	80 mg (Single Dose) for MAD Study[b] (mg)
Verproside	47.94	95.88	30.64
Veratric acid	2.10	4.20	1.08
Catalpolside	3.77	7.54	4.08
Picroside II	3.43	6.86	3.36
Isovanilloyl catalpol	3.53	7.06	4.72
6-*O*-veratroyl catalpol	7.88	15.76	3.62
Total	68.65	137.30	47.50

[a] Traditional medicine dosage from Chinese Medical Great Dictionary; Zhong Yao Da Ci Dian.
[b] Proposed dosage of YPL-001 in MAD study

11. RISK/BENEFIT

YPL-001 is being developed as a potential oral treatment for long term control of persistent asthma and COPD. YPL-001 belongs most closely with the leukotriene modifier class of drug and has the potential to inhibit the accumulation of neutrophils the increase of several proinflammatory cytokines and chemokines which play a major role in tissue remodeling. The development of a product to improve the treatment of asthma and COPD will be of benefit to the wider community/patients with respiratory disease.

The safety monitoring practices employed by this protocol (i.e., physical examination, vital signs, pulse oximetry, 12-lead ECG, hematology, serum chemistry, urinalysis, AE monitoring, and AE questioning) are deemed adequate to protect the patients' safety and should detect all expected TEAEs. The procedures employed in this study to assess efficacy are primarily non-invasive and present no undue risk to the patient.

The approximate volume of blood planned for collection from each patient over the course of the study (see Section 14.5), presents no undue risk to the patients nor does the possibility of collection (for wasting to ensure clean sample) of additional blood in the event an angiocatheter is utilized and the possibility of additional blood collection for recheck of safety labs if deemed necessary by the Investigator.

12. STUDY OBJECTIVES AND ENDPOINTS

12.1 Study Objectives

The primary objective of the study is to assess the safety and tolerability of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients.

The secondary objective of the study is to assess the number and magnitude of daily respiratory symptoms of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients.

The exploratory objectives of the study are to evaluate the following in moderate to severe COPD patients:

1. To assess BAL epithelial brushings for YPL-001 component levels.
2. To compare BAL samples for total cell count (cells/mL) macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; neutrophil, macrophage, lymphocyte, and eosinophil counts as absolute inflammatory cell numbers in YPL-001 groups versus placebo group.
3. To compare BAL samples for TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9 in YPL-001 groups versus placebo group.
4. To compare blood inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) and concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9 in YPL-001 groups versus placebo group.
5. To compare spirometric functions (FEV_1, FVC, FEV_1/FVC, and IC) in YPL-001 groups versus placebo group.
6. To compare patient reported outcomes (BDI/TDI, CAT) in YPL-001 groups versus placebo group.
7. To assess verproside and picroside II concentration in plasma and BAL and verproside and picroside II PK in plasma following multiple oral doses administration of two YPL-001 dose levels.

12.2 Study Endpoints

The primary endpoint is the number and severity of TEAEs following multiple oral doses of YPL-001 or placebo.

The secondary endpoint is the number of symptom free days and overall symptom burden following multiple oral doses of YPL-001 or placebo, assessed by measuring:

- daily PEF;
- major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation;

- dyspnea (using the Modified Borg Dyspnea Scale); and
- activity (using the DASI).

The exploratory endpoints are:

1. YPL-001 component levels in epithelial brushings;
2. BAL biomarkers following multiple oral doses of YPL-001 or placebo, measuring:
   - total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells
   - total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers
   - concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9.
3. Blood biomarkers following multiple oral doses of YPL-001 or placebo, measuring:
   - inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils, and lymphocytes)
   - concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9.
4. Pulmonary function results (spirometry) following multiple oral doses of YPL-001 or placebo.
5. Quality of life scores using the BDI/TDI, CAT questionnaires.
6. Concentrations and PK of verproside and picroside II in plasma following multiple oral doses of YPL-001.
7. Concentrations of verproside and picroside II in BAL following multiple oral doses of YPL-001.

13. INVESTIGATIONAL PLAN

13.1 Overall Study Design and Plan

This is a Phase 2a, proof-of-concept, multicenter, randomized, double-blind, double-dummy, 3-treatment, parallel study, with low and high YPL-001 doses (80 mg and 160 mg BID) and a placebo control, in moderate to severe COPD patients.

At least 60 patients will be enrolled and randomized into 3 treatment groups (20 patients per group). Patients will participate only once. An approximately equal number of current and ex-smokers will be enrolled in the study.

Safety and tolerability will be assessed throughout the study. Assessment of respiratory symptoms and symptom burden in YPL-001 and placebo treatments will be performed daily through patient self-report of PEF, major and minor symptoms of COPD exacerbation, dyspnea, and activity in their e-diary. Spirometry measurement, BAL, and blood samples will be collected for the PD assessment of YPL-001 and placebo treatments. Serial blood samples will also be collected for PK assessment of verproside (the principal active ingredient of YPL-001) and picroside II. Other components of YPL-001 and its metabolites may also be analyzed in plasma.

Following screening, eligible patients will discontinue non permitted respiratory drugs if already receiving them and enter a 14 ± 2 days Run-in Period during which patients will be given albuterol taken on an as required basis and daily tiotropium 18 µg (one capsule inhaled daily in the morning) to be administered at home. On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their daily symptoms throughout the Run-in Period.

Patients will return to the CRU on the morning of Day -1 of the Treatment Period to confirm their eligibility and assess their health conditions. If they still meet all of the inclusion criteria and none of the exclusion criteria, they will undergo Day -1 scheduled study procedures. Patients will return to the CRU the next day (Day 1) to be randomized and receive one of the 3 treatments and undergo all scheduled study procedures. Patients will return on the morning of Days 15, 29, 43, 55, and 56 of the Treatment Period for study drug administration and procedures. Prior to each release from the CRU, patients will receive a properly labeled kit and/or any unused wallets from previously provided kits (when applicable) with sufficient doses which will be self-administered by patients at home until the next morning visit at the CRU. Patients will continue recording their daily symptoms via the e-diary throughout the Treatment Period. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff.

The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

Patients will be instructed to call the Investigator if breathing worsens or if they need to take more than 8 puffs per day of albuterol for more than 2 consecutive days. If the Investigator determines that the patient is too unstable to continue in the study, he/she

will be discontinued. Rescue medication will be used for any patient with an exacerbation of COPD and will be administered in accordance with the study center standard of care.

Discontinued patients may be replaced at the discretion of the Sponsor.

13.2 Study Conduct

Please see the Study Events Flow Chart for a summary of the schedule of study participation and procedures in Section 6.

13.2.1 Screening

Screening will begin within 14 days of Day 1 (inclusive) of the Run-in Period. Informed consent will be obtained at screening (see Section 16.1.3) and prior to any study procedures being performed. Patients will have to meet all eligibility criteria before being enrolled in the study (see Section 13.3). Patients will be informed of the study restrictions (see Section 13.3.5).

The following will be recorded at screening: medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI, and history of tobacco use (including number of pack-year and cigarette smoked per day).

Screening procedures are listed in Section 6.

13.2.2 Patient Confinement

Patients will be admitted to the CRU on the morning of each scheduled visit at a time designated by the CRU as delineated in the Study Events Flow Chart (Section 6). Patients will remain in the clinic through completion of all scheduled study procedures.

13.2.3 Run-In Period (Days 1 to 14 [± 2 days])

Eligible patients will be admitted to the CRU on the morning of Day 1 of the Run-in Period at a time designated by the CRU. Patients will discontinue all restricted concomitant medications as indicated in Section 13.3.5.1 and undergo the Run-in procedures as listed in Section 6.

During the Run-in Period, patients will self-administer tiotropium (Spiriva® HandiHaler®) daily for 14 ± 2 days before Day 1 of the Treatment Period. Patients will be instructed to inhale 1 capsule of tiotropium (Spiriva® HandiHaler®) every morning. Patients will also receive albuterol for as needed use. Patient will keep this rescue albuterol throughout the Run-in Period.

Prior to release from the CRU, patients will receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. They must return the container (empty or not) at the next schedule visit, which is scheduled after 14 ± 2 days.

Each patient will also be issued and trained on the use of the e-diary to record their self-administered doses and their daily respiratory symptoms. Prior to each morning dose, patients will record at home their daily PEF, major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat,

nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

13.2.4 Treatment Period (Days 1 to 56)

Patients who completed the Run-in Period and still meet all the inclusion criteria and none of the exclusion criteria will be randomized to receive one of the assigned treatments (80 mg or 160 mg YPL-001 BID, or placebo BID) on Day 1 through Day 56 (see Section 13.4.1 and Section 13.4.2).

Safety and tolerability will be monitored throughout the Treatment Period as listed in Section 6. Patients will continue to record their self-administered doses and their daily respiratory symptoms on their e-diary. Prior to each morning dose, patients will record at home their daily PEF, major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

BAL samples for YPL-001 concentrations and PD assessments will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

Spirometry and quality of life questionnaires for PD assessments will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

Blood samples for PD and PK assessment will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

13.2.4.1 Meal Schedule

Patients will be required to fast overnight for at least 12 hours before bronchoscopy and BAL collection on Days -1 and 55. On Days 1 and 56, patients will be required to fast overnight for at least 8 hours before and for at least 4 hours after the morning dose. On all other days, patients will be asked to fast for at least 2 hours before and 2 hours after each morning dose. Patients will also be asked to fast for at least 2 hours before and after each evening dose.

Patients will also be required to fast for at least 8 hours before the scheduled serum chemistry tests at the time points delineated in the Study Events Flow Chart (Section 6).

During in-clinic dosing, water (except that administered with dosing) will not be permitted from 1 hour before until 1 hour after each dosing. Water will be allowed as desired at all other times. On all other days, patients will be informed to follow the same restrictions.

On Days 1 and 56, patients will fast from all food and drink except water between meals and snacks. Foods and beverages containing alcohol, xanthines, caffeine, vegetables from the mustard green family, mustard, tea (especially speedwell tea), or grapefruit/Seville oranges will not be served in the CRU. Across all CRUs, menus should be similar in content. The same menu and meal (except for snacks) schedule will be administered uniformly for all patients confined within the same CRU, across all treatment groups. Meals are not required to be completed by patients.

13.2.4.2 Early Termination

Early termination evaluations will be performed on patients prior to early termination. Patients who want to terminate from the study and are not currently on-site will be contacted and asked to return to the CRU to perform the early termination procedures.

The early termination procedures are listed in Section 6.

13.2.5 Follow-up Call (14 ± 2 days)

The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

13.2.6 Scheduled End of Study

The end of the study is scheduled after completion of the evaluations in the 3 treatment groups or after dose-limiting clinical safety endpoints have been reached to preclude continuation of the study. The clinical conduct of the study is intended to last approximately 12 to 24 months.

This time period may change in the event that the study is terminated early, additional time is required to review safety, or a decision is made to complete an unscheduled analysis for a group.

13.3 Selection of Study Population

13.3.1 Number of Patients

The study is planned to enroll at least 60 patients. An approximately equal number of current and ex-smokers will be enrolled. Patients will be divided in 3 treatment groups with 20 patients to receive one of the 3 treatments (i.e., low and high YPL-001 doses [80 mg and 160 mg BID] and a placebo control) as per the randomization schedule. Each treatment group will consist of an approximately equal number of current and ex-smokers.

13.3.2 Inclusion Criteria

Patient candidates must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Adult males and/or females, 40 to 80 years of age (inclusive).
2. History of COPD for at least 12 months prior to screening.
3. Diagnosed with COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines with symptoms compatible with COPD for at least 12 months prior to screening.
4. Classified as moderate to severe COPD based on the current severity classification GOLD Stage 2-3 disease in terms of post-bronchodilator spirometry at screening:

- Post-bronchodilator FEV_1/FVC ratio of <70%
- Post-bronchodilator FEV_1 ≥30 % and <80 % of predicted normal values

5. Weigh at least 52 kg for males and 45 kg for females and within the normal range according to accepted normal values of the Body Mass Index (BMI) chart 18.5-32.0 kg/m^2 inclusive.
6. In the judgment of the Investigator, the patient is medically stable with no change in symptoms, medication, or with clinical laboratory results that in the Investigator's opinion are compatible with the diagnosis of either COPD or a complication thereof and are judged acceptable for inclusion with predominantly bronchitic symptoms at screening.
7. Must be on a stable medical regimen for COPD ≥ 30 days prior to screening.
8. In the Investigator's opinion patients should be able to withhold tiotropium 24 hours prior to Day 1 of the Run-in Period, if already receiving it and prior to each scheduled CRU visit.
9. Must have oxygen saturation on room air > 93%.
10. Hemoglobin must be equal to or above the lower limit of normal at screening and check-in.
11. Current or ex-smoker with a history of >10 pack years. Ten pack years are defined as: 20 cigarettes a day for 10 years; 10 cigarettes a day for 20 years; or 40 cigarettes a day for 5 years (i.e., [number of cigarettes smoked per day × number of years smoked]/20). Patients, who undergo smoking cessation therapy, must be completed 3 months prior to screening visit and smoking status should not change between the patient's screening visit and patient's last study visit.
12. For a female of childbearing potential: either be sexually inactive (abstinent) for 14 days prior to the first dose and throughout the study or be using one of the following acceptable birth control methods:
    a. non-hormone releasing intrauterine device in place for at least 3 months prior to the first dose.
    b. surgical sterilization of the partner (vasectomy for 4 months minimum).
    c. physical barrier method (e.g., condom, diaphragm) with spermicide for at least 14 days prior to the first dose and throughout the study.
13. A female patient who claims to be sexually inactive, but becomes sexually active during the course of the study must agree to use a physical barrier method (e.g., condom, diaphragm) with spermicide from the time of the start of sexual activity through to the completion of the study.
14. For a female of non-childbearing potential: must have undergone one of the following sterilization procedures at least 6 months prior to the first dose:
    a. hysteroscopic sterilization;
    b. bilateral tubal ligation or bilateral salpingectomy;
    c. hysterectomy;

d. bilateral oophorectomy;

or be postmenopausal with amenorrhea for at least 1 year prior to the first dose and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status as per Investigator judgment.

15. Non-vasectomized males must agree to be sexually abstinent or to use a condom with spermicide when engaging in sexual activity from the first dose through completion of the last scheduled study procedures on Day 56 or upon early termination. Patients will be advised to use a condom with spermicide for 90 days following the last administration of the study drug, and to not donate sperm during this same period of time. In the event that the sexual partner is surgically sterile, use of a condom with spermicide is not necessary. No restrictions are required for vasectomized males provided their vasectomy has been performed 120 days or more prior to study start. Males who have been vasectomized less than 120 days prior to study start must follow the same restrictions as non-vasectomized males.
16. Understands study procedures and provides written informed consent for the trial.
17. Be able to comply with the protocol, such as all the study restrictions, and the assessments therein.

13.3.3 Exclusion Criteria

Patients will be excluded from the study if there is evidence of any of the following criteria at screening or check-in, as appropriate.

1. History of life-threatening COPD including respiratory arrest, intensive care unit admission and/or requiring intubation.
2. History of more than 2 hospitalizations for COPD within 12 months prior to screening.
3. Presentation of an acute exacerbation of COPD that will be associated with increase sputum volume or change in sputum color within 4 weeks before Day 1 of the Run-in Period.
4. Evidence of cor pulmonale, or clinically significant pulmonary hypertension.
5. Continuous use of more than 2L/day of oxygen.
6. History or presence of other respiratory disorders, such as asthma, α-1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis or other chronic pulmonary diseases.
7. A chest X-ray at screening (or within 3 months prior to screening) showing abnormalities, which in the opinion of the Investigator are clinically significant and unrelated to COPD.
8. A history of chronic disease including, but not limited to, unstable or uncontrolled hypertension (or been diagnosed with hypertension in the 6 months before screening), sleep apnea, cardiovascular, endocrine, neurological, hepatic, gastrointestinal, renal, hematological, urological, immunological or ophthalmic diseases that the Investigator believes are clinically significant e.g., unstable and could impact patient safety by participation in the study.

9. History or presence of:
    - significant cardiac arrhythmia;
    - prostatic hyperplasia;
    - bladder-neck obstruction;
    - urinary retention;
    - narrow-angle glaucoma.
10. Evidence of clinically relevant abnormal baseline hematology, serum chemistry, or urinalysis. Patients with an AST > 2 x ULN, ALT > 2 x ULN, bilirubin > 2 x ULN or creatinine > 2 x ULN (confirmation of results may be done once).
11. Evidence of hepatic impairment with a Child-Pugh class A score or higher.
12. Lung resection or lung reduction surgery within 12 months.
13. Positive urine drug/alcohol testing at screening or at each CRU visit.
14. Positive testing for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C antibodies (HCV).
15. History or presence of alcoholism or drug abuse within the 2 years prior to Day 1 of the Treatment Period.
16. Hypersensitivity or idiosyncratic reaction to compounds related to YPL-001, including Speedwell tea and herbal remedies.
17. Requires one (or more) routine therapies for COPD during the indicated restricted time period as listed in Section 13.3.5.1.1.
18. Use of any drugs or substances known to be significant inhibitors (strong or moderate) of UDP-glucuronosyltransferase (UGT) and/or sulfotransferases (SULT), within 12 hours prior to Day 1 of the Run-in Period (refer to Appendix 1 and Appendix 2).
19. Blood donation or significant blood loss within 56 days prior to Day 1 of the Treatment Period.
20. Plasma donation within 7 days prior to Day 1 of the Treatment Period.
21. Participation in another clinical trial within 30 days prior to Day 1 of the Run-in Period.
22. Females who are pregnant or lactating.
23. Surgery within the past 3 months prior to Day 1 of the Treatment Period determined by the Investigator to be clinically relevant.
24. Active or history of any disease or condition that would, in the opinion of the Investigator and/or medical monitor, place the patient at an unacceptable risk to participate in this study.

13.3.4 Removal of Patients from the Study

Patient participation in this trial may be discontinued for any of the following reasons:

1. Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol.
2. Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient.
3. The patient interrupts trial study drug administration for more than 7 consecutive days of dosing or missed a total of 17 doses (15%) throughout the Treatment Period.
4. Patient's decision to withdraw.
5. Requirement for prohibited concomitant medication.
6. Patient failure to comply with protocol requirements or study related procedures.
7. Termination of the study by the Investigator, Sponsor, FDA, Celerion, or other regulatory authorities.

The clinical report will include reason(s) for patient withdrawals as well as details relevant to the patient withdrawal. If a patient is withdrawn from the trial prior to study completion, the patient will undergo all procedures scheduled for study completion (early termination evaluations) as the situation allows (see Section 13.2.4.2). Any patient withdrawn due to an AE (whether serious or non-serious) or clinically significant abnormal laboratory test values will be evaluated by the Investigator and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

Patients withdrawn may be replaced at the Sponsor's discretion.

13.3.5 Study Restrictions

13.3.5.1 Concomitant Therapy

All medications taken during the 30 days prior to the first dose will be recorded and reviewed by the Investigator.

Any medication taken by patients during the course of the study will be recorded. Concomitant medication will be coded using the most current WHO drug dictionary available at Celerion (e.g., 01-MAR-2014 or later). If drug therapy other than that specified by the protocol is taken, a joint decision will be made by the Investigator and Sponsor to continue or discontinue the patient.

13.3.5.1.1 Prohibited Therapy

The following medications are not permitted within the time delineated below and during the study (from Day 1 of the Run-in Period to the completion of the last scheduled study procedures on Day 56 or upon early termination). Intake of these medications during the Run-in Period constitutes a non-eligibility criterion and the patients will not be randomized into the study. If any of these medications are taken during the Treatment

Period, the need for this patient to be withdrawn from the study will be carefully evaluated by the Investigator and the Sponsor on the basis of the potential impact on efficacy or safety evaluation and in the patient's best interest:

1. Any medications administered for the treatment of worsening of COPD within 4 weeks prior to Day 1 of the Run-in Period:
   - nebulized, inhaled, oral, IV, IM corticosteroids;
   - oral or parenteral β2 agonists;
   - Antibiotics.
2. Inhaled corticosteroids (ICS), LABA, and/or inhaled ICS/LABA fixed combinations within 12 hours prior to Day 1 of the Run-in Period;
3. Inhaled long acting anticholinergic agents other than tiotropium within 2 weeks prior to Day 1 of the Run-in Period;
4. Inhaled short-acting β2-agonists (SABA) other than albuterol (e.g., terbutaline, fenoterol) within 12 hours prior to Day 1 of the Run-in Period;
5. Inhaled short-acting anticholinergic agents (SAMA) (e.g., ipratropium) within 12 hours prior to Day 1 of the Run-in Period;
6. PDE inhibitors (including roflumilast) within 2 weeks prior to Day 1 of the Run-in Period.
7. Leukotriene modifiers and xanthines derivatives within 2 weeks prior to Day 1 of the Run-in Period.
8. Drugs or substances known to be significant inhibitors (strong or moderate) of UGT and/or SULT, within 12 hours prior to Day 1 of the Run-in Period and through collection of the final PK sample.
9. Acetaminophen will be prohibited 24 hours prior to Day 1 of the Treatment Period and through collection of the final PK sample.
10. Vitamin supplements and herbal products (especially Speedwell) will be prohibited 7 days prior Day 1 of the Treatment Period and through collection of the final PK sample.

13.3.5.1.2 Permitted Therapy

Throughout the study Period (from Day 1 of the Run-in Period to the completion of the last scheduled study procedures on Day 56 or upon early termination) patients will be permitted to take the following medications in addition to the study drugs:

1. Albuterol, as required (except approximately 4 hours before schedule pulmonary function test);
2. Tiotropium (Spiriva® HandiHaler®) 18 µg once a day (except approximately 24 hours before schedule pulmonary function test);
3. Ibuprofen, as required, up to 1200 mg per day for intercurrent illness or AEs. Ibuprofen should not be taken for 2 hours before or after each dosing.
4. In the case of a concomitant disease, appropriate treatment will be permitted if it does not interfere with the study evaluation parameters and does not qualify under the section "Prohibited Therapy" (see Section 13.3.5.1.1)

13.3.5.2 Prohibitions

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/caffeine (other than coffee and tea): 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Alcohol (other than red wine and beer): 48 hours prior to each CRU visit, 48 hours prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts), and mustard: 14 days prior to Day 1 of the Treatment Period through collection of Day 56 last PK sample.
- Fruit Juice: 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Tea (especially Speedwell tea), coffee, and red wine: 7 days prior to Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Grapefruit/Seville orange and beer: 14 days prior to Day 1 of the Treatment Period through collection of Day 56 last PK sample.

13.3.5.3 Activity

Patients will remain ambulatory or seated upright for 1 hour following each study medication administration.

Patients will be advised to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

13.4 Treatments

13.4.1 Treatments administered

13.4.1.1 Drug Administration During Run-in Period

Tiotropium (Spiriva® HandiHaler®) will be supplied as 18 µg capsules for inhalation.

Albuterol will be supplied as 100 µg albuterol base (1 actuation = 100 µg albuterol base) for oral inhalation. Albuterol may be administered via a nebulizer or a metered-dose inhaler.

Multiple oral inhalation of tiotropium (Spiriva® HandiHaler®) 18 µg capsule will be administered QD every morning for 14 ± 2 days during the Run-in Period. Albuterol will be administered on an as needed basis.

13.4.1.2 Drug Administration During Treatment Period

YPL-001 will be supplied as 80 mg tablets for oral administration.

Placebo will be supplied as YPL-001 80 mg matching placebo tablets for oral administration.

Treatments A, B, and C are described as follows:

Treatment A: Multiple oral YPL-001 80 mg doses (1 x 80 mg tablet + 1 x 1 YPL-001 80 mg matching placebo tablet) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56.

Treatment B: Multiple oral YPL-001 160 mg doses (2 x 80 mg tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56.

Treatment C: Multiple oral matching placebo (2 x 1 YPL-001 80 mg matching placebo tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56.

Each dose of Treatments A, B and C will be administered with approximately 240 mL of water.

In all treatments, one tiotropium (Spiriva® HandiHaler®) 18 µg capsule will also be administered QD every morning prior to study drugs administration. Albuterol will be administered on an as needed basis.

YPL-001 or placebo will be dispensed in accordance with the Randomization and Drug Dispensing Instructions provided in a separate document.

Prior to release from the CRU on Days 1, 15, and 29, of the Treatment Period, patients will receive a properly labeled new kit, which contains 4 wallets of 2 blister cards, with the appropriate doses which will be self-administered by patients at home. Any unused wallets from previously provided kits will also be dispensed to patients on Days 15 and 29. Prior to release from the CRU on Days 43, and 55, patients will received unused wallets from previously provided kits with the appropriate doses which will be self-administered by patients at home. Patients will also receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. Patients will record their self-administered doses in their e-diary, and whether the dose was administered with food, and must return the YPL-001 used and unused wallets and the tiotropium and albuterol container (empty or not) at the next schedule visit at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.

Patients will be instructed not to crush, split or chew the study drug.

The exact clock time of dosing will be recorded on on-site dosing days. Patients will be

given instructions on how to record their drug administration in their e-diary on home-dosing days.

Each dose will be administered under fasting conditions as described in Section 13.2.4.1.

13.4.1.3 Stopping Rules

A decision to stop or suspend the study will be made jointly by the Sponsor and the Investigator following the review of all pertinent safety and tolerability. Together they will make one of the following determinations:

1. To continue with the study as planned.
2. To continue with the study and add additional safety evaluations.
3. To continue with the study by adjusting to a lower dose if 2 patients at any dose level meets any of the following criteria and the patient was determined to have received YPL-001 after unblinding:
   a. Has a drug–related, unexpected SAE.
   b. Experiences drug-related grade ≥ 3 toxicity.
4. The study will be terminated if ≥ 3 patients at any dose level meet any of the following criteria and the patients were determined to have received YPL-001 after unblinding:
   a. Has a drug–related, unexpected SAE.
   b. Experience drug related grade ≥ 3 toxicity.

PK data will not be required for the dose-escalation decision.

When applicable, a written statement fully documenting the reasons for study termination will be provided to the Institutional Review Board (IRB).

13.4.2 Method of Assigning Patients to Treatment Groups

Each patient will be assigned a unique screening identification number upon screening. Patients who complete the study screening assessments, complete the Run-in Period, and meet all the eligibility criteria will be assigned a unique randomization identification number, different from the screening number, and receive the corresponding product, according to a randomization scheme generated at Celerion. Each treatment group will consist of an approximately equal number of current and ex-smokers.

Patients will receive one of the 3 treatments (Treatments A, B, or C) on one occasion.

If replacement patients are used, the replacement patient number will be 100 more than the original (e.g., Patient No. 0101 will replace Patient No. 0001).

13.4.3 Blinding

This is a double-blind, double-dummy, randomized study.

13.4.3.1 Maintenance of Randomization

A computerized randomization scheme will be created by a Celerion unblinded statistician (who is not otherwise involved in the study) and shall be considered blinded (per the following).

The randomization will not be made available to the Sponsor, patients, or members of the staff responsible for the monitoring and evaluation of safety assessments.

The bioanalytical department will also be blinded to the randomization scheme.

13.4.3.2 Procedures for Breaking the Blind Prior to Study Completion

The site Pharmacist/Study Coordinator will receive two sets of randomization code envelopes, one set for “Current Smokers” and another for “Ex-Smokers”. Each individual envelope is marked on the outside with one of the randomization numbers and contains the treatment for that patient. These envelopes must be kept in a secure locked location.

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the patient.

In the event of a medical emergency, it is requested that the Investigator make every effort to contact the medical monitor or designee prior to breaking the blind. If breaking the blind is required because of a medical emergency, the treatment identity would be revealed by the qualified designee, for that patient only. In the event that the emergency is one, in which it appears that the other patients may be at imminent risk, the blind may be broken for all patients dosed at that dose level. The unblinding should be noted in the patient’s electronic case report form (eCRF).

In all cases where the code is broken, the Investigator should record the date, reason for code breaking and his/her name for signature on the envelope.

At the end of the study, the envelopes will be reviewed by the Sponsor.

13.4.3.3 Revealing of Randomization

In the absence of a medical emergency, the blinded randomization for this entire trial will not be revealed until the following conditions are fulfilled:

1. All data are entered in the database, edits checks are performed, queries closed, CRFs signed by the Investigator, and the database is officially locked.
2. All PK/PD samples have been analyzed and quality checked by the responsible analytical associate.

13.4.4 Treatment Compliance

During in-clinic dosing, a qualified designate will be responsible for monitoring the administration of timed oral doses. When appropriate, a mouth check will be performed by the qualified designate to ensure that the patients have swallowed the study medication. Once a patient has finished the water, the qualified designate will use a flashlight and a tongue depressor to check the side of the mouth, the sides of the upper and lower gums and the area under the tongue. Patients’ hands will also be verified to ensure that the medication was ingested.

Self-administration by patients at home will be monitored via the e-diary and attempted phone calls will be performed to remind patients to take their medication, if they did not record their self-administration on the e-diary.

14. STUDY PROCEDURES

14.1 Safety Assessments

This study primarily assesses the safety and tolerability of YPL-001. Safety will be determined by evaluating physical examinations, vital signs, pulse oximetry, ECGs, clinical laboratory parameters, and AEs.

If deemed necessary, additional safety measurements will be performed at the discretion of the Investigator.

Study procedures should be completed as close to the prescribed/scheduled time as possible. The Quality of Life questionnaire should be performed prior to any other procedures. When the following procedures are scheduled at the same time, they will be performed in the following order:

1. Vital signs
2. ECG
3. Pulmonary function measurement
4. Bronchoscopy and BAL collection

All other procedures can be performed without specific order.

14.1.1 Body Height and Weight

Body height (centimeters) and body weight (kilograms) will be measured as outlined in the Study Events Flow Chart (Section 6).

14.1.2 Physical Examination

All full physical examinations will include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose and throat, respiratory system, cardiovascular system, gastrointestinal system, neurological condition, blood and lymphatic systems, and the musculoskeletal system.

A licensed physician will examine each patient as outlined in the Study Events Flow Chart (Section 6).

Medical history will be recorded at screening.

Physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator.

14.1.3 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate will be measured as outlined in the Study Events Flow Chart (Section 6).

Vital signs may be taken at any other times, if deemed necessary. Blood pressure and heart rate measurements will be performed with patients in a seated position for at least 1 minute, except when they are supine or semi-reclined because of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the Investigator.

When performed prior to the morning dose, blood pressure and heart rate will be measured within 2 hours prior to dosing. When scheduled postdose, vital signs readings will be performed within approximately 10 minutes of the scheduled time point. When performing the bronchoscopy, vital signs (body temperature, respiratory rate, blood pressure, and heart rate) will be monitored continuously until the end of the procedure.

14.1.4 Pulse Oximetry

Oxygen saturation (%), and heart rate will be assessed using a pulse oximeter. All readings will be performed with a pulse oximeter (oxygen saturation [%], and heart rate) as outlined in the Study Events Flow Chart in Section 6.

When performed prior to the morning dose, pulse oximetry monitoring will be measured within 2 hours prior to dosing. Readings may be taken at other times, if deemed necessary by the Investigator. When performing the bronchoscopy, oxygen saturation will be monitored continuously until the end of the procedure.

Any clinically relevant oxygen saturation reading below 93% will be documented as an AE, as per Investigator discretion.

14.1.5 Electrocardiogram Monitoring

When performed prior to the morning dose, ECG will be measured within 2 hours prior to dosing. When performing the bronchoscopy, ECG will be monitored continuously until the end of the procedure.

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6). Patients will be required to lie quietly in a supine position for at least 5 minute prior to ECG measurements. Single 12-lead ECGs may be performed at various unscheduled time points, if deemed necessary by the Investigator.

Single 12-lead ECGs will be interpreted and signed and dated by the Investigator. The ECGs will be classified as normal, having a non-clinically significant abnormality (NCS), or having a clinically significant abnormality (CS). In addition, ECG parameters of ventricular rate, PQ or PR interval, QRS duration, and QT interval (corrected according to Bazett's formula [QTcB] and uncorrected) will be noted on the CRF.

14.1.6 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 6). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator. The clinical laboratory tests include the following:

14.1.6.1 Hematology

- Hemoglobin
- Hematocrit
- RBC count (including a reticulocytes count)
- Platelet count
- Mean Corpuscular Hemoglobin (MCH)
- Mean Corpuscular Volume (MCV)
- Mean Corpuscular Hemoglobin Concentration (MCHC)
- RDW
- White blood cell (WBC) count with differential (including eosinophil, neutrophil, basophil, lymphocytes, and monocytes)

14.1.6.2 Serum Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.

- BUN
- Creatinine*
- Bilirubin (total and direct)
- Uric acid
- Albumin
- Alkaline phosphatase (ALP)
- Creatine kinase (CK)
- Lactate dehydrogenase (LDH)
- Estimated glomerular filtration rate
- Alpha-1 Antitrypsin**
- AST
- ALT
- Amylase
- Lipase
- Glucose (fasting)
- Carbon dioxide (CO_2)/Bicarbonate (HCO_3)
- Sodium
- Potassium
- Chloride

* Creatinine clearance will be calculated using Cockcroft-Gault formula at screening.

** To be performed at screening only.

14.1.6.3 Serology

- HIV
- HBsAg
- HCV

14.1.6.4 Human Chorionic Gonadotropin (Serum Pregnancy Test)

The test will be performed for females only.

14.1.6.5 Follicle-Stimulating Hormone

The test will be performed in postmenopausal females only.

14.1.6.6 Urinalysis

- pH
- Specific gravity
- Protein
- Glucose
- Ketones
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Leukocyte Esterase

If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination will be performed.

14.1.6.7 Urine Drug/Alcohol Screen

- Cannabinoids
- Alcohol
- Cocaine
- Amphetamines
- Barbiturates
- Benzodiazepines
- Opiates

14.1.7 Chest X-Ray

A baseline chest x-ray will be performed at the screening visit. If the patient has had an x-ray within the last 3 months prior to the screening visit, and the CRU has access to the report and images, this can be used as the baseline chest x-ray and does not need to be repeated.

14.1.8 Adverse Events

14.1.8.1 Adverse Event Definition

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.[3]

14.1.8.2 Monitoring

The patients will be instructed to inform the Investigator or clinic staff of any AEs and intercurrent illnesses experienced during the trial. Additionally, a specific inquiry regarding AEs will be conducted prior to each dosing at the CRU, after the last scheduled study procedures on Day 56 (or upon early withdrawal), and at the follow-up phone call. The inquiry will be made in a non-specific manner using open-ended questions so as not to bias the response (e.g., How have you been feeling since your last visit?).

All symptoms will be evaluated by the Investigator.

Any patient who has a clinically significant AE (whether serious or non-serious) or clinically significant abnormal laboratory test value will be evaluated by the Investigator, or other monitoring physician, and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

Treatment of SAEs will be performed by a physician, either at the CRU or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal or unknown (lost to follow-up).

14.1.8.3 Reporting

AEs will be coded using the most current MedDRA® available at Celerion (e.g., 17.0 or higher). The Sponsor will inform the Celerion Global Project Manager which version is to be used prior to initiation of the study.

The Investigator will review each event and assess its relationship to drug treatment (unrelated, unlikely, possible, probable, definite). The severity of each sign or symptom reported will be graded based on the NIH NCI CTCAE toxicity grading scale 5-point severity scale (Grade 1, 2, 3, 4 and 5) [4] and the date and time of onset, time relationship to drug dosing, duration, and outcome (resolved, improved, unchanged, worse, fatal, or unknown/lost to follow-up) of each event will be noted.

The relationship of each AE will be assessed using the following definitions:

Unrelated	▪ Event occurring before dosing. ▪ Event or intercurrent illness due wholly to factors other than drug treatment.
Unlikely	▪ Poor temporal relationship with drug treatment. ▪ Event easily explained by patient's clinical state or other factors.
Possible	▪ Reasonable temporal relationship with drug treatment. ▪ Event could be explained by patient's clinical state or other factors.
Probable	▪ Reasonable temporal relationship with drug treatment. ▪ Likely to be known reaction to agent or chemical group, or predicted by known pharmacology. ▪ Event cannot easily be explained by patient's clinical state or other factors.
Definite	▪ Distinct temporal relationship with drug treatment. ▪ Known reaction to agent or chemical group, or predicted by known pharmacology. ▪ Event cannot be explained by patient's clinical state or other factors.

The following definitions for rating severity will be used:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**. Note**:** An experience may be severe but may not be serious, e.g., severe headache).
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A semi-colon indicates 'or' within the description of the grade; ADL = Activities of Daily Living

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

14.1.8.4 Serious Adverse Events

If any AEs are serious, as defined by the Food and Drug Administration (FDA) Code of Federal Regulations (CFR), Chapter 21, special procedures will be followed. All SAEs will be reported to the Medical Monitor via fax or e-mail within one working day of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012[3]. The institutional review board (IRB) will be notified of the Alert Reports as per FDA regulations.

If an SAE occurs to a patient on this study, the Medical Monitor is to be contacted (see Section 4).

A SAE is any AE or suspected adverse reaction that in the view of either the Investigator or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood

dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

14.2 Symptom Assessments

14.2.1 Electronic Diary

On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their self-administered doses, whether the dose was administered with food, and daily respiratory symptoms throughout the Run-in and Treatment Periods. Patients will return the e-diary device on Day 56 (or prior to early termination) to CRU staff.

Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

14.2.2 Peak Expiratory Flow

PEF assessments will be made daily prior to each dose from Day 1 of the Run-in Period to Day 56 of the Treatment Period. Three measurements will be made at each time point using a hand held PEF meter. Readings not performed in the CRU will be recorded in the patient e-diary. All PEF assessments should be performed before administration of a bronchodilator where possible.

14.2.3 Symptoms of Chronic Obstructive Pulmonary Disease Exacerbation

Patient will be asked to record the major (e.g., estimated sputum quality (e.g., color, consistency) and quantity,) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation via the e-diary before each dosing.

14.2.4 Dyspnea (Modified Borg Dyspnea Scale)

Severity level of patient's dyspnea will be assessed via the modified Borg dyspnea scale programmed within the e-diary. The modified Borg dyspnea scale is a self-administered categorical scale with a score from 0 to 10, where 0 (as a measure of dyspnea) corresponds to the sensation of normal breathing (absence of dyspnea) and 10 corresponds to the patient's maximum possible sensation of dyspnea.

14.2.5 Activity (Duke Activity Status Index)

Patient's functional capacity and activity status will be assessed via the DASI programmed within the e-diary. DASI is a self-administered 12-item questionnaire that assesses daily activities such as personal care, ambulation, household tasks, sexual function and recreation with respective metabolic costs. Each item has a specific weight based on the metabolic cost. The final score ranges between 0 and 58.2 points. The higher the score, the better the functional capacity.

14.3 Pharmacodynamic Assessments

14.3.1 Pulmonary Function (Spirometry)

Spirometry measures will be taken at the time points delineated in the Study Events Flow Chart (Section 6) using a standard calibrated spirometer to determine the parameters detailed below.

- FEV_1;
- FVC (forced vital capacity);
- FEV_1/FVC;
- IC.

Short acting β2-agonist and anticholinergic bronchodilators (e.g., albuterol, ipratropium bromide) and long acting β2-agonist and anticholinergic bronchodilators (e.g., salmeterol, tiotropium) agents will be withheld approximately 4 and 24 hours, respectively, before each pre-bronchodilator spirometry.

Every effort will be made to perform all assessments for a given patient on the same instrument throughout the study.

At screening, baseline pre-bronchodilator spirometry will be performed (prior to albuterol administration) for a minimum of 3 times and a maximum of 8 times in order to obtain 3 manoeuvers with FEV_1 values within 150 mL of each other, using the manoeuver with the highest value of FEV_1 and FVC as the basis for comparison.

Patients shall receive 4 inhalations of albuterol (100 µg/inhalation) for a total dose of 400 µg via metered-dose inhaler using a spacer. Within approximately 20 to 30 minutes after albuterol administration, the baseline post-bronchodilator spirometry will be performed.

Assessment of FEV_1 stability will take place:

1. Prior to Day 1 dosing of the Treatment Period (Day -1 measurement): Predose FEV_1 is defined as the time point prior to Day 1 dosing in the Treatment Period and will be performed pre- and post-bronchodilatator administration. Predose FEV_1 will be compared to the corresponding baseline measurement. If the best FEV_1 measurement at predose on Day -1 of the Treatment Period has declined by greater than 20% from the best FEV_1 at screening, the visit may be rescheduled up to 3 times, at the discretion of the Investigator.

2. Following Day 1 dosing: At all other spirometry time point, measurements will be performed once. If the value shows a difference of greater than 150 mL decline than the best FEV_1 value collected predose on Day -1, up to 3 measures will be performed.

   Consideration should be given, if a patient experiences any change in post Day 1 dose FEV_1 from the Day 1 predose FEV_1 value (measured following dosing with albuterol) equal to or greater than 20 % and should alert the Investigator to consider whether individual patients should continue to dose. The pulmonary function manoeuver(s) used to make this assessment must be valid and meet acceptable quality spirometry standards.

The Investigator may also use his or her discretion as to the completion of dosing for any period in which an FEV_1 decline and/or respiratory symptoms occur(s).

14.3.2 Bronchoscopy and Bronchoalveolar Lavage (BAL) Biomarkers

Patients will be asked to refrain from smoking approximately 48 hours before the bronchoscopy procedures and will be fasted for 12 hours before. If required, blood pressure medications can be taken with small sip of water based on preapproval of local Investigator.

14.3.2.1 Bronchoscopy

The bronchoscopy with bronchial brushings will be performed at the time points delineated in the Study Events Flow Chart (Section 6) by a licensed physician experienced in conducting the procedure according to guidelines published on the use of bronchoscopy for research on airway diseases such as COPD.[5,6]

Albuterol will be administered 20 minutes prior to the beginning of the bronchoscopy. An intravenous line will also be established to administer conscious sedation, and to administer emergency medications if the need were to arise. During the procedure, oxygen saturation (S_PO_2), blood pressure, and heart rate and rhythm (continuous electrocardiogram) will be monitored. Oxygen 2-4 L via nasal cannula will be administered during bronchoscopy and oxygen saturation will be maintained at ≥95%. Conscious sedation will be achieved with incremental doses of 1–4 mg midazolam and 50-100 µg fentanyl. Local upper and lower airway topical anesthesia will be achieved with 1% or 2% lidocaine. The dose of lidocaine administered during the procedure will not exceed a total of 450 mg. The bronchoscope will usually be inserted preferably through the nares into trachea. The bronchoscope will be wedged into 2 subsegments of the right middle or lower lobe, as deemed appropriate by the Investigator. Emergency treatments for cardiopulmonary arrest and pneumothorax will be immediately available in the bronchoscopy room. The patient will remain in the recovery suite for observation for a minimum of 2 hours after the procedure.

14.3.2.2 Bronchial Brushings

Prior to BAL, a cytology brush is inserted into the bronchoscope channel and brushings are collected twice from each of 4 quadrants of visible subsegments of the right middle or lower lobe, as deemed appropriate by the Investigator, under direct visualization. The cellular material is washed off in saline following each brushing. The brushing is performed a total of 8 times. The liquid is centrifuged and the cell pellet is stored at -70°C.

Samples must be protected from UV light during collection, processing, and storage.

14.3.2.3 Bronchoalveolar Lavage (BAL)

BAL in the right middle or lower lobe, as deemed appropriate by the Investigator, will be performed at the time points delineated in the Study Events Flow Chart (Section 6) by a licensed physician experienced in conducting the procedure. A total of 180 mL BAL, using 6 x 30 mL aliquots of normal saline warmed to room temperature, will be performed using each subsegment of the right middle or lower lobe, as deemed appropriate by the Investigator. BAL fluid will be aspirated following each 30 mL instillation. The lavage material, which averages 25% return in COPD patients, typically yields 1-10 x 10^6 macrophages. The centrifuged cell pellet and supernatant will be kept cooled until processed or stored as indicated in the laboratory manual to be provided as a separate document.

Samples must be protected from UV light during collection, processing, and storage.

14.3.2.4 Biomarkers

BAL samples will be analyzed for:

- YPL-001 component levels in epithelial brushings;
- total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells
- total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers
- concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9.

14.3.3 Blood Biomarkers

Blood samples will be collected via direct venipuncture or an angiocatheter at the time points delineated in the Study Events Flow Chart (Section 6) for PD assessments of biomarkers. Biomarker assessments include:

- inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils, and lymphocytes)
- concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9.

Blood will be drawn into 3 tubes. A manual for blood sampling, collection, processing, and sample shipment will be provided in a separate document.

14.3.4 Quality of Life Questionnaires

14.3.4.1 Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI)

Dyspnea at baseline (Day -1 of the Treatment Period) will be assessed with the BDI. This instrument has 3 domains (functional impairment, magnitude of task, and magnitude of effort) with the values added for a combined focal score. Functional impairment determines the impact of breathlessness on the ability to carry out activities; magnitude of task determines the type of task that causes breathlessness, magnitude of effort establishes the level of effort that results in breathlessness. The BDI scores range from 0 (very severe impairment) to 4 (no impairment) for each domain with the baseline focal score consisting of the sum of each domain (0 to 12).

Dyspnea throughout the study will be performed at the time points delineated in the Study Events Flow Chart (Section 6). The change from baseline is measured by the TDI score which ranges from -3 (major deterioration) to +3 (major improvement) for each domain with the TDI focal score consisting in the sum of each domain (-9 to +9).

The same Investigator or designee will interview specifically the patients during the study.

A copy of the questionnaire to be used will be kept in the study binder.

14.3.4.2 COPD Assessment Test (CAT)

CAT is a short and simple questionnaire of 8 items completed by patients to be performed at the time points delineated in the Study Events Flow Chart (Section 6). Scores for each of the 8 items are summed to give a single, final score ranging from 0 (no impact on daily activities) to 40 (very high impact on daily activity). This is a measure of the overall impact of a patient's condition on their life. Scores for the individual items within the questionnaire will provide insight into the relative influence that the different components of COPD have on its overall impact on a patient's life.[7,8]

A copy of the questionnaire to be used will be kept in the study binder.

14.4 Pharmacokinetic Assessments

The sampling schedule and/or collection intervals delineated in the Study Events Flow Chart (Section 6) may be modified based on the results from previously dosed patients.

14.4.1 Blood Sampling and Processing

Samples must be protected from UV light during collection, processing, and storage.

Samples will be collected via direct venipuncture or an angiocatheter at the time points delineated in the Study Events Flow Chart (Section 6).

Blood will be drawn into 4 mL pre-chilled evacuated tubes containing K_2EDTA. A manual for blood sampling, collection, processing, and sample shipment will be provided in a separate document.

14.5 Blood Volume for Study Assessments

Table 5: Blood Volume during Study

Sample Type	Number of Time Points	Volume per Time Point*	Sample Volume Over Course of Study
Screening laboratory safety tests (including hematology, serum chemistry, serology), FSH (for postmenopausal female patients only) and serum pregnancy (for female patients only).	1	~ 17 mL	~ 17 mL
On-study serum chemistry and serum pregnancy (for female patients only) when scheduled at the same time	3	~ 8.5 mL	~ 25.5 mL
Additional on-study serum pregnancy (for female patients only)	2	~ 3.5 mL	~ 7 mL
On-study hematology	3	~ 4 mL	~ 12 mL
Blood samples for PD biomarkers (except CRP and fibrinogen)	8	~ 6 mL	~ 48 mL
Blood samples for PD biomarker - CRP	8	~ 4	~ 32
Blood samples for PD biomarker - Fibrinogen	8	~ 3.5	~ 28
Blood samples for PK of verproside and picroside II	37	~ 4 mL	~ 148 mL
Total Blood Volume for males →			~ 310.5 mL**
Total Blood Volume for females →			~ 317.5 mL**

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

** If an angiocatheter is used, up to 5 mL of blood will be used to flush the catheter prior to each collection of PK and/or PD blood samples. Hence the total blood volume collected may increase by approximately 205 mL.

15. DATA ANALYSIS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCPs.

15.1 Statistical Analysis

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a SAP. The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP.

15.1.1 Sample Size Calculation

According to the exploratory nature of this study no formal statistical hypotheses will be tested. However, a sample size of 60 evaluable patients is deemed to be sufficient to assess the safety and tolerability and to provide an indication of the potential effect of YPL-001 on COPD exacerbation symptoms, selected biomarkers and pulmonary function parameters.

15.1.2 Patients to Analyze

Safety population: the safety population data set will include all available data for patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo. Safety data for all discontinued patients will be included in this set for the time points for which their data are available.

Symptom monitoring population: the symptom monitoring population data set will include all available data for patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo. Symptom monitoring data for all discontinued patients will be included in this set for the time points for which their data are available.

PK population:

- The PK full data set will include all patients receiving at least one dose of YPL-001 and having at least one measurable plasma concentration of verproside and picroside II.
- The PK per-protocol data set will include all patients receiving all scheduled doses of YPL-001 and having sufficient samples collected to determine PK parameters from plasma concentrations of verproside and picroside II on Days 1 and/or 56.

PD population:

- The PD full data set will include all patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo and provide at least 1 post-baseline PD measurement.
- The PD per-protocol data set will include all patients receiving all scheduled doses of

the investigational product (i.e., YPL-001) or placebo and having measurable PD data.

PK/PD population: All patients who receive at least one dose of YPL-001 and having any measurable concentration of verproside and picroside II and measurable PD data will be included in the PK/PD relationship assessment, as applicable.

15.1.3 Safety Analysis

The following analyses will be performed. Safety analyses will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data, when appropriate.

Medical History:

Medical history will be listed by patient.

Adverse Events:

AEs will be coded using the most current MedDRA® available at Celerion (e.g., 17.0 or higher) and data will be summarized by SOC and preferred term. The number of TEAEs will be reported. In addition, the number and percent of patients reporting each TEAE will be summarized separately for each treatment.

A by-patient AE data listing, including verbatim term, preferred term, treatment, severity, outcome, and relationship to treatment, will be provided.

Physical Examination:

Changes in physical examinations will be described in the text of the final report and significant findings will be reported as AEs.

Clinical Laboratory Tests, Electrocardiograms, Vital Signs and Pulse Oximetry:

All clinical laboratory tests, 12-lead ECGs, vital signs, and pulse oximetry measurements and their change from baseline, if applicable, will be summarized by treatment and time point of collection.

A shift table describing out-of-normal range shifts will be provided for clinical laboratory results.

A normal-abnormal shift table will be presented for ECGs.

Peak Expiratory Flow:

PEF measurements and its change from baseline, will be summarized by treatment and time point of collection.

Concomitant Medications:

Concomitant medications will be listed by patient and coded using the most current WHO drug dictionary available at Celerion (e.g., 01-MAR-2014 or later).

15.1.4 Symptom Monitoring Analysis

Symptom free days and overall symptom burden will be evaluated and compared across treatment groups. Secondary outcome analysis will be based on treatment actually

received by patients. Descriptive statistics will be calculated for quantitative data and frequency counts will be compiled for classification of qualitative data, when appropriate.

Peak Expiratory Flow and Symptoms of COPD Exacerbation:

PEF measurements and symptoms of COPD exacerbation and their change from baseline will be summarized by treatment and time point of collection.

Dyspnea and Activity:

The Modified Borg Dyspnea Scale and DASI scores will be listed and presented descriptively.

Additional analysis may be performed if deemed appropriate.

15.1.5 Pharmacodynamic Analysis

15.1.5.1 Biomarkers

When applicable, the following PD biomarkers will be summarized by treatment group using descriptive statistics (arithmetic means, SD, CV, N, minimum, maximum, and median). Figures will be created to display mean and individual level or activity as a function of time, as appropriate:

- Pulmonary biomarker (i.e., Pulmonary Function measurements [Spirometry]): pre- and post-bronchodilator change in activity by time point will be calculated relative to the pre- and post-bronchodilator baseline activity;
- BAL biomarkers (i.e., total cell count [cells/mL] of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; total cell count [cells/mL] of neutrophils, macrophages, lymphocytes and eosinophils as absolute inflammatory cell numbers; and concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9): raw and % change from baseline levels; and
- Blood biomarkers (i.e., inflammatory markers [total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes] and concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9): raw and % change from baseline levels.

PK/PD relationship may be explored graphically using scatter plots and an appropriate regression model.

15.1.5.2 Quality of Life

The quality of life parameters reported from the BDI/TDI and CAT questionnaires will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.

15.1.6 Pharmacokinetic Analysis

15.1.6.1 Pharmacokinetic Parameters

15.1.6.1.1 Plasma

PK parameters will be computed from the individual plasma verproside and picroside II concentrations using a noncompartmental approach. Appropriate validated PK software (e.g., WinNonlin Professional) will be used. PK parameters for other components of YPL-001 and its metabolites may also be computed, as appropriate.

The following PK parameters will be computed following Day 1 morning dose:

AUC_{0-12}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to 12 hours.
AUC_{0-t}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (C_t). This parameter will be reported only if plasma concentrations fall below the lower limit of quantitation before the last time point prior to the evening drug administration on Day 1 for at least one patient. Otherwise, only AUC_{0-12} will be reported.
AUC_{0-inf}	Area under the drug concentration-time curve from time zero to infinity, $AUC_{0-inf} = AUC_{0-t} + C_t/k_{el}$, where k_{el} is the terminal elimination rate constant. †
C_{max}	Maximum observed drug concentration.
t_{max}	Time of the maximum drug concentration (obtained without interpolation).
k_{el}	Apparent terminal elimination rate constant, calculated by linear regression of the terminal linear portion of the log concentration vs. time curve. †
$t_{1/2}$	Apparent elimination half-life, calculated as $\ln(2)/k_{el}$. †
CL/F	Oral clearance [$Dose/AUC_{0-inf}$]. †
V_Z/F	Apparent volume of distribution at the terminal phase, calculated as $Dose/(k_{el} * AUC_{0-inf})$.†

† All k_{el} and related PK parameters (AUC_{0-inf}, $t_{1/2}$, CL/F, and V_z/F) will be reported only if the half-life of verproside or picroside II can be appropriately estimated from a 12-hour sampling period following dosing.

The following PK parameters will be computed following Day 56 morning dose:

AUC_{τ}	The area under the plasma concentration versus time curve over the final dosing interval, as calculated by the log-linear trapezoidal method (e.g., 0-12 hours).
AUC_{0-t}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (C_t).
C_{max_ss}	Maximum observed drug concentration at steady-state.
$C_{min,ss}$	Minimum observed/measured non-zero concentration at steady-state.
C_{trough}	Concentration at the end of a dosing interval.
C_{avg}	Ratio of AUC_{τ} to the dosing interval, τ.
%Fluc	Percent fluctuation will be calculated as follows: $\frac{C_{\max\_ss} - C_{\min\_ss}}{C_{avg}} x\ 100$
Swing	Percent swing will be calculated as follows: $\frac{C_{\max\_ss} - C_{\min\_ss}}{C_{\min\_ss}} \text{ x } 100$
t_{max_ss}	Time to reach the maximum drug concentration (obtained without interpolation) at steady-state.
CL_{ss}/F	Total body clearance estimated at steady-state after oral administration, calculated as Dose/AUC_{τ}.
V_{z_ss}/F	Apparent volume of distribution at steady-state, calculated as $(CL_{ss}/F)/k_{el}$.*

* All k_{el} and related PK parameters ($t_{1/2}$ or V_{z_ss}/F) will not be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

If metabolite data are available, metabolite to parent ratios may be calculated for AUC_{0-t}, AUC_{τ}, and C_{max_ss}.

15.1.6.1.2 Bronchoalveolar Lavage

Levels of YPL-001 components in epithelial brushing will be listed.

15.1.6.2 Statistical Methods for Pharmacokinetic Analyses

PK parameters will be summarized by treatment group using descriptive statistics (arithmetic means, SD, CV, N, minimum, maximum, and median). In addition, geometric means will be calculated for AUC_{τ} and C_{max_ss}, as appropriate. Figures will be created to display mean and individual verproside and picroside II concentration-time curves. Additional PK analyses may be performed if deemed appropriate.

No value for k_{el}, $t_{1/2}$, and V_{z_ss}/F, as appropriate, will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

An estimate of the relative systemic exposure of AUC_{τ} and C_{max_ss} will be performed by dose normalized ratio analysis expressing the geometric mean ratio and 90% CI of the geometric mean ratio.

Steady-state will be assessed by visual inspection of predose plasma C_{trough} values on Days 15, 29, 43, and 56 following multiple oral dose administration of YPL-001.

Additional analyses will be performed as deemed necessary upon review of the data.

15.1.7 Assessment of Efficacy

Efficacy will not be assessed in this study.

16. STUDY ADMINISTRATION

16.1 Ethics

16.1.1 Institutional Review Board

This protocol will be reviewed by an IRB and the study will not start until the Board has approved the protocol or a modification thereof. The Board is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The board is ICH compliant.

16.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, GCP, 21 CFR Parts 50, 56, and 312, the ethical princliples set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

16.1.3 Patient Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the patients in non-technical terms. Patients will be required to read, sign and date an informed consent form summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Patients will be given a copy of their informed consent form.

16.2 Termination of the Study

The Sponsor reserves the right to discontinue this study and the Investigator reserves the right to terminate their participation at any time.

16.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion relevant to the quality of this study. Designated personnel of Celerion will be responsible for maintaining quality assurance (QA) and quality control (QC) to ensure that the trial is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and Good Laboratory Practice requirements as well as applicable regulatory requirements.

The Clinical Study Report will be audited by the QA department and the quality assurance audit certificate will be included in the study report.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to statistical database lock.

Patient compliance will be monitored throughout the study via procedures such as questioning at check-in to review inclusion and exclusion criteria, urine drug screen at

check-in, mouth check following dosing, and confinement for all conduct procedures with clinical research staff on site at all times.

16.4 Direct Access to Source Data/Documents

The Investigator must maintain, at all times, the primary records (i.e., source documents) of each patient's data. Examples of source documents are laboratory reports, drug inventory, study drug label records, and eCRFs that are used as the source.

Celerion will ensure that the sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6] 5.1.2 & 6.10). In the event that other trial-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

16.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of YPL-001 80 mg tablets, and matching placebo tablets to allow completion of this study. The lot numbers and expiration dates (where available) of the drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the drugs supplied. At the conclusion of the study, any unused drugs (including placebo) will either be retained by the CRU, or returned to the Sponsor, depending on the specific requirements of the regulatory bodies to whom the study report will be submitted. If no supplies remain, this fact will be indicated in the Drug Accountability section of the final report.

16.6 Data Handling and Record Keeping

Celerion standard eCRFs will be used. Each eCRF is reviewed and signed off by the Investigator.

All raw data generated in connection with this study, together with the original copy of the final report, will be retained at each CRU in a designated storage facility, until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

16.7 Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be discussed between Sponsor and the Investigator. All revisions and/or amendments to the protocol in writing must be approved by the Sponsor, the Investigator, and the IRB before implementation.

16.8 Finance and Insurance

Finance and insurance will be addressed in a separate document.

16.9 Publication Policy

All unpublished information given to Celerion by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor's written consent to publish the article.

17. REFERENCES

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[3] FDA Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies-Small Entity Compliance Guide. December 2012. Available online: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332846.pdf

[4] National Cancer Institute. Common Terminology Criteria for Adverse Events v4.0. NCI, NIH, DHHS. May 29, 2009. NIH publication # 09-7473. Available online at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm The quick reference guide is available online at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[5] Busse WW, et al. Investigative bronchoprovocation and bronchoscopy in airway diseases. Am J Respir Crit Care Med. 2005;172(7):807-816

[6] Jarjour NN, Peters SP, Djukanović R, and Calhoun WJ. Investigative use of bronchoscopy in asthma. Am J Respir Crit Care Med. 1998;157(3 Pt 1):692-697.

[7] Jones PW, et al. Development and First Validation of the COPD Assessment Test. Eur Respir J. 2009;34:648-654.

[8] The COPD Assessment Test healthcare professional user guide: expert guidance on frequently asked questions (issue 3: February 2012). Jones PW, Jenkins C, Bauerle O (on behalf of the CAT Development Steering Group).

18. APPENDIXES

18.1 Appendix 1 - UGT Drug Interaction Table

The following list provides medications that are substrates or inhibitors of UGT. Adapted from Williams JA, et al. Drug-drug interactions for UDP-glucuronosyltransferase substrates: a pharmacokinetic explanation for typically observed low exposure (AUCi/AUC) ratios. Drug Metab Dispos. 2004;32(11):1201-8. Epub 2004 Aug 10.

Substrates	Inhibitors
17-beta-estradiol glucuronide Amitriptyline Carvedilol Clofibric acid Codeine Cyclobenzaprine Diclofenac DMXAA Fenofibrate Flavopiridol Furosemide Gemfibrozil Glipizide Irbesartan Lamotrigine Levothyroxine Metoclopramide Metronidazole Morphine Naloxone Naproxen Olanzapine Oxazepam Paracetamol Propofol Raloxifene Tramadol Valdecoxib Valproic acid Zidovudine	17-beta-estradiol glucuronide Flavonoids (citrus fruit) Silybin (herb supplement milk thistle)

18.2 Appendix 2 - SULT Drug Interaction Table

The following list provides medications that are substrates and inhibitors of sulfotransferase. Adapted from Zhang H, Cui D, Wang B, Han YH, et al. Pharmacokinetic drug interactions involving 17alpha-ethinylestradiol: a new look at an old drug. Clin Pharmacokinet. 2007;46(2):133-57; Coughtrie MW, Johnston LE. Interactions between dietary chemicals and human sulfotransferases-molecular mechanisms and clinical significance. Drug Metab Dispos. 2001;29(4 Pt 2):522-528; King RS, Ghosh AA, and Wu J Inhibition of human phenol and estrogen sulfotransferase by certain non-steroidal anti-inflammatory agents. Curr Drug Metab. 2006;7(7):745–753; Nagai M, et al. Inhibitory effects of herbal extracts on the activity of human sulfotransferase isoform sulfotransferase 1A3 (SULT1A3). Biol Pharm Bull. 2009;32(1):105-109; and Harris, R. M.; Waring, R. H. Sulfotransferase inhibition: potential impact of diet and environmental chemicals on steroid metabolism and drug. Current Drug Metabolism 2008;9(4):269-275.

Substrates	Inhibitors
17-beta-estradiol glucuronide Vitamin C Acetaminophen	17-beta-estradiol glucuronide Vitamin C Brown rice Beer Meclofenamate Nimesulide Salicylic acid Acetylsalicylic acid Naproxen Banaba extract Rafuma extract Grape seed extract Peanut seed coat extract Gingko extract Biloba leaf extract St. John’s wort Gymnema Milk thistle

Celerion Project No.: AA98497

Sponsor Project No.: YPL-001-YJP-130403

IND No.: 114903

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

GCP Statement

This study is to be performed in full compliance with the protocol, Good Clinical Practices (GCP), and applicable regulatory requirements. All required study documentation will be archived as required by regulatory authorities.

Confidentiality Statement

1. PROTOCOL REVISION HISTORY

DATE/NAME	DESCRIPTION
16-Feb-2015 by Caroline Engel	Final Protocol, Amendment 2 This protocol amendment is generated to clarify and adjust study procedures as listed below. **Number of Subjects:** The sample size was revised to 60 subjects as it is sufficient to meet the objectives of the study. In case of dropouts, discontinued patients may be replaced at the discretion of the Sponsor as indicated throughout the protocol. Therefore the following sections were corrected accordingly to indicate that at least 60 subjects are planned to be enrolled and randomized with 20 patients to receive one of the 3 treatments: • Section 5 Synopsis (the 1st sentence of the 2nd paragraph under Summary of Study Design and the 1st and 2nd sentences under Number of Patients). • The 1st sentence of the 2nd paragraph of Section 13.1 Overall Study Design and Plan. • The 1st and 3rd sentences of Section 13.3.1 Number of Patients. • The last sentence of Section 15.1.1 Sample Size Calculation. **Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) and COPD Assessment Test (CAT):** BDI/TDI and CAT questionnaires will not be used as a diagnostic tool to assess the patient's potential to meet all inclusion criteria and none of the exclusion criteria. Therefore these questionnaires are not required at screening. In addition, it is not required to perform them for 2 consecutive days to meet the study objectives and therefore, Day 55 assessments were removed. Section 6 Study Events Flow Chart was corrected accordingly. The first sentence in Section 14.3.4.1 Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI) was also corrected to be consistent with Section 6. **Early Termination Procedures:** Weight, and oxygen levels, saturation (%), and heart rate assessed using a pulse oximeter were added to the procedures performed at the end of the Treatment Period on Day 56 or prior to early termination from the study to monitor subject's safety appropriately. A pulmonary function (spirometry) test was also added prior to early termination for safety monitoring. Section 6 Study Events Flow Chart was corrected accordingly.

DATE/NAME	DESCRIPTION
16-Feb-2015 by Caroline Engel	**Recording Concomitant Medication:** Concomitant medication will be recorded at each study visit by the clinical staff in to the electronic data capture system. Therefore, concomitant medications was removed from the list of events that will be recorded by the patients via their e-diary throughout the protocol. The following sections were corrected accordingly: • Footnotes in Section 6 Study Events Flow Chart. • The first sentence of the 4th paragraph of Section 13.2.3 Run-In Period (Days 1 to 14 [± 2 days]). • The 2nd sentence of the 2nd paragraph of Section 13.2.4 Treatment Period (Days 1 to 56). • The 2nd sentence of the first paragraph of Section 14.2.1 Electronic Diary. **Subject Numbering:** The first paragraph of Section 13.4.2 Method of Assigning Patients to Treatment Groups was modified to clarify that the screening number and randomization number are two separate identification number given to each subject at different stages of the study. **Adverse Events Reporting** Footnotes were added to clarify the rating severity definitions in Section 14.1.8.3 Reporting. Minor editorial and typographical corrections were made where applicable.
20-Nov-2014 by Ziv Machnes	Final Protocol, Amendment 1 This protocol amendment is generated to update the study population with regards to smoking frequency, to update the handling procedures for BAL samples, and to clarify other study procedures as listed below. **Study Population:** Section 13.3.2 - Inclusion Criteria, bullet 11 was updated to indicate that the study population will consist only of current and ex-smokers with a history of >10 pack years. As such, the indications for 'packs/year' were replaced with 'pack years' and the allowance for current smokers with <10 pack/years was removed. Wording was added to indicate an approximately equal number of current and ex-smokers will be enrolled, and that each treatment group will consist of an approximetly equal number of smokers and ex-smokers. In addition, the stratification criteria for the randomization was updated to consist of either current or ex-smokers. The following sections were affected: • Section 5 – Synopsis (under Study Population and Number of

DATE/NAME	DESCRIPTION
20-Nov-2014 by Ziv Machnes	Patients) • Section 13.1 - Overall Study Design and Plan (second paragraph) • Section 13.3.1 – Number of Patients. • Section 13.4.2 - Method of Assigning Patients to Treatment Groups. **BAL Sample Handling:** Section 14.3.2.3 - Bronchoalveolar Lavage (BAL) was updated to indicate that sample handling, processing and storage procedures will be provided in a separate document. **Follow-up Procedures:** The wording in regards to follow-up procedures to be conducted on 14 days (± 2 day), after the last study drug administration, was updated to indicated a phone-call and not a visit, as indicated correctly in Section 6 – Study Event Flow Chart. Study event were updated accordingly. The following sections were affected: • Section 5 – Synopsis (under Duration of Participation for Patients, and Exploratory Outcome Measures [under Blood Assessments, Pulmonary Assessment, and Quality of Life Assessments]) • Section 13.3.5.2 – Prohibitions (under Alcohol) • Section 14.1.8.2 – Monitoring (first paragraph). **Study Duration:** The total duration of the study indicated in Section 5 – Synopsis (under Duration of Participation for Patients) was corrected to 12 weeks to correspond with the actual study duration as indicated throughout the protocol. **Inflammatory Markers in Blood Samples:** The list of cell types to be evaluated as part of the inflammatory markers in the blood was updated to include monocytes instead of macrophages, as macrophages are not expected to be present in blood. The following sections were affected: • Section 5 – Synopsis (under Study Objectives, fourth exploratory objective, and under Exploratory Outcome Measures [under Pharmacodynamic Assesments, Blood Assessments, first bullet]) • Section 12.1 - Study Objectives (fourth exploratory objective) • Section 12.2 - Study Endpoints (third exploratory endpoint) • Section 14.3.3 - Blood Biomarkers (first bullet) • Section 15.1.5.1 - Biomarkers (third bullet)

DATE/NAME	DESCRIPTION
20-Nov-2014 by Ziv Machnes	**Neutrophil Evaluation in BAL Samples** Neutrophils were added to the list of cell types to be evaluated as a percentage of the total cell count in BAL samples. The following sections were affected: • Section 5 – Synopsis (under Study Objectives, second exploratory objective and under Exploratory Outcome Measures [under Pharmacodynamic Assessments, Bronchoalveolar Lavage Assessments, second bullet]) • Section 12.1 - Study Objectives (second exploratory objective) • Section 12.2 - Study Endpoints (second exploratory endpoint) • Section 14.3.2.4 - Biomarkers (second bullet) • Section 15.1.5.1 – Biomarkers (second bullet) **Location of Study Drug Administration**: Wording was added in Section 6 – Study Events Flow Chart for Day 56, to clarify that the study drug will be administered at the CRU. **Meal Schedule**: The indication for fasting requirement in Section 13.2.4.1 – Meal Schedule, was corrected to indicate patients will fast overnight for at least 12 hours before bronchoscopy and BAL collection on Days -1 and 55 instead of Days -1 and 56, as correctly indicated in Section 6 – Study Events Flow Chart. **ECG Monitoring:** Following an update in Celerion's standard operating procedure, Section 14.1.5 – Electrocardiogram Monitoring was updated to include at least 5 minutes of rest prior to each ECG measurement (instead of at least 1 minute as previously indicated). **Hematology:** The tests included in the hematology panel Section 14.1.6.1 – Hematology were updated to indicate that the red blood cell (RBC) count will include a reticulocytes count, and that the white blood cell (WBC) count with differential will include monocytes but will not include reticulocytes. **Bronchoscopy and BAL:** Due to the sensitivity of YPL-001 components to UV light, a warning was added to protect all samples from exposure to UV light, as indicated for the PK blood samples. The following sections were affected: • Section 14.3.2.2 - Bronchial Brushings • Section 14.3.2.3 - Bronchoalveolar Lavage (BAL)

DATE/NAME	DESCRIPTION
20-Nov-2014 by Ziv Machnes	**PK Population:** The indication for measurable concentration of verproside and picroside II in urine was removed from the definition of PK population in Section 15.1.2 - Patients to Analyze, as there is no urine PK sampling planned for this study. Minor typographic and editorial corrections were made where applicable.
18-Sep-2014 by Caroline Engel	Final Protocol

2. SPONSOR – SIGNATORIES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

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Ryoo, Byung Hwan — Signature

24/02/2015 — Date

3. INVESTIGATORS SIGNATURES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

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3/10/15

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Investigator (Signature)

Date

INVESTIGATORS SIGNATURES (*CONTINUED*)

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

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Investigator (Signature)

3/9/2015
Date

4. ADDITIONAL KEY CONTACTS FOR THE STUDY

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5. SYNOPSIS

Compound:	YPL-001
Clinical Indication:	Treatment of inflammatory diseases of the respiratory tract such as asthma and chronic obstructive pulmonary disease (COPD)
Study Type	Phase 2a, proof of concept
Study Objectives	The **primary objective** of the study is to assess the safety and tolerability of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients. The **secondary objective** of the study is to assess the number and magnitude of daily respiratory symptoms of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients. The **exploratory objectives** of the study are to evaluate the following in moderate to severe COPD patients: 1. To assess bronchoalveolar lavage (BAL) epithelial brushings for YPL-001 component levels. 2. To compare BAL samples for total cell count (cells/mL) macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; neutrophil, macrophage, lymphocyte and eosinophil counts as absolute inflammatory cell numbers in YPL-001 groups versus placebo group. 3. To compare BAL samples for tumor necrosis factors alpha (TNF-α), interleukin (IL)-1β, IL-4, IL-5, IL-6, IL-8, IL-13, myeloperoxidase (MPO), neutrophil elastase, monocyte chemotactic protein (MCP)-1, and matrix metalloproteinase (MMP)-9 in YPL-001 groups versus placebo group. 4. To compare blood inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) and concentrations of C-reactive protein (CRP), fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9 in YPL-001 groups versus placebo group. 5. To compare spirometric functions (forced expiratory volume in one second [FEV_1], forced vital capacity [FVC], FEV_1/FVC, and inspiratory capacity [IC]) in YPL-001 groups versus placebo group. 6. To compare patient reported outcomes (Baseline Dyspnea Index [BDI]/Transition Dyspnea Index [TDI], COPD Assessment Test [CAT]) in YPL-001 groups versus placebo group. 7. To assess verproside and picroside II concentration in plasma and BAL and verproside and picroside II pharmacokinetics (PK) in plasma following multiple oral doses administration of two YPL-001 dose levels.

Summary of Study Design	This is a Phase 2a, proof-of-concept, multicenter, randomized, double-blind, double-dummy, 3-treatment, parallel study, with low and high YPL-001 doses (80 mg and 160 mg twice daily [BID]) and a placebo control in moderate to severe COPD patients. At least 60 patients will be enrolled and randomized into 3 treatment groups (20 patients per group). Patients will participate only once. Safety and tolerability will be assessed throughout the study. Assessment of respiratory symptoms and symptom burden in YPL-001 and placebo treatments will be performed daily through patient self-report of peak expiratory flow (PEF), major and minor symptoms of COPD exacerbation, dyspnea, and activity in their electronic diary (e-diary). Spirometry measurement, bronchoalveolar lavage (BAL), and blood samples will be collected for the pharmacodynamic (PD) assessment of YPL-001 and placebo treatments. Serial blood samples will also be collected for PK assessment of verproside (the principal active ingredient of YPL-001) and picroside II. Other components of YPL-001 and its metabolites may also be analyzed in plasma. Following screening, eligible patients will discontinue non permitted respiratory drugs if already receiving them and enter a 14 ± 2 days Run-in Period during which patients will be given albuterol taken on an as required basis and daily tiotropium 18 µg (one capsule inhaled daily in the morning) to be administered at home. On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their daily symptoms throughout the Run-in Period. Patients will return to the clinical research unit (CRU) on the morning of Day -1 of the Treatment Period to confirm their eligibility and assess their health conditions. If they still meet all of the inclusion criteria and none of the exclusion criteria, they will undergo Day -1 scheduled study procedures. Patients will return to the CRU the next day (Day 1) to be randomized and receive one of the 3 treatments and undergo all scheduled study procedures. Patients will return on the morning of Days 15, 29, 43, 55, and 56 of the Treatment Period for study drug administration and procedures. Prior to each release from the CRU, patients will receive a properly labeled container with sufficient doses which will be self-administered by patients at home until the next morning visit at the CRU. Patients will continue recording their daily symptoms via the e-diary throughout the Treatment Period. Patients will return the e-diary device on Day 56 to CRU staff. The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any adverse event (AE) has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary. Patients will be instructed to call the Investigator if breathing worsens or if they need to take more than 8 puffs per day of albuterol for more than 2 consecutive days. If the Investigator determines that the patient is too unstable to continue in the study, he/she will be discontinued. Rescue medication will be used for any patient with an exacerbation of COPD and will be administered in accordance with the study center standard of care.

Study Population	Patients will be adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3) with a predominant bronchitic component and a history of frequent (>2/year) COPD exacerbations, between 40 and 80 years of age (inclusive). An approximately equal number of current and ex-smokers will be enrolled.
Number of Patients	The study is planned to enroll at least 60 patients. Patients will be divided in 3 treatment groups with 20 patients to receive one of the 3 treatments (i.e., low and high YPL-001 doses [80 mg and 160 mg BID] and a placebo control) as per the randomization schedule. Each treatment group will consist of an approximately equal number of current and ex-smokers.
Duration of Participation for Patients	The planned length of participation in the study for each patient is approximately 12 weeks (from Day 1 of the Run-in Period through completion of the follow-up procedures on Day 70 [± 2 days]).
Duration of Study Conduct	The study is planned to take place over approximately 12 to 24 months (from screening of the first patient through completion of all study procedures for the last patient). This time period may change in the event that the study is terminated early, additional time is required to review safety, or a decision is made to complete an unscheduled analysis for a group.
Study Products	YPL-001 will be supplied as 80 mg tablets for oral administration. Placebo will be supplied as YPL-001 80 mg matching placebo tablets for oral administration. An unblinded pharmacist will be responsible for providing YPL-001 or placebo to the blinded study personnel for administration.
Dosage, Dosage Form, Route, and Dose Regimen	Treatments are described as follows: Treatment A: Multiple oral YPL-001 80 mg doses (1 x 80 mg tablet + 1 x 1 YPL-001 80 mg matching placebo tablet) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56. Treatment B: Multiple oral YPL-001 160 mg doses (2 x 80 mg tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56. Treatment C: Multiple oral matching placebo (2 x 1 YPL-001 80 mg matching placebo tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56. In all treatments, one tiotropium (Spiriva® HandiHaler®) 18 µg capsule will also be administered QD every morning prior to study drugs administration. Albuterol will be administered on an as needed basis. Each dose of Treatments A, B, and C will be administered orally with approximately 240 mL of water.

Stopping Rules	A decision to stop or suspend the study will be made jointly by the Sponsor and the Investigator following the review of all pertinent safety and tolerability. Together they will make one of the following determinations: 1. To continue with the study as planned. 2. To continue with the study and add additional safety evaluations. 3. To continue with the study by adjusting to a lower dose if 2 patients at any dose level meets any of the following criteria and the patient was determined to have received YPL-001 after unblinding: a. Has a drug–related, unexpected serious adverse event (SAE). b. Experiences drug-related grade ≥ 3 toxicity. 4. The study will be terminated if ≥ 3 patients at any dose level meet any of the following criteria and the patients were determined to have received YPL-001 after unblinding: a. Has a drug–related, unexpected SAE. b. Experience drug related grade ≥ 3 toxicity.
Primary Outcome Measures	Safety and tolerability will be monitored through physical examinations, vital signs, pulse oximetry, ECGs, clinical laboratory tests, and AEs.
Safety and Tolerability Analysis	The following analyses will be performed. Safety analyses will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data, when appropriate. **Medical History:** Medical history will be listed by patient. **Adverse Events:** AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion (e.g., 17.0 or higher) and data will be summarized by System organ class (SOC) and preferred term. The number of treatment-emergent AEs (TEAEs) will be reported. In addition, the number and percent of patients reporting each TEAE will be summarized separately for each treatment. A by-patient AE data listing, including verbatim term, preferred term, treatment, severity, outcome, and relationship to treatment, will be provided. **Physical Examination:** Changes in physical examinations will be described in the text of the final report and significant findings will be reported as AEs. **Clinical Laboratory Tests, Electrocardiograms, Vital Signs, and Pulse Oximetry Measurements:** All clinical laboratory tests, 12-lead ECGs, vital signs, and pulse oximetry measurements and their change from baseline, if applicable, will be summarized by treatment and time point of collection. A shift table describing out-of-normal range shifts will be provided for clinical laboratory results. A normal-abnormal shift table will be presented for ECGs.

Safety and Tolerability Analysis (continued)	**Concomitant Medications:** Concomitant medications will be listed by patient and coded using the most current World Health Organization (WHO) drug dictionary available at Celerion (e.g., 01-MAR-2014 or later).
Secondary Outcome Measures	PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (Duke Activity Status Index [DASI]) self-reported daily by the patients using an e-diary.
Symptom Monitoring Analysis	Symptom free days and overall symptom burden will be evaluated and compared across treatment groups. Secondary outcome analysis will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative data and frequency counts will be compiled for classification of qualitative data, when appropriate. **Peak Expiratory Flow and Symptoms of COPD Exacerbation:** PEF measurements and symptoms of COPD exacerbation and their change from baseline, will be summarized by treatment and time point of collection. **Dyspnea and Activity:** The Modified Borg Dyspnea Scale and DASI scores will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.
Exploratory Outcome Measures	**Pharmacodynamic Assessments:** <u>Bronchoalveolar Lavage Assessments:</u> BAL samples will be collected at baseline and again at the completion of the study for PD assessments of biomarkers. Biomarker assessments include: 1. epithelial brushings for YPL-001 component levels; 2. total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells 3. total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers 4. concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9. <u>Blood Assessments:</u> Blood samples will be collected at screening, and throughout the study for PD assessments of biomarkers. Biomarker assessments include: 1. inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) 2. concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9. <u>Pulmonary Assessment:</u> Pulmonary function measurements (spirometry [FEV_1, FVC, FEV_1/FVC, and IC] will be performed at screening, and throughout the study.

Exploratory Outcome Measures (continued)	Quality of Life Assessments: Patient reported outcomes (e-diary, BDI/TDI, CAT) will be performed at baseline, and throughout the study. **Pharmacokinetic Assessments:** Bronchoalveolar Lavage Assessments: BAL samples will be collected at baseline and again at the completion of the study to determine verproside and picroside II concentrations in BAL. Other components of YPL-001 and its metabolites may also be analyzed. Plasma Assessments: Serial blood samples will be collected prior to the initial dosing and through 12 hours following dosing on Days 1 and 56 to determine verproside and picroside II concentrations in plasma. Predose samples will also be collected in the morning of Days 15, 29, 43 and 56 for C_{trough} determination. Other components of YPL-001 and its metabolites may also be analyzed. The sampling schedule and/or collection intervals may be modified based on the results as the study progress.
Pharmacodynamic Analysis	**Blood, Plasma, and Pulmonary biomarkers:** When applicable, the raw data and % change from baseline or placebo, as appropriate, for PD markers (BAL biomarkers, blood biomarkers, and pulmonary biomarker) will be summarized by time point and treatment using descriptive statistics (arithmetic means, standard deviations [SD], coefficients of variation [CV], sample size [N], minimum, maximum, and median). Figures will be created to display mean and individual level or activity as a function of time. **Quality of Life:** The quality of life parameters will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.
Pharmacokinetic Parameters and Analysis	Noncompartmental PK parameters, including AUC_{0-t}, AUC_{0-inf}, AUC_{τ}, k_{el}, C_{max}, C_{max_ss}, C_{min_ss}, C_{trough}, t_{max}, t_{max_ss}, CL/F, CL_{ss}/F, V_z/F, V_{z_ss}/F, and $t_{1/2}$, as appropriate, will be calculated from plasma concentrations of verproside and picroside II from patients who received YPL-001 only. Additional PK parameters may be calculated if deemed appropriate. Plasma PK parameters may also be calculated for other components of YPL-001 and its metabolites. PK parameters will be summarized by treatment using descriptive statistics. Relative exposure of verproside and picroside II will be assessed between the two YPL-001 dose levels, and steady-state will be assessed by visual inspection in the active treatment groups. Verproside and picroside II concentration in BAL samples from patients who received YPL-001 only will be listed.

6. STUDY EVENTS FLOW CHART

Study Procedures[a]	Screen[b]	Run-in Period		Treatment Period																			
Days →		1	2-14 (±2)	-1	1																		
Hours →					Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12
Administrative Procedures																							
Informed Consent	X																						
Inclusion/Exclusion Criteria	X	X																					
Medical History	X																						
Randomization																							
Safety Evaluations																							
Physical Examination[c]	X			X[d]																			
Height	X																						
Weight	X			X[d]																			
Chest X-ray[e]	X																						
12-Lead Electrocardiogram	X			X[f]																			
Vital Signs[g]	X			X[f]	X						X		X						X				
Pulse Oximetry	X			X[f]																			
Hem, Chem, and UA[h]	X			X[d]																			
Serum Pregnancy Test (♀ only)	X			X[d]																			
Serum FSH (postmenopausal ♀ only)	X																						
Urine Alcohol & Drug Screen	X			X[d]																			
HIV/Hepatitis Screen	X																						
AE Inquiries																							
AE Monitoring										X													
ConMeds Monitoring	X									X													
Symptoms Monitoring																							
Diary Training		X																					
Diary Use[i]										X													
PEF, COPD exacerbation, dyspnea and activity[j]										X													
Study Drug Administration																							
Tiotropium Administration		X	X	X	X																		
Study Drug Administration at CRU[k]						X																	X
Pharmacodynamic																							
Pulmonary Function (Spirometry)[l]	X			X[d]																			

Study Procedures[a]	**Screen**[b]	**Run-in Period**		**Treatment Period**																		
Days →		1	2-14 (±2)	-1	1																	
Hours →					Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12
Pharmacodynamic																						
Bronchoscopy and BAL Biomarkers[m]				X																		
Blood Biomarkers	X				X						X											
BDI/TDI & CAT				X[d]																		
Pharmacokinetic																						
Blood for Verproside & Picroside II PK					X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]
Other Procedures																						
Visit & Return Visits[o]	X	X		X	X																	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.
b. Within 14 days of Day 1 (inclusive) of the Run-in Period.
c. A full physical examination will be performed at screening. Symptom-driven physical examinations will be performed at other scheduled times, and may be performed at other times at the Investigator's discretion.
d. To be performed prior to the bronchoscopy procedures.
e. To be performed at screening or within 3 months (inclusive) of screening.
f. ECGs, vital sign and pulse oximetry will be measured within 2 hours of bronchoscopy procedures. During the bronchoscopy procedures and BAL sample collection, patients will be continuously monitored for ECGs, vital signs (blood pressure, heart rate, respiration rate, and body temperature), and oxygen saturation.
g. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
h. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.
i. Patients will be provided with an e-diary device to record their self-administered doses, whether the dose was administered with food, and daily respiratory symptoms.
j. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).
k. Prior to release from the CRU, patients will receive a properly labeled container with sufficient study drug for their assigned treatment which will be self-administered by patients at home until the next morning visit at the CRU. Patients must return the container (empty or not) at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.
l. Pulmonary function will be performed prior to and 20 to 30 minutes after inhalation of approximately 400 µg albuterol.
m. Bronchoscopy and BAL sample collection will be performed following a 12-hour fast.
n. To be performed prior to dosing.
o. Patients will be admitted to the CRU at the time indicated by the CRU.

STUDY EVENTS FLOW CHART *(CONTINUED)*

Study Procedures[a]	**Treatment Period**											
Days →	2-14	15		16-28	29		30-42	43		44-54	55	
Hours →		AM	PM		AM	PM		AM	PM		AM	PM
Safety Evaluations												
Physical Examination[b]					X[c]						X[d]	
Weight					X[c]						X[d]	
12-Lead Electrocardiogram					X[c]						X[e]	
Vital Signs[f]		X[c]			X[c]			X[c]			X[e]	
Pulse Oximetry											X[e]	
Hem, Chem, and UA[g]					X[c]						X[d]	
Serum Pregnancy Test (♀ only)		X[c]			X[c]			X[c]			X[d]	
Urine Alcohol & Drug Screen		X[c]			X[c]			X[c]			X[d]	
AE Inquiries		X[c]			X[c]			X[c]			X[d]	
AE Monitoring	X											
ConMeds Monitoring	X											
Symptoms Monitoring												
Diary Use[h]	X											
PEF, COPD exacerbation, dyspnea and activity[i]	X											
Study Drug Administration												
Tiotropium Administration	X											
Study Drug Administration at CRU		X			X			X			X	
Study Drug Administration at Home[j]	X		X	X		X	X		X	X		X
Pharmacodynamic												
Pulmonary Function (Spirometry)[k]		X[c]			X[c]			X[c]			X[n]	
Bronchoscopy and BAL Biomarkers[l]											X[c]	
Blood Biomarkers		X[c]			X[c]			X[c]				
BDI/TDI & CAT		X[d]			X[d]			X[d]				
Pharmacokinetic												
Blood for Verproside & Picroside II PK		X[c]			X[c]			X[c]				
Other Procedures												
Visit & Return Visits[m]		X			X			X			X	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.
b. Symptom-driven physical examinations will be performed at scheduled times, and may be performed at other times at the Investigator's discretion.
c. To be performed or completed prior to dosing.
d. To be performed or completed prior to bronchoscopy procedures and/or dosing.
e. ECGs, vital sign and pulse oximetry will be measured within 2 hours of bronchoscopy procedures. During the bronchoscopy procedures and BAL sample collection, patients will be continuously monitored for ECGs, vital signs (blood pressure, heart rate, respiration rate, and body temperature), and oxygen saturation.
f. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
g. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.
h. Patients will be provided with an e-diary device to record their self-administered doses, whether the dose was administered with food, and daily respiratory symptoms.
i. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).
j. Prior to release from the CRU, patients will receive a properly labeled container with sufficient study drug for their assigned treatment which will be self-administered by patients at home until the next morning visit at the CRU. Patients must return the container (empty or not) at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.
k. Pulmonary function will be performed prior to and 20 to 30 minutes after inhalation of approximately 400 µg albuterol.
l. Bronchoscopy and BAL sample collection will be performed following a 12-hour fast.
m. Patients will be admitted to the CRU at the time indicated by the CRU.
n. To be completed prior to bronchoscopy procedures and dosing, or upon early termination.

STUDY EVENTS FLOW CHART *(CONTINUED)*

Study Procedures[a]	**Treatment Period**																		**EOT or ET**[b]	**FU**[c]
Days →	56																			
Hours →	Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12		
Safety Evaluations																				
Physical Examination[d]																			X	
Weight																			X	
12-Lead Electrocardiogram																			X	
Vital Signs[e]	X						X		X						X				X	
Pulse Oximetry																			X	
Hem, Chem, and UA[f]																			X	
Serum Pregnancy Test (females only)																				
Urine Alcohol & Drug Screen	X																			
AE Inquiries	X																		X	
AE Monitoring									X											X
Concomitant Medication Monitoring									X											
Symptoms Monitoring																				
Diary Use[g]	X																			
PEF, COPD exacerbation, dyspnea and activity[h]	X																			
Study Drug Administration																				
Tiotropium Administration	X																			
Study Drug Administration at CRU		X																		
Pharmacodynamic																				
Blood Biomarkers	X[i]						X													
BDI/TDI & CAT	X[i]																			
Pharmacokinetic																				
Blood for Verproside Pharmacokinetics	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Other Procedures																				
Return Visits[j]								X											X	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.

b. To be performed at the end of the Treatment Period on Day 56 or prior to early termination from the study.

c. The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

d. Symptom-driven physical examinations will be performed at scheduled times, and may be performed at other times at the Investigator's discretion.

e. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.

f. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, Patients may not have fasted for 8 hours before the serum chemistry sample is taken.

g. Patients will return the e-diary device on Day 56 to CRU staff.

h. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

i. To be performed at predose on Day 56 or upon early termination.

j. Patients will be admitted to the CRU at the time indicated by the CRU.

Abbreviations: ♀ = Female, AE = Adverse events, AM = Morning, BAL = bronchoalveolar lavage, BDI/TDI = Baseline Dyspnea Index/Transition Dyspnea Index Test, CAT = COPD Assessment Test, Chem = Serum chemistry, COPD = chronic obstructive pulmonary disease, CRU = Clinical research unit, ConMeds = Concomitant medication, DASI = Duke Activity Status Index, ECG = Electrocardiogram, e-diary = electronic diary, EOT/ET = End-of-Treatment or early termination, FSH = Follicle-stimulating hormone, Hem = Hematology, HIV = Human immunodeficiency virus, IL= interleukin, PEF = Peak expiratory flow, PK = Pharmacokinetics, PM = Evening, Preg = Serum pregnancy, Screen = Screening, UA = Urinalysis.

7. TABLE OF CONTENTS

8. ABBREVIATIONS

Only those uncommon abbreviations specific to this study are listed. Pharmacokinetic (PK) parameter abbreviations and definitions may be found in Section 15.1.6.1.

AE	Adverse event
AHR	Airway hyper-responsiveness
ALD	Approximate lethal dose
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
BALF	Bronchoalveolar lavage fluid
BDI	Baseline Dyspnea Index
BID	Twice daily
BLQ	Below the lower limit of quantification
BMI	Body mass index
bpm	Beat per minute
BUN	Blood urea nitrogen
°C	Degrees Celsius
CAT	COPD Assessment Test
Chem	Chemistry
CFR	Code of Federal Regulations
CK	Creatine kinase
CNS	Central nervous system
CO_2	Carbon dioxide
Coag	Coagulation
COPD	Chronic obstructive pulmonary disease
CRO	Contract Research Organization
CRP	C-reactive protein
CRU	Clinical research unit

CS	Clinically significant abnormality
CSC	Cigarette smoking condensate
CXCL	Chemokine (C-X-C motif) ligand
CV	Coefficient of variation
DASI	Duke Activity Status Index
dL	Deciliter
DRF	Dose range finding
e-diary	Electronic diary
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
ERS	European Respiratory Society
F	Female
°F	Degrees Fahrenheit
FDA	Unites States Foods and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FU	Follow-up
FVC	Forced vital capacity
g	gram
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HBsAg	hepatitis B surface antigen
HCO_3	Bicarbonate
HCV	hepatitis C antibodies
HED	Human equivalent dose
Hem	Hematology
HIV	Human immunodeficiency virus
hr	Hour
IC	Inspiratory capacity
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroid

IgE	Immunoglobulin E
IL	Interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
kg	Kilogram
kg/m^2	Kilogram per meter squared
LABA	long acting beta agonist
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
LOQ	Limit of quantitation
LPS	Lipopolysaccharide
LSM	Least-squares means
µg	Microgram
m^2	Square meter
M	Male
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCO	Myeloperoxidase
MCP	Monocyte chemotactic protein
MCV	Mean Corpuscular Volume
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
MIP	Monocyte inhibitory protein
mL	Milliliter
mmHg	Millimetre of mercury
MMP	Matrix metalloproteinase
msec	Millisecond
MTD	Maximum Tolerated Dose
N	Sample size
NCS	Not clinically significant

ng	Nanogram
No.	Number
NOAEL	No observed adverse effect levels
OTC	Over-the-counter
OVA	Ovalbumin
PD	Pharmacodynamic(s)
PEF	Peak expiratory flow
PK	Pharmacokinetic(s)
QA	Quality Assurance
QC	Quality Control
QT	Interval between the Q and T waves on the electrocardiogram tracing
QTcF	Corrected QT interval with Fridericia's formula
RBC	Red blood cell
RDW	Red cell distribution width
Resp	Respiration
ROS	Reactive oxygen species
SABA	Short-acting β2-agonist
SAD	Single ascending dose
SAE	Serious adverse event
SAMA	Short-acting anticholinergic agent
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SULT	Sulfotranferase
TBIL	Total bilirubin
TDI	Transition Dyspnea Index
TEAE	Treatment-emergent adverse event
Th	T helper
TNF-α	Tumor necrosis factors alpha
UA	Urinalysis
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal

US	United States
WBC	White blood cell
WHO	World Health Organization

9. INTRODUCTION AND BACKGROUND

This study is being conducted as the third in a series of studies for the clinical development of YPL-001. The trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. The patient population will be comprised of moderate to severe (GOLD Stage 2-3) COPD patients.

9.1 YPL-001

YPL-001 drug product is an oral dosage form of an herbal extract from the aerial parts of the plant Speedwell (*Pseudolysimachion rotundum* subsp. *Subintegrum*). *Pseudolysimachion* (*Veronica*) is a perennial herb which has been used as a traditional medicine in Korea and China for the treatment of inflammatory diseases of the respiratory tract such as asthma and COPD.

As a botanical drug product, the drug substance is a mixture of chemical species (iridoids [including verproside] and other related compounds) and biological activity is considered to be from the mixture and not from an individual component. It is unknown if the total activity from individual components is additive or synergistic. Five active constituents, classified as iridoids, have been identified in the herbal extract: verproside, picroside II, catalpolside, isovanilloyl catalpol, and 6-*O*-veratroylcatalpol. Recent experimentation has revealed that the principal active ingredient in *Pseudolysimachion* is verproside, a dihydroxylated catalpol derivative.

YPL-001, containing verproside and other active ingredients, is being developed as a potential oral treatment for long term inflammatory diseases of the respiratory tract such as asthma or bronchitic COPD. Current long term control medications include corticosteroids, cromolyn sodium, immunomodulators, long acting beta agonists, (LABAs), methylxanthines, and leukotriene modifiers. YPL-001 belongs most closely with the leukotriene modifier class of drug.

A brief overview of available information regarding YPL-001 follows below. Details can be found in the YPL-001 Investigator's Brochure of March 1, 2013. [1]

9.1.1 Preclinical Trials

9.1.1.1 Pharmacology

Five *in vivo* primary pharmacology studies have been completed.

In ovalbumin-sensitized mice, an animal model for asthma, YPL-001 reduced elevated immunoglobulin E (IgE), IL-4, IL-5, IL-13, airway hyper-responsiveness, and mucus hyper-secretion.

In the lipopolysaccharide (LPS)- and cigarette smoking condensate (CSC)-induced COPD mice model, verproside and roflumilast treatment inhibited the accumulation of neutrophils in Bronchoalveolar lavage fluid (BALF) as well as the increase of several proinflammatory cytokines and chemokines. Neutrophil infiltration induced by LPS and CSC treatments was associated with a significant increase in BALF levels of the chemoattractants, TNF-α, chemokine (C-X-C motif) ligand (CXCL)-1, and monocyte inhibitory protein (MIP)-2. These data also demonstrated that the effect of YPL-001 and verproside involves down-regulation of the influx of neutrophils and production of TNF-α,

CXCL-1, and MIP-2 molecules which play a major role in tissue remodeling.

YPL-001 significantly suppressed the increase of inflammatory cell counts, particularly neutrophils in BALF and also effectively suppressed elevated levels of TNF-α, CXCL-1 and MIP-2 with the reduction in airway inflammatory responses in CSC- and LPS-induced COPD mice.

YPL-001 also effectively suppressed the increased inflammatory cell count, particularly neutrophils in BALF and also significantly inhibited elevated levels of TNF-α, IL-1β and IL-6 with the reduction in reactive oxygen species (ROS) production and elastase activity in cigarette smoke- and LPS-induced COPD mice.

In the LPS- and cigarette smoke-induced COPD rats model, YPL-001 significantly inhibited the increase of inflammatory cell count, particularly neutrophils in BALF and also effectively suppressed elevated levels of TNF-α, IL-1β, IL-6, MIP-2 and CRP.

YPL-001 effectively inhibited development of both T helper (Th)2 and Th1/Th17 type asthma in these murine models. These effects resulted from inhibition of cytokine and chemokine production by infiltrated inflammatory cells and antigen specific T cells in lymph nodes. YPL-001 did not inhibit development of COPD which was induced by *E.coli* extracellular vesicles.

9.1.1.2 Pharmacokinetics

After oral administration of YPL-001 at 12.5, 25, and 50 mg/kg doses (5.225, 10.45, and 20.9 mg/kg as verproside) in rats, verproside was rapidly absorbed; verproside was detected at the first blood sampling time (5 min) and absorbed rapidly, with the t_{max} achieved at 0.46-0.61 hour for all three doses. The post-absorption phase of the mean plasma verproside concentration-time profiles showed a poly-exponential decay.

The area under the plasma concentration-time curve (AUC) and the maximum plasma concentration (C_{max}) of verproside were linearly increased as the oral dose of YPL-001 increased. Alternately, the dose normalized (based on 12.5 mg/kg) AUCs and C_{max} of verproside were comparable among different doses studied. The elimination half-lives ($t_{1/2}$), 2.14 – 3.91 hours, and other PK parameters of verproside for all three doses were also comparable. These findings indicate that the PK parameters of verproside were independent of doses.

The fraction of dose of verproside excreted unchanged in urine at 24 hours was less than 0.10%. Verproside was not detected in the 24 hours feces sample for all three doses studied. These results indicate that verproside is almost completely eliminated by the first pass metabolism due to O-methylation, glucuronidation, sulfation, and intestinal microflora-mediated metabolism. Verproside is metabolized to verproside glucuronides (M1 and M2), verproside sulfates (M3 and M4), O-methylverproside such as picroside II (M5) and isovanilloylcatalpol (M6), 3,4-dihydroxybenzoic acid (M11), 3-methyoxy-4-hydroxybenzoic acid (M15) and 3-hydroxy-4-methoxybenzoic acid (M16), which are further metabolized to their glucuronides and sulfates including M5 glucuronide (M7), M5 sulfate (M9), M6 glucuronide (M8), M6 sulfate (M10), M11 glucuronide (M12), M11 sulfates (M13 and M14), M15 glucuronides (M17 and M18), M15 sulfate (M20), M16 glucuronide (M19), and M16 sulfate (M21). The O-methylation of verproside to picroside II (M5) and isovanilloylcatalpol (M6) followed by glucuronidation and sulfation

were identified as the major metabolic pathway in bile and urine samples.

Picroside II, a major metabolite of verproside, was detected in plasma samples but most plasma concentrations in 12.5 and 25 mg/kg YPL-001 treated groups were below the lower limit of quantification (LLOQ, 2.5 ng/mL) compared to 50 mg/kg YPL-001 treated group. The picroside II-to-verproside AUC ratios in the 50 mg/kg YPL-001 treated group were 13.9-65.1%, suggesting that picroside II may be one of the major YPL-001 metabolites. Plasma concentrations of isovanilloylcatalpol, a metabolite of verproside and isomer of picroside II, were below LLOQ (2.5 ng/mL) after oral administration of all three YPL-001doses tested.

Verproside, catalposide, and picroside II were not considerably bound to human plasma proteins; the binding values were 36.3-55.0% at verproside concentrations of 0.1, 1.0, and 10.0 μg/mL, 31.2-49.5% at catalposide concentrations of 0.5, 1, and 10 μg/mL, and 34.0-41.2% at picroside II concentrations of 0.5, 1, and 10 μg/mL.

9.1.1.3 Toxicology

Two single dose toxicity studies with YPL-001 have been completed in rat and dog. In the rat study, polyuria was observed in the 5,000 mg/kg dosing group of each sex between 2-4 hours after YPL-001 administration. Discolored stool was observed dose-dependently in the all dosing groups of each sex at 1-3 days post administration. Soft stool, mucous stool and soiled perineal region were observed at 1 day after administration in the 2,500 and 5,000 mg/kg dosing group of each gender. There were no notable changes of body weight in any study group. There were no notable gross necropsy findings in any of the study groups. Based on the results above, when YLP-001 is administered orally to Sprague-Dawley rats, the approximate lethal dose (ALD) is higher than 5,000 mg/kg. In the dog study, There were no changes with respect to the toxicity of the test article in the clinical signs, body weight change and necropsy findings after a single dose. Vomiting and discoloration of stool was noted. The Maximum Tolerated Dose (MTD) was determined to be 2,000 mg/kg for males and 1,000 mg/kg for females.

Two dose range finding (DRF) studies with YPL-001 have been completed in rat and dog, followed by two pivotal, 4-week, GLP repeated-dose toxicology studies in the same species. In the rat DRF study, YPL-001 induced anemia and hemolysis at 667 mg/kg/d and at higher doses. In addition, enlargement of cecum was observed at 667 mg/kg/d and at higher doses. The NOEL for this study was 74 mg/kg/d in both genders. In the dog DRF study, decreases in red blood cell (RBC) values were present in males at the high dose level (1000 mg/kg/d). In females the TBIL values were elevated at the 1000 mg/kg/d dose levels. Females had enlarged spleens at 125, 250 and 1000 mg/kg dose levels without dose relationship (trend was toward significance). The MTD for this study was 1000 mg/kg/d.

Primary results from the pivotal, 4-week rat study included:

There were no abnormal clinical signs observed in any group during dosing or the recovery periods and no mortality was reported.

Hematology: Compared to controls, there were decreases in values of RBC, hematocrit, and hemoglobin at all dose levels of both genders in a dose-dependent fashion. The

values of hemoglobin distribution width, red cell distribution width (RDW) and reticulocyte at all dose levels of both genders were higher or significantly higher than those of vehicle control.

Clinical Biochemistry: There were significant increases in the values of TBIL at all dose levels of both genders when compared with that of vehicle control. After the recovery period, there were no noticeable changes related to the test article.

Organ Weights: Slight increase in absolute & relative weights of the spleen at 540 mg/kg/d in males and notable increase in absolute & relative weights of the spleen at all dose levels of females were observed. Weights of left and right kidneys in female at 540 mg/kg/d were significantly higher than that of vehicle control. After the recovery period, the absolute weights of the spleen and both kidneys in both genders at 540 mg/kg/d were significantly higher than that of vehicle control.

Necropsy Findings: At necropsy, 6 cases of dark reddish discoloration of spleen were observed at 540 mg/kg/d in both genders, and 1 case of enlargement of cecum was observed at 540 mg/kg/d in female. After the recovery period, one case of dark reddish discoloration of spleen was observed at 540 mg/kg/d in the female. The histopathology examination revealed increased hematopoiesis of spleen at the high dose in both genders.

No Observed Adverse Effect Levels (NOAEL): The NOAEL for this study was 180 mg/kg/d for both genders.

Primary results from the pivotal, 4-week dog study included:

YPL-001 colored stool with/without soft stool or diarrhea was persistently observed in both sexes at 1000 mg/kg/d during the dosing period. It was not observed during the recovery period. No mortality was reported.

Hematology: There were no treatment-related changes.

Clinical Biochemistry: The TBIL increased in a dose-dependent manner in both genders at 111, 333 and 1000 mg/kg/d, and it was not recovered completely after the 2-week recovery period.

Organ Weights: There were no treatment-related changes.

Necropsy Findings: Slight red discoloration of mucous membranes in the stomach or duodenum was observed in female treatment groups but not observed after the 2-week recovery period.

NOAEL: The NOAEL for this study was 1000 mg/kg/d for both genders.

9.1.2 Clinical Experience

To date, 2 studies have been conducted in healthy subjects, a randomized, double-blind, placebo-controlled, sequential single ascending dose (SAD) clinical study (AA98496) and a randomized, double-blind, placebo-controlled, sequential multiple ascending dose (MAD) clinical study (AA98495).

9.1.2.1 SAD study

All 5 cohorts of 8 subjects (6 active and 2 placebo), with one cohort crossing over to assess food effect, were dosed and completed. All dosed levels (i.e., 40, 80, 160, 240, and 320 mg) were well tolerated with no SAEs reported during the conduct of the study. All 9 AEs reported in 7 subjects were mild in severity and the most frequent AE reported, regardless of causality, was headache. Of the 7 AEs experienced by subjects receiving the active drug, the Investigator considered 2 of these to be possibly related (nausea, and vomiting), 2 unlikely related, and 3 unrelated. Of the 2 AEs experienced by subjects receiving placebo, the Investigator considered 1 of these to be possibly related (headache), and 1 unrelated.

Plasma samples were analyzed using a validated bioanalytical method. Verproside concentrations were lower than concentrations observed from the animal PK data. The limit of quantitation (LOQ) was approximately 20% of the C_{max} after a single 160 mg dose and approximately 10% of the C_{max} after a single 320 mg dose. Therefore, the half-life could not be well characterized since only a few PK concentrations were available for the estimation.

Verproside appeared to be rapidly absorbed following oral administration and independent on dose, as suggested by median t_{max} values of approximately 0.5 to 0.67 hours under fasting conditions. Verproside appeared to be cleared rapidly from plasma, with mean $t_{1/2}$ values under 1 hour; plasma verproside concentrations were below the lower limit of quantification (BLQ) for all subjects by 6 hours postdose. Table 1 below summaries the PK parameters of verproside following single-dose administrations of YPL-001 at each dose level:

Table 1 Summary of PK Parameters

Pharmacokinetic Parameters	Dose Level Mean ± SD					
	40 mg (N = 1)[a]	80 mg (N = 6)[b]	160 mg (fasting) (N = 6)[c]	160 mg (fed) (N = 6)[d]	240 mg (N = 6)[e]	320 mg (N = 6)[f]
C_{max} (ng/mL)	1.19	1.14 ± 0.328	2.90 ± 1.76	1.08 ± 0.287	4.78 ± 5.66	4.49 ± 1.44
t_{max} (hr)[g]	0.4969	0.6682 (0.5158, 1.0025)	0.5074 (0.3331, 0.6700)	1.2538 (0.9994, 2.0008)	0.5867 (0.3486, 1.5022)	0.5057 (0.3419, 1.5014)
AUC_{0-t} (ng·hr/mL)	0.7422	0.7520 ± 0.3818	2.5616 ± 1.7947	1.2822 ± 0.3599	5.4567 ± 5.0158	5.3612 ± 0.8664
AUC_{0-inf} (ng·hr/mL)	·	·	3.8048 ± 1.8238	·	8.2199 ± 5.3327	6.2162 ± 0.7776
$t_{1/2}$ (hr)	·	·	0.677 ± 0.263	·	0.919 ± 0.176	0.713 ± 0.100

[a] Individual values are presented for the 40 mg dose level
[b] N=5 for AUC_{0-t}
[c] N=3 for AUC_{0-inf} and $t_{1/2}$,
[d] N=4 for AUC_{0-t}
[e] N=3 for AUC_{0-inf}, and $t_{1/2}$,
[f] N=5 for AUC_{0-inf}, and $t_{1/2}$,
[g] t_{max} is presented as Median (Minimum, Maximum)
· = Value missing or not reportable

9.1.2.2 MAD Study

In total, 2 cohorts of 8 subjects and 1 cohort of 10 subjects received multiple YPL-001 doses of 80, 160, or 240 mg BID. Each cohort was constituted of 2 subjects receiving placebo and the remaining subjects receiving the active drug. All dose levels were well tolerated. There were no deaths or SAEs in this study. One (1) subject was discontinued due to the AE of chest pain. Overall, TEAEs were experienced by 38% of subjects in this study. The Investigator considered 1 AE (chest pain) to be possibly related to study drug and the remaining AEs unlikely or unrelated. There were no treatment-related trends in physical examination, laboratory, vital sign, or ECG assessments in this study.

Verproside appeared to be rapidly absorbed following multiple-dose oral administration, as suggested by median t_{max} values of approximately 0.5 - 0.9 hours and independent of dose. Following a multiple oral doses of YPL-001, verproside appeared to be cleared rapidly from plasma, with mean $t_{½}$ values under 1.6 hours, and plasma verproside concentrations were BLQ for most subjects by 12 hours postdose.

Picroside II appeared to be also rapidly absorbed following single- and multiple-dose oral administration, as suggested by median t_{max} values of approximately 0.6 to 0.9 hours and independent of dose. Following a single oral dose of YPL-001, picroside II appeared to be cleared rapidly from plasma, with mean $t_{1/2}$ values under 1 hour, CL/F values of 14000 – 18500 L/hour, and plasma picroside II concentrations BLQ by 10 - 12 hours postdose. Following multiple oral doses, mean $t_{1/2}$ values were under 2.5 hours, and plasma picroside II concentrations were BLQ for most subjects by 12 hours postdose.

For all 3 dose levels, minimal to modest accumulation of verproside and picroside II was observed following BID administration of YPL-001 for 2 weeks. The mean peak and total exposure of verproside and picroside II in plasma appeared to increase in a dose-dependent manner between 80 and 160 mg of YPL-001, but no increase in plasma bioavailability was observed between 160 and 240 mg dose levels. Table 2 and Table 3 below summaries the PK parameters of verproside and picroside II, respectively, following multiple-dose administrations of YPL-001 at each dose level:

Table 2 Summary of Verproside PK Parameters

Pharmacokinetic Parameters	YPL-001 Dose Level Mean ± SD		
	80 mg	**160 mg**	**240 mg**
AUC_t (pg*hr/mL)	4709 ± 4080 (N=6)	10860 ± 11424 (N=6)	9658 ± 9246 (N=5)
AUC_{0-t}(pg*hr/mL)	4596 ± 4127 (N=6)	10770 ± 11489 (N=6)	9566 ± 9298 (N=5)
$C_{max\ ss}$ (pg/mL)	2414 ± 1281 (N=6)	6737 ± 7342 (N=6)	5458 ± 4387 (N=5)
t_{max_ss} (hr)*	0.756 (0.252, 2.00) (N=6)	0.759 (0.329, 1.50) (N=6)	0.528 (0.272, 0.751) (N=5)
$t_{½}$ (hr)	1.47 ± 0.425 (N=6)	1.30 ± 0.406 (N=6)	1.57 ± 0.236 (N=5)

* = t_{max_ss} is presented as median (minimum, maximum)

Table 3 Summary of Picroside II PK Parameters

Pharmacokinetic Parameters	YPL-001 Dose Level Mean ± SD		
	80 mg	160 mg	240 mg
AUC_t (pg*hr/mL)	2556 ± 599 (N=2)†	4287 ± 4369 (N=4)†	1985 ± 1024 (N=5)
AUC_{0t} (pg*hr/mL)	1124 ± 1044 (N=6)	3024 ± 3877 (N=6)	1804 ± 949 (N=5)
$C_{max\ ss}$ (pg/mL)	419 ± 240 (N=6)	1116 ± 1391 (N=6)	751 ± 490 (N=5)
$t_{max\ ss}$ (hr)*	0.756 (0.252, 2.00) (N=6)	0.759 (0.329, 1.50) (N=6)	0.748 (0.524, 0.751) (N=5)
$t_{½}$ (hr)	2.23 ± 0.254 (N=6)	1.84 ± 0.395 (N=6)	2.08 ± 0.793 (N=5)

* = t_{max_ss} is presented as median (minimum, maximum)
. = Value missing or not reportable

10. RATIONALE

10.1 Purpose of the Study

This study will be the initial exploration of multiple-dose administration of YPL-001 in COPD patients. The assessments of the safety, tolerability, COPD symptoms, PD, and PK of verproside and picroside II following administration of multiple doses of YPL-001 will guide decisions to further develop the drug and support the compound as a useful clinical candidate in the treatment of inflammatory diseases of the respiratory tract such as asthma and COPD and the data generated will support larger studies in patients with inflammatory diseases of the respiratory tract such as asthma and COPD to demonstrate safety and evidence of efficacy and clinical benefit.

10.2 Dose Selection

This will be the first COPD patient study of YPL-001.

YPL-001 appeared well tolerated in a panel of standard animal toxicology studies. In the initial studies in humans, the initial dose of YPL-001 was justified conservatively according to the United States (US) Food and Drug Administration (FDA) guidance document “Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers”.[2]

Accordingly, the single and multiple dose escalation study (AA98496) initiated single doses at the 40 mg and 80 mg level, respectively. Dose escalations up to 320 mg and 240 mg in the SAD and MAD studies, respectively, were reached. All cohorts have been completed and all doses administered were well tolerated in human subjects and no clear pattern of toxicity is apparent.

Based on the review of safety, tolerability, and PK data from Cohorts 1 to 5 of the SAD study (AA98496) and Cohorts 1 to 3 of the MAD study, and the in vivo efficacy data in rat and mouse models, it is predicted that the therapeutic range should be between 1.2 mg/kg and 4.8 mg/kg which is equivalent to 84 mg to 336 mg daily in a 70 kg patient. Therefore, a low YPL-001 dose of 80 mg BID and the high YPL-001 dose of 160 mg BID were selected for this proof-of-concept study.

The total strength (23.75 mg) of identified compounds in YPL-001 as a whole in the 40 mg starting dose administered in the first-time-in-human dose escalation study (AA98496) corresponded to approximately 35% of the dosages that have been used in the traditional medicine setting in China (68.65 mg). In this present proof-of-concept study the total strength (47.50 mg) of identified compounds in the initial starting dose of 80 mg is still lower than the dosages that have been used in the traditional medicine setting in China, as shown in Table 4, corresponding to 70% of the traditional Chinese medicine.

Table 4: Traditional Chinese Medicine Use Versus Proposed Clinical Starting Dose

Identified Compounds in YPL-001	1.40 g (Single Dose) Traditional Chinese Medicine[a] (mg)	2.80 g/day (Divided Dose) Traditional Chinese Medicine[a] (mg)	80 mg (Single Dose) for MAD Study[b] (mg)
Verproside	47.94	95.88	30.64
Veratric acid	2.10	4.20	1.08
Catalpolside	3.77	7.54	4.08
Picroside II	3.43	6.86	3.36
Isovanilloyl catalpol	3.53	7.06	4.72
6-*O*-veratroyl catalpol	7.88	15.76	3.62
Total	68.65	137.30	47.50

[a] Traditional medicine dosage from Chinese Medical Great Dictionary; Zhong Yao Da Ci Dian.
[b] Proposed dosage of YPL-001 in MAD study

11. RISK/BENEFIT

YPL-001 is being developed as a potential oral treatment for long term control of persistent asthma and COPD. YPL-001 belongs most closely with the leukotriene modifier class of drug and has the potential to inhibit the accumulation of neutrophils the increase of several proinflammatory cytokines and chemokines which play a major role in tissue remodeling. The development of a product to improve the treatment of asthma and COPD will be of benefit to the wider community/patients with respiratory disease.

The safety monitoring practices employed by this protocol (i.e., physical examination, vital signs, pulse oximetry, 12-lead ECG, hematology, serum chemistry, urinalysis, AE monitoring, and AE questioning) are deemed adequate to protect the patients' safety and should detect all expected TEAEs. The procedures employed in this study to assess efficacy are primarily non-invasive and present no undue risk to the patient.

The approximate volume of blood planned for collection from each patient over the course of the study (see Section 14.5), presents no undue risk to the patients nor does the possibility of collection (for wasting to ensure clean sample) of additional blood in the event an indwelling cannula is utilized (as a last resort solution when venipuncture becomes difficult for a patient) and the possibility of additional blood collection for recheck of safety labs if deemed necessary by the Investigator.

12. STUDY OBJECTIVES AND ENDPOINTS

12.1 Study Objectives

The primary objective of the study is to assess the safety and tolerability of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients.

The secondary objective of the study is to assess the number and magnitude of daily respiratory symptoms of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients.

The exploratory objectives of the study are to evaluate the following in moderate to severe COPD patients:

1. To assess BAL epithelial brushings for YPL-001 component levels.
2. To compare BAL samples for total cell count (cells/mL) macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; neutrophil, macrophage, lymphocyte, and eosinophil counts as absolute inflammatory cell numbers in YPL-001 groups versus placebo group.
3. To compare BAL samples for TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9 in YPL-001 groups versus placebo group.
4. To compare blood inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) and concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9 in YPL-001 groups versus placebo group.
5. To compare spirometric functions (FEV_1, FVC, FEV_1/FVC, and IC) in YPL-001 groups versus placebo group.
6. To compare patient reported outcomes (BDI/TDI, CAT) in YPL-001 groups versus placebo group.
7. To assess verproside and picroside II concentration in plasma and BAL and verproside and picroside II PK in plasma following multiple oral doses administration of two YPL-001 dose levels.

12.2 Study Endpoints

The primary endpoint is the number and severity of TEAEs following multiple oral doses of YPL-001 or placebo.

The secondary endpoint is the number of symptom free days and overall symptom burden following multiple oral doses of YPL-001 or placebo, assessed by measuring:

- daily PEF;
- major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation;

- dyspnea (using the Modified Borg Dyspnea Scale); and
- activity (using the DASI).

The exploratory endpoints are:

1. YPL-001 component levels in epithelial brushings;
2. BAL biomarkers following multiple oral doses of YPL-001 or placebo, measuring:
   - total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells
   - total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers
   - concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9.
3. Blood biomarkers following multiple oral doses of YPL-001 or placebo, measuring:
   - inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils, and lymphocytes)
   - concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9.
4. Pulmonary function results (spirometry) following multiple oral doses of YPL-001 or placebo.
5. Quality of life scores using the BDI/TDI, CAT questionnaires.
6. Concentrations and PK of verproside and picroside II in plasma following multiple oral doses of YPL-001.
7. Concentrations of verproside and picroside II in BAL following multiple oral doses of YPL-001.

13. INVESTIGATIONAL PLAN

13.1 Overall Study Design and Plan

This is a Phase 2a, proof-of-concept, multicenter, randomized, double-blind, double-dummy, 3-treatment, parallel study, with low and high YPL-001 doses (80 mg and 160 mg BID) and a placebo control, in moderate to severe COPD patients.

At least 60 patients will be enrolled and randomized into 3 treatment groups (20 patients per group). Patients will participate only once. An approximately equal number of current and ex-smokers will be enrolled in the study.

Safety and tolerability will be assessed throughout the study. Assessment of respiratory symptoms and symptom burden in YPL-001 and placebo treatments will be performed daily through patient self-report of PEF, major and minor symptoms of COPD exacerbation, dyspnea, and activity in their e-diary. Spirometry measurement, BAL, and blood samples will be collected for the PD assessment of YPL-001 and placebo treatments. Serial blood samples will also be collected for PK assessment of verproside (the principal active ingredient of YPL-001) and picroside II. Other components of YPL-001 and its metabolites may also be analyzed in plasma.

Following screening, eligible patients will discontinue non permitted respiratory drugs if already receiving them and enter a 14 ± 2 days Run-in Period during which patients will be given albuterol taken on an as required basis and daily tiotropium 18 µg (one capsule inhaled daily in the morning) to be administered at home. On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their daily symptoms throughout the Run-in Period.

Patients will return to the CRU on the morning of Day -1 of the Treatment Period to confirm their eligibility and assess their health conditions. If they still meet all of the inclusion criteria and none of the exclusion criteria, they will undergo Day -1 scheduled study procedures. Patients will return to the CRU the next day (Day 1) to be randomized and receive one of the 3 treatments and undergo all scheduled study procedures. Patients will return on the morning of Days 15, 29, 43, 55, and 56 of the Treatment Period for study drug administration and procedures. Prior to each release from the CRU, patients will receive a properly labeled container with sufficient doses which will be self-administered by patients at home until the next morning visit at the CRU. Patients will continue recording their daily symptoms via the e-diary throughout the Treatment Period. Patients will return the e-diary device on Day 56 to CRU staff.

The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

Patients will be instructed to call the Investigator if breathing worsens or if they need to take more than 8 puffs per day of albuterol for more than 2 consecutive days. If the Investigator determines that the patient is too unstable to continue in the study, he/she will be discontinued. Rescue medication will be used for any patient with an exacerbation of COPD and will be administered in accordance with the study center

standard of care.

Discontinued patients may be replaced at the discretion of the Sponsor.

13.2 Study Conduct

Please see the Study Events Flow Chart for a summary of the schedule of study participation and procedures in Section 6.

13.2.1 Screening

Screening will begin within 14 days of Day 1 (inclusive) of the Run-in Period. Informed consent will be obtained at screening (see Section 16.1.3) and prior to any study procedures being performed. Patients will have to meet all eligibility criteria before being enrolled in the study (see Section 13.3). Patients will be informed of the study restrictions (see Section 13.3.5).

The following will be recorded at screening: medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI, and history of tobacco use (including number of pack-year and cigarette smoked per day).

Screening procedures are listed in Section 6.

13.2.2 Patient Confinement

Patients will be admitted to the CRU on the morning of each scheduled visit at a time designated by the CRU as delineated in the Study Events Flow Chart (Section 6). Patients will remain in the clinic through completion of all scheduled study procedures.

13.2.3 Run-In Period (Days 1 to 14 [± 2 days])

Eligible patients will be admitted to the CRU on the morning of Day 1 of the Run-in Period at a time designated by the CRU. Patients will discontinue all restricted concomitant medications as indicated in Section 13.3.5.1 and undergo the Run-in procedures as listed in Section 6.

During the Run-in Period, patients will self-administer tiotropium (Spiriva® HandiHaler®) daily for 14 ± 2 days before Day 1 of the Treatment Period. Patients will be instructed to inhale 1 capsule of tiotropium (Spiriva® HandiHaler®) every morning. Patients will also receive albuterol for as needed use. Patient will keep this rescue albuterol throughout the Run-in Period.

Prior to release from the CRU, patients will receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. They must return the container (empty or not) at the next schedule visit, which is scheduled after 14 ± 2 days.

Each patient will also be issued and trained on the use of the e-diary to record their self-administered doses and their daily respiratory symptoms. Prior to each morning dose, patients will record at home their daily PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

13.2.4 Treatment Period (Days 1 to 56)

Patients who completed the Run-in Period and still meet all the inclusion criteria and none of the exclusion criteria will be randomized to receive one of the assigned treatments (80 mg or 160 mg YPL-001 BID, or placebo BID) on Day 1 through Day 56 (see Section 13.4.1 and Section 13.4.2).

Safety and tolerability will be monitored throughout the Treatment Period as listed in Section 6. Patients will continue to record their self-administered doses and their daily respiratory symptoms on their e-diary. Prior to each morning dose, patients will record at home their daily PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

BAL samples for YPL-001 concentrations and PD assessments will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

Spirometry and quality of life questionnaires for PD assessments will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

Blood samples for PD and PK assessment will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

13.2.4.1 Meal Schedule

Patients will be required to fast overnight for at least 12 hours before bronchoscopy and BAL collection on Days -1 and 55. On Days 1 and 56, patients will be required to fast overnight for at least 8 hours before and for at least 4 hours after the morning dose. On all other days, patients will be asked to fast for at least 2 hours before and 2 hours after each morning dose. Patients will also be asked to fast for at least 2 hours before and after each evening dose.

Patients will also be required to fast for at least 8 hours before the scheduled serum chemistry tests at the time points delineated in the Study Events Flow Chart (Section 6).

During in-clinic dosing, water (except that administered with dosing) will not be permitted from 1 hour before until 1 hour after each dosing. Water will be allowed as desired at all other times. On all other days, patients will be informed to follow the same restrictions.

On Days 1 and 56, patients will fast from all food and drink except water between meals and snacks. Foods and beverages containing alcohol, xanthines, caffeine, vegetables from the mustard green family, mustard, tea (especially speedwell tea), or grapefruit/Seville oranges will not be served in the CRU. Across all CRUs, menus should be similar in content. The same menu and meal (except for snacks) schedule will be administered uniformly for all patients confined within the same CRU, across all treatment groups. Meals are not required to be completed by patients and all meals and snacks eaten by patients will be recorded on the CRFs.

13.2.4.2 End-of-Treatment or Early Termination (Day 56)

End-of-treatment evaluation will be performed on all patients before leaving the CRU or prior to early termination.

The end-of-treatment procedures are listed in Section 6.

13.2.5 Follow-up Call (14 ± 2 days)

The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

13.2.6 Scheduled End of Study

The end of the study is scheduled after completion of the evaluations in the 3 treatment groups or after dose-limiting clinical safety endpoints have been reached to preclude continuation of the study. The clinical conduct of the study is intended to last approximately 12 to 24 months.

This time period may change in the event that the study is terminated early, additional time is required to review safety, or a decision is made to complete an unscheduled analysis for a group.

13.3 Selection of Study Population

13.3.1 Number of Patients

The study is planned to enroll at least 60 patients. An approximately equal number of current and ex-smokers will be enrolled. Patients will be divided in 3 treatment groups with 20 patients to receive one of the 3 treatments (i.e., low and high YPL-001 doses [80 mg and 160 mg BID] and a placebo control) as per the randomization schedule. Each treatment group will consist of an approximately equal number of current and ex-smokers.

13.3.2 Inclusion Criteria

Patient candidates must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Adult males and/or females, 40 to 80 years of age (inclusive).
2. History of COPD for at least 12 months prior to screening.
3. Diagnosed with COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines with symptoms compatible with COPD for at least 12 months prior to screening.
4. Classified as moderate to severe COPD based on the current severity classification GOLD Stage 2-3 disease in terms of post-bronchodilator spirometry at screening:
   - Post-bronchodilator FEV_1/FVC ratio of <70%
   - Post-bronchodilator FEV_1 ≥30 % and <80 % of predicted normal values
5. Weigh at least 52 kg for males and 45 kg for females and within the normal range according to accepted normal values of the Body Mass Index (BMI) chart 18.5-32.0 kg/m^2 inclusive.
6. In the judgment of the Investigator, the patient is medically stable with no change in symptoms, medication, or with clinical laboratory results that in the Investigator's opinion are compatible with the diagnosis of either COPD or a complication thereof and are judged acceptable for inclusion with predominantly bronchitic symptoms at screening.
7. Must be on a stable medical regimen for COPD ≥ 30 days prior to screening.
8. In the Investigator's opinion patients should be able to withhold tiotropium 24 hours prior to Day 1 of the Run-in Period, if already receiving it and prior to each scheduled CRU visit.
9. Must have oxygen saturation on room air > 93%.
10. Hemoglobin must be equal to or above the lower limit of normal at screening and check-in.
11. Current or ex-smoker with a history of >10 pack years. Ten pack years are defined as: 20 cigarettes a day for 10 years; 10 cigarettes a day for 20 years; or 40 cigarettes a day for 5 years (i.e., [number of cigarettes smoked per day × number of years smoked]/20). Patients, who undergo smoking cessation therapy, must be completed 3 months prior to screening visit and smoking status should not change between the patient's screening visit and patient's last study visit.
12. For a female of childbearing potential: either be sexually inactive (abstinent) for 14 days prior to the first dose and throughout the study or be using one of the following acceptable birth control methods:
    a. non-hormone releasing intrauterine device in place for at least 3 months prior to the first dose.
    b. surgical sterilization of the partner (vasectomy for 4 months minimum).

c. physical barrier method (e.g., condom, diaphragm) with spermicide for at least 14 days prior to the first dose and throughout the study.

A female patient who claims to be sexually inactive, but becomes sexually active during the course of the study must agree to use a physical barrier method (e.g., condom, diaphragm) with spermicide from the time of the start of sexual activity through to the completion of the study.

13. For a female of non-childbearing potential: must have undergone one of the following sterilization procedures at least 6 months prior to the first dose:

    a. hysteroscopic sterilization;

    b. bilateral tubal ligation or bilateral salpingectomy;

    c. hysterectomy;

    d. bilateral oophorectomy;

    or be postmenopausal with amenorrhea for at least 1 year prior to the first dose and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status as per Investigator judgment.

14. Non-vasectomized males must agree to be sexually abstinent or to use a condom with spermicide when engaging in sexual activity from the first dose through completion of the end-of-treatment evaluations. Patients will be advised to use a condom with spermicide for 90 days following the last administration of the study drug, and to not donate sperm during this same period of time. In the event that the sexual partner is surgically sterile, use of a condom with spermicide is not necessary. No restrictions are required for vasectomized males provided their vasectomy has been performed 120 days or more prior to study start. Males who have been vasectomized less than 120 days prior to study start must follow the same restrictions as non-vasectomized males.

15. Understands study procedures and provides written informed consent for the trial.

16. Be able to comply with the protocol, such as all the study restrictions, and the assessments therein.

13.3.3 Exclusion Criteria

Patients will be excluded from the study if there is evidence of any of the following criteria at screening or check-in, as appropriate.

1. History of life-threatening COPD including respiratory arrest, intensive care unit admission and/or requiring intubation.
2. History of more than 2 hospitalizations for COPD within 12 months prior to screening.
3. Presentation of an acute exacerbation of COPD that will be associated with increase sputum volume or change in sputum color within 4 weeks before Day 1 of the Run-in Period.
4. Evidence of cor pulmonale, or clinically significant pulmonary hypertension.
5. Continuous use of more than 2L/day of oxygen.

6. History or presence of other respiratory disorders, such as asthma, α-1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis or other chronic pulmonary diseases.
7. A chest X-ray at screening (or within 3 months prior to screening) showing abnormalities, which in the opinion of the Investigator are clinically significant and unrelated to COPD.
8. A history of chronic disease including, but not limited to, unstable or uncontrolled hypertension (or been diagnosed with hypertension in the 6 months before screening), sleep apnea, cardiovascular, endocrine, neurological, hepatic, gastrointestinal, renal, hematological, urological, immunological or ophthalmic diseases that the Investigator believes are clinically significant e.g., unstable and could impact patient safety by participation in the study.
9. History or presence of:
    - significant cardiac arrhythmia;
    - prostatic hyperplasia;
    - bladder-neck obstruction;
    - urinary retention;
    - narrow-angle glaucoma.
10. Evidence of clinically relevant abnormal baseline hematology, serum chemistry, or urinalysis. Patients with an AST > 2 x ULN, ALT > 2 x ULN, bilirubin > 2 x ULN or creatinine > 2 x ULN (confirmation of results may be done once).
11. Evidence of hepatic impairment with a Child-Pugh class A score or higher.
12. Lung resection or lung reduction surgery within 12 months.
13. Positive urine drug/alcohol testing at screening or at each CRU visit.
14. Positive testing for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C antibodies (HCV).
15. History or presence of alcoholism or drug abuse within the 2 years prior to Day 1 of the Treatment Period.
16. Hypersensitivity or idiosyncratic reaction to compounds related to YPL-001, including Speedwell tea and herbal remedies.
17. Requires one (or more) routine therapies for COPD during the indicated restricted time period as listed in Section 13.3.5.1.1.
18. Use of any drugs or substances known to be significant inhibitors (strong or moderate) of UDP-glucuronosyltransferase (UGT) and/or sulfotransferases (SULT), within 12 hours prior to Day 1 of the Run-in Period (refer to Appendix 1 and Appendix 2).
19. Blood donation or significant blood loss within 56 days prior to Day 1 of the Treatment Period.

20. Plasma donation within 7 days prior to Day 1 of the Treatment Period.
21. Participation in another clinical trial within 30 days prior to Day 1 of the Run-in Period.
22. Females who are pregnant or lactating.
23. Surgery within the past 3 months prior to Day 1 of the Treatment Period determined by the Investigator to be clinically relevant.
24. Active or history of any disease or condition that would, in the opinion of the Investigator and/or medical monitor, place the patient at an unacceptable risk to participate in this study.

13.3.4 Removal of Patients from the Study

Patient participation in this trial may be discontinued for any of the following reasons:

1. Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol.
2. Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient.
3. The patient interrupts trial study drug administration for more than 7 consecutive days of dosing or missed a total of 17 doses (15%) throughout the Treatment Period.
4. Patient's decision to withdraw.
5. Requirement for prohibited concomitant medication.
6. Patient failure to comply with protocol requirements or study related procedures.
7. Termination of the study by the Investigator, Sponsor, FDA, Celerion, or other regulatory authorities.

The clinical report will include reason(s) for patient withdrawals as well as details relevant to the patient withdrawal. If a patient is withdrawn from the trial prior to study completion, the patient will undergo all procedures scheduled for study completion (end-of-treatment evaluations) as the situation allows (see Section 13.2.5). Any patient withdrawn due to an AE (whether serious or non-serious) or clinically significant abnormal laboratory test values will be evaluated by the Investigator and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

Patients withdrawn may be replaced at the Sponsor’s discretion.

13.3.5 Study Restrictions

13.3.5.1 Concomitant Therapy

All medications taken during the 30 days prior to the first dose will be recorded and reviewed by the Investigator.

Any medication taken by patients during the course of the study will be recorded. Concomitant medication will be coded using the most current WHO drug dictionary available at Celerion (e.g., 01-MAR-2014 or later). If drug therapy other than that specified by the protocol is taken, a joint decision will be made by the Investigator and Sponsor to continue or discontinue the patient.

13.3.5.1.1 Prohibited Therapy

The following medications are not permitted within the time delineated below and during the study (from Day 1 of the Run-in Period to the completion of the end-of-treatment procedures). Intake of these medications during the Run-in Period constitutes a non-eligibility criterion and the patients will not be randomized into the study. If any of these medications are taken during the Treatment Period, the need for this patient to be withdrawn from the study will be carefully evaluated by the Investigator and the Sponsor on the basis of the potential impact on efficacy or safety evaluation and in the patient's best interest:

1. Any medications administered for the treatment of worsening of COPD within 4 weeks prior to Day 1 of the Run-in Period:
   - nebulized, inhaled, oral, IV, IM corticosteroids;
   - oral or parenteral β2 agonists;
   - Antibiotics.
2. Inhaled corticosteroids (ICS), LABA, and/or inhaled ICS/LABA fixed combinations within 12 hours prior to Day 1 of the Run-in Period;
3. Inhaled long acting anticholinergic agents other than tiotropium within 2 weeks prior to Day 1 of the Run-in Period;
4. Inhaled short-acting β2-agonists (SABA) other than albuterol (e.g., terbutaline, fenoterol) within 12 hours prior to Day 1 of the Run-in Period;
5. Inhaled short-acting anticholinergic agents (SAMA) (e.g., ipratropium) within 12 hours prior to Day 1 of the Run-in Period;
6. PDE inhibitors (including roflumilast) within 2 weeks prior to Day 1 of the Run-in Period.
7. Leukotriene modifiers and xanthines derivatives within 2 weeks prior to Day 1 of the Run-in Period.
8. Drugs or substances known to be significant inhibitors (strong or moderate) of UGT and/or SULT, within 12 hours prior to Day 1 of the Run-in Period and through collection of the final PK sample.
9. Acetaminophen will be prohibited 24 hours prior to Day 1 of the Treatment Period and through collection of the final PK sample.
10. Vitamin supplements and herbal products (especially Speedwell) will be prohibited 7 days prior Day 1 of the Treatment Period and through collection of the final PK sample.

13.3.5.1.2 Permitted Therapy

Throughout the study Period (from Day 1 of the Run-in Period to the completion of the end-of-treatment procedures) patients will be permitted to take the following medications in addition to the study drugs:

1. Albuterol, as required (except approximately 4 hours before schedule pulmonary function test);
2. Tiotropium (Spiriva® HandiHaler®) 18 µg once a day (except approximately 24 hours before schedule pulmonary function test);
3. Ibuprofen, as required, up to 1200 mg per day for intercurrent illness or AEs. Ibuprofen should not be taken for 2 hours before or after each dosing.
4. In the case of a concomitant disease, appropriate treatment will be permitted if it does not interfere with the study evaluation parameters and does not qualify under the section "Prohibited Therapy" (see Section 13.3.5.1.1)

13.3.5.2 Prohibitions

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/caffeine: 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Alcohol: 48 hours prior to each CRU visit, 48 hours prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts), and mustard: 14 days prior to Day 1 of the Treatment Period through collection of Day 56 last PK sample.
- Fruit Juice: 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Tea (especially Speedwell tea), Coffee and Red Wine: 7 days prior to Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Grapefruit/Seville orange and beer: 14 days prior to Day 1 of the Treatment Period through collection of Day 56 last PK sample.

13.3.5.3 Activity

Patients will remain ambulatory or seated upright for 1 hour following each study medication administration.

Patients will be advised to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

13.4 Treatments

13.4.1 Treatments administered

13.4.1.1 Drug Administration During Run-in Period

Tiotropium (Spiriva® HandiHaler®) will be supplied as 18 µg capsules for inhalation.

Albuterol will be supplied as 100 µg albuterol base (1 actuation = 100 µg albuterol base) for oral inhalation. Albuterol may be administered via a nebulizer or a metered-dose inhaler.

Multiple oral inhalation of tiotropium (Spiriva® HandiHaler®) 18 µg capsule will be administered QD every morning for 14 ± 2 days during the Run-in Period. Albuterol will be administered on an as needed basis.

13.4.1.2 Drug Administration During Treatment Period

YPL-001 will be supplied as 80 mg tablets for oral administration.

Placebo will be supplied as YPL-001 80 mg matching placebo tablets for oral administration.

Treatments A, B, and C are described as follows:

Treatment A: Multiple oral YPL-001 80 mg doses (1 x 80 mg tablet + 1 x 1 YPL-001 80 mg matching placebo tablet) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56.

Treatment B: Multiple oral YPL-001 160 mg doses (2 x 80 mg tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56.

Treatment C: Multiple oral matching placebo (2 x 1 YPL-001 80 mg matching placebo tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56.

Each dose of Treatments A, B and C will be administered with approximately 240 mL of water.

In all treatments, one tiotropium (Spiriva® HandiHaler®) 18 µg capsule will also be administered QD every morning prior to study drugs administration. Albuterol will be administered on an as needed basis.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each patient, as per the randomization scheme.

Prior to release from the CRU on Days 1, 15, 29, 43, and 55 of the Treatment Period, patients will receive a properly labeled container with the appropriate doses which will be self-administered by patients at home. Patients will record their self-administered doses

in their e-diary, and whether the dose was administered with food, and must return the container (empty or not) at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.

Patients will be instructed not to crush, split or chew the study drug.

The exact clock time of dosing will be recorded on on-site dosing days. Patients will be given instructions on recording of dosing times in their e-diary on home-dosing days.

Each dose will be administered under fasting conditions as described in Section 13.2.4.1.

13.4.1.3 Stopping Rules

A decision to stop or suspend the study will be made jointly by the Sponsor and the Investigator following the review of all pertinent safety and tolerability. Together they will make one of the following determinations:

1. To continue with the study as planned.
2. To continue with the study and add additional safety evaluations.
3. To continue with the study by adjusting to a lower dose if 2 patients at any dose level meets any of the following criteria and the patient was determined to have received YPL-001 after unblinding:
   a. Has a drug–related, unexpected SAE.
   b. Experiences drug-related grade ≥ 3 toxicity.
4. The study will be terminated if ≥ 3 patients at any dose level meet any of the following criteria and the patients were determined to have received YPL-001 after unblinding:
   a. Has a drug–related, unexpected SAE.
   b. Experience drug related grade ≥ 3 toxicity.

PK data will not be required for the dose-escalation decision.

When applicable, a written statement fully documenting the reasons for study termination will be provided to the Institutional Review Board (IRB).

13.4.2 Method of Assigning Patients to Treatment Groups

Each patient will be assigned a unique screening identification number upon screening. Patients who complete the study screening assessments, complete the Run-in Period, and meet all the eligibility criteria will be assigned a unique randomization identification number, different from the screening number, and receive the corresponding product, according to a randomization scheme generated at Celerion. Each treatment group will consist of an approximately equal number of current and ex-smokers.

Patients will receive one of the 3 treatments (Treatments A, B, or C) on one occasion.

If replacement patients are used, the replacement patient number will be 100 more than the original (e.g., Patient No. 0101 will replace Patient No. 0001).

13.4.3 Blinding

This is a double-blind, double-dummy, randomized study.

13.4.3.1 Maintenance of Randomization

A computerized randomization scheme will be created by a Celerion unblinded statistician (who is not otherwise involved in the study) and shall be considered blinded (per the following).

The randomization is available only to the clinic pharmacy staff preparing the drug who are not involved in any other aspect of the study including administration of the drug. It will not be made available to the Sponsor, patients, or members of the staff responsible for the monitoring and evaluation of safety assessments.

The bioanalytical department will also be blinded to the randomization scheme.

13.4.3.2 Procedures for Breaking the Blind Prior to Study Completion

One set of the sealed envelopes containing the randomization code will be available to the Investigator at the start of the trial.

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the patient.

In the event of a medical emergency, it is requested that the Investigator make every effort to contact the study monitor or designee prior to breaking the blind. If breaking the blind is required because of a medical emergency, the treatment identity would be revealed by the qualified designee, for that patient only. In the event that the emergency is one, in which it appears that the other patients may be at imminent risk, the blind may be broken for all patients dosed at that dose level. The unblinding should be noted in the patient's electronic case report form (eCRF).

In all cases where the code is broken, the Investigator should record the date, reason for code breaking and his/her name for signature on the envelope.

At the end of the study, the envelopes will be reviewed by the Sponsor.

13.4.3.3 Revealing of Randomization

In the absence of a medical emergency, the blinded randomization for this entire trial will not be revealed until the following conditions are fulfilled:

1. All data are entered in the database, edits checks are performed, queries closed, CRFs signed by the Investigator, and the database is officially locked.
2. All PK/PD samples have been analyzed and quality checked by the responsible analytical associate.

13.4.4 Treatment Compliance

During in-clinic dosing, a qualified designate will be responsible for monitoring the administration of timed oral doses. When appropriate, a mouth check will be performed by the qualified designate to ensure that the patients have swallowed the study medication. Once a patient has finished the water, the qualified designate will use a flashlight and a tongue depressor to check the side of the mouth, the sides of the upper and lower gums and the area under the tongue. Patients' hands will also be verified to ensure that the medication was ingested.

Self-administration by patients at home will be monitored by the CRU via the e-diary and attempted phone calls will be performed to remind patients to take their medication, if they did not record their self-administration on the e-diary.

14. STUDY PROCEDURES

14.1 Safety Assessments

This study primarily assesses the safety and tolerability of YPL-001. Safety will be determined by evaluating physical examinations, vital signs, pulse oximetry, ECGs, clinical laboratory parameters, and AEs.

If deemed necessary, additional safety measurements will be performed at the discretion of the Investigator.

Study procedures should be completed as close to the prescribed/scheduled time as possible. The Quality of Life questionnaire should be performed prior to any other procedures. When the following procedures are scheduled at the same time, they will be performed in the following order:

1. Vital signs
2. ECG
3. Pulmonary function measurement
4. Bronchoscopy and BAL collection

All other procedures can be performed without specific order.

14.1.1 Body Height and Weight

Body height (centimeters) and body weight (kilograms) will be measured as outlined in the Study Events Flow Chart (Section 6).

14.1.2 Physical Examination

All full physical examinations will include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose and throat, respiratory system, cardiovascular system, gastrointestinal system, neurological condition, blood and lymphatic systems, and the musculoskeletal system.

A licensed physician will examine each patient as outlined in the Study Events Flow Chart (Section 6).

Medical history will be recorded at screening.

Physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator.

14.1.3 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate will be measured as outlined in the Study Events Flow Chart (Section 6).

Vital signs may be taken at any other times, if deemed necessary. Blood pressure and heart rate measurements will be performed with patients in a seated position for at least 1 minute, except when they are supine or semi-reclined because of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the Investigator.

When performed prior to the morning dose, blood pressure and heart rate will be measured within 2 hours prior to dosing. When scheduled postdose, vital signs readings will be performed within approximately 10 minutes of the scheduled time point. When performing the bronchoscopy, vital signs (body temperature, respiratory rate, blood pressure, and heart rate) will be monitored continuously until the end of the procedure.

14.1.4 Pulse Oximetry

Oxygen levels, saturation [%], and heart rate will be assessed using a pulse oximeter. All readings will be performed with a pulse oximeter (oxygen levels, saturation [%], and heart rate) as outlined in the Study Events Flow Chart in Section 6.

When performed prior to the morning dose, pulse oximetry monitoring will be measured within 2 hours prior to dosing. Readings may be taken at other times, if deemed necessary by the Investigator. When performing the bronchoscopy, oxygen saturation will be monitored continuously until the end of the procedure.

Any clinically relevant oxygen saturation reading below 93% will be documented as an AE, as per Investigator discretion.

14.1.5 Electrocardiogram Monitoring

When performed prior to the morning dose, ECG will be measured within 2 hours prior to dosing. When performing the bronchoscopy, ECG will be monitored continuously until the end of the procedure.

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6). Patients will be required to lie quietly in a supine position for at least 5 minute prior to ECG measurements. Single 12-lead ECGs may be performed at various unscheduled time points, if deemed necessary by the Investigator.

Single 12-lead ECGs will be interpreted and signed and dated by the Investigator. The ECGs will be classified as normal, having a non-clinically significant abnormality (NCS), or having a clinically significant abnormality (CS). In addition, ECG parameters of ventricular rate, PQ or PR interval, QRS duration, and QT interval (corrected according to Bazett's formula [QTcB] and uncorrected) will be noted on the CRF.

14.1.6 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 6). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator. The clinical laboratory tests include the following:

14.1.6.1 Hematology

- Hemoglobin
- Hematocrit
- RBC count (including a reticulocytes count)
- Platelet count
- Mean Corpuscular Hemoglobin (MCH)
- Mean Corpuscular Volume (MCV)
- Mean Corpuscular Hemoglobin Concentration (MCHC)
- RDW
- White blood cell (WBC) count with differential (including eosinophil, neutrophil, basophil, lymphocytes, and monocytes)

14.1.6.2 Serum Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.

- BUN
- Creatinine*
- Bilirubin (total and direct)
- Uric acid
- Albumin
- Alkaline phosphatase (ALP)
- Creatine kinase (CK)
- Lactate dehydrogenase (LDH)
- Estimated glomerular filtration rate
- Alpha-1 Antitrypsin**
- AST
- ALT
- Amylase
- Lipase
- Glucose (fasting)
- Carbon dioxide (CO_2)/Bicarbonate (HCO_3)
- Sodium
- Potassium
- Chloride

* Creatinine clearance will be calculated using Cockcroft-Gault formula at screening.

** To be performed at screening only.

14.1.6.3 Serology

- HIV
- HBsAg
- HCV

14.1.6.4 Human Chorionic Gonadotropin (Serum Pregnancy Test)

The test will be performed for females only.

14.1.6.5 Follicle-Stimulating Hormone

The test will be performed in postmenopausal females only.

14.1.6.6 Urinalysis

- pH
- Specific gravity
- Protein
- Glucose
- Ketones
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Leukocyte Esterase

If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination will be performed.

14.1.6.7 Urine Drug/Alcohol Screen

- Cannabinoids
- Alcohol
- Cocaine
- Amphetamines
- Barbiturates
- Benzodiazepines
- Opiates

14.1.7 Chest X-Ray

A baseline chest x-ray will be performed at the screening visit. If the patient has had an x-ray within the last 3 months prior to the screening visit, and the CRU has access to the report and images, this can be used as the baseline chest x-ray and does not need to be repeated.

14.1.8 Adverse Events

14.1.8.1 Adverse Event Definition

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.[3]

14.1.8.2 Monitoring

The patients will be instructed to inform the Investigator or clinic staff of any AEs and intercurrent illnesses experienced during the trial. Additionally, a specific inquiry regarding AEs will be conducted prior to each dosing at the CRU, at the end-of treatment (or upon early withdrawal), and at the follow-up phone call. The inquiry will be made in a non-specific manner using open-ended questions so as not to bias the response (e.g., How have you been feeling since your last visit?).

All symptoms will be evaluated by the Investigator.

Any patient who has a clinically significant AE (whether serious or non-serious) or clinically significant abnormal laboratory test value will be evaluated by the Investigator, or other monitoring physician, and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

Treatment of SAEs will be performed by a physician, either at the CRU or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal or unknown (lost to follow-up).

14.1.8.3 Reporting

AEs will be coded using the most current MedDRA® available at Celerion (e.g., 17.0 or higher). The Sponsor will inform the Celerion Global Project Manager which version is to be used prior to initiation of the study.

The Investigator will review each event and assess its relationship to drug treatment (unrelated, unlikely, possible, probable, definite). The severity of each sign or symptom reported will be graded based on the NIH NCI CTCAE toxicity grading scale 5-point severity scale (Grade 1, 2, 3, 4 and 5) [4] and the date and time of onset, time relationship to drug dosing, duration, and outcome (resolved, improved, unchanged, worse, fatal, or unknown/lost to follow-up) of each event will be noted.

The relationship of each AE will be assessed using the following definitions:

Unrelated	▪ Event occurring before dosing. ▪ Event or intercurrent illness due wholly to factors other than drug treatment.
Unlikely	▪ Poor temporal relationship with drug treatment. ▪ Event easily explained by patient's clinical state or other factors.
Possible	▪ Reasonable temporal relationship with drug treatment. ▪ Event could be explained by patient's clinical state or other factors.
Probable	▪ Reasonable temporal relationship with drug treatment. ▪ Likely to be known reaction to agent or chemical group, or predicted by known pharmacology. ▪ Event cannot easily be explained by patient's clinical state or other factors.
Definite	▪ Distinct temporal relationship with drug treatment. ▪ Known reaction to agent or chemical group, or predicted by known pharmacology. ▪ Event cannot be explained by patient's clinical state or other factors.

The following definitions for rating severity will be used:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**. Note**:** An experience may be severe but may not be serious, e.g., severe headache).
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

A semi-colon indicates 'or' within the description of the grade; ADL = Activities of Daily Living

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

14.1.8.4 Serious Adverse Events

If any AEs are serious, as defined by the Food and Drug Administration (FDA) Code of Federal Regulations (CFR), Chapter 21, special procedures will be followed. All SAEs will be reported to the Sponsor via fax or e-mail within one working day of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012[3]. The institutional review board (IRB) will be notified of the Alert Reports as per FDA regulations.

If an SAE occurs to a patient on this study, the Sponsor's Medical Expert is to be contacted (see Section 3).

A SAE is any AE or suspected adverse reaction that in the view of either the Investigator or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood

dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

14.2 Symptom Assessments

14.2.1 Electronic Diary

On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their self-administered doses, whether the dose was administered with food, and daily respiratory symptoms throughout the Run-in and Treatment Periods. Patients will return the e-diary device on Day 56 to CRU staff.

Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

14.2.2 Peak Expiratory Flow

PEF assessments will be made daily prior to each dose from Day 1 of the Run-in Period to Day 56 of the Treatment Period. Three measurements will be made at each time point using a hand held PEF meter. Readings not performed in the CRU will be recorded in the patient e-diary. All PEF assessments should be performed before administration of a bronchodilator where possible.

14.2.3 Symptoms of Chronic Obstructive Pulmonary Disease Exacerbation

Patient will be asked to record the major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation via the e-diary before each dosing.

14.2.4 Dyspnea (Modified Borg Dyspnea Scale)

Severity level of patient’s dyspnea will be assessed via the modified Borg dyspnea scale programmed within the e-diary. The modified Borg dyspnea scale is a self-administered categorical scale with a score from 0 to 10, where 0 (as a measure of dyspnea) corresponds to the sensation of normal breathing (absence of dyspnea) and 10 corresponds to the patient's maximum possible sensation of dyspnea.

14.2.5 Activity (Duke Activity Status Index)

Patient's functional capacity and activity status will be assessed via the DASI programmed within the e-diary. DASI is a self-administered 12-item questionnaire that assesses daily activities such as personal care, ambulation, household tasks, sexual function and recreation with respective metabolic costs. Each item has a specific weight based on the metabolic cost. The final score ranges between 0 and 58.2 points. The higher the score, the better the functional capacity.

14.3 Pharmacodynamic Assessments

14.3.1 Pulmonary Function (Spirometry)

Spirometry measures will be taken at the time points delineated in the Study Events Flow Chart (Section 6) using a standard calibrated spirometer to determine the parameters detailed below.

- FEV_1;
- FVC (forced vital capacity);
- FEV_1/FVC;
- IC.

Short acting β2-agonist and anticholinergic bronchodilators (e.g., albuterol, ipratropium bromide) and long acting β2-agonist and anticholinergic bronchodilators (e.g., salmeterol, tiotropium) agents will be withheld approximately 4 and 12 hours, respectively, before each pre-bronchodilator spirometry.

Every effort will be made to perform all assessments for a given patient on the same instrument throughout the study and all sites should be using the same brand and model of spirometer for this study.

At screening, baseline pre-bronchodilator spirometry will be performed (prior to albuterol administration) for a minimum of 3 times and a maximum of 8 times in order to obtain 3 manoeuvers with FEV_1 values within 150 mL of each other, using the manoeuver with the highest value of FEV_1 and FVC as the basis for comparison.

Patients shall receive 4 inhalations of albuterol, (100 µg/inhalation), for a total dose of 400 µg via metered-dose inhaler using a spacer. Within approximately 20 to 30 minutes after albuterol administration, the baseline post-bronchodilator spirometry will be performed.

Assessment of FEV_1 stability will take place:

1. Prior to Day 1 dosing of the Treatment Period (Day -1 measurement): Predose FEV_1 is defined as the time-point prior to Day 1 dosing in the Treatment Period and will be performed pre- and post-bronchodilatator administration. Predose FEV_1 will be compared to the corresponding baseline measurement. If the best FEV_1 measurement at predose on Day -1 of the Treatment Period has declined by greater than 20% from the best FEV_1 at screening, the visit may be rescheduled up to 3 times, at the discretion of the Investigator.

2. Following Day 1 dosing: At all other spirometry time point, measurements will be performed once. If the value shows a difference of greater than 150 mL decline than the best FEV_1 value collected predose on Day -1, up to 3 measures will be performed.

   Consideration should be given, if a patient experiences any change in post Day 1 dose FEV_1 from the Day 1 predose FEV_1 value (measured following dosing with albuterol) equal to or greater than 20 % and should alert the Investigator to consider whether individual patients should continue to dose. The pulmonary function manoeuver(s) used to make this assessment must be valid and meet acceptable quality spirometry standards.

The Investigator may also use his or her discretion as to the completion of dosing for any period in which an FEV_1 decline and/or respiratory symptoms occur(s).

14.3.2 Bronchoscopy and Bronchoalveolar Lavage (BAL) Biomarkers

Patients will be asked to refrain from smoking approximately 48 hours before the bronchoscopy procedures and will be fasted for 12 hours before. If required, blood pressure medications can be taken with small sip of water based on preapproval of local Investigator.

14.3.2.1 Bronchoscopy

The bronchoscopy with bronchial brushings will be performed at the time points delineated in the Study Events Flow Chart (Section 6) by a licensed physician experienced in conducting the procedure according to guidelines published on the use of bronchoscopy for research on airway diseases such as COPD.[5,6]

Albuterol will be administered 20 minutes prior to the beginning of the bronchoscopy. An intravenous line will also be established to administer conscious sedation, and to administer emergency medications if the need were to arise. During the procedure, oxygen saturation (S_PO_2), blood pressure, and heart rate and rhythm (continuous electrocardiogram) will be monitored. Oxygen 2-4 L via nasal canula will be administered during bronchoscopy and oxygen saturation will be maintained at ≥95%. Conscious sedation will be achieved with incremental doses of 1–4 mg midazolam and 50-100 µg fentanyl. Local upper and lower airway topical anesthesia will be achieved with 1% or 2% lidocaine. The dose of lidocaine administered during the procedure will not exceed a total of 450 mg. The bronchoscope will usually be inserted preferably through the nares into trachea. The bronchoscope will be wedged into 2 subsegments of the right middle or lower lobe, as deemed appropriate by the Investigator. Emergency treatments for cardiopulmonary arrest and pneumothorax will be immediately available in the bronchoscopy room. The patient will remain in the recovery suite for observation for a minimum of 2 hours after the procedure.

14.3.2.2 Bronchial Brushings

Prior to BAL, a cytology brush is inserted into the bronchoscope channel and brushings are collected twice from each of 4 quadrants of visible subsegments of the right middle or lower lobe, as deemed appropriate by the Investigator, under direct visualization. The cellular material is washed off in saline following each brushing. The brushing is performed a total of 8 times. The liquid is centrifuged and the cell pellet is stored at -70°C.

Samples must be protected from UV light during collection, processing, and storage.

14.3.2.3 Bronchoalveolar Lavage (BAL)

BAL in the right middle or lower lobe, as deemed appropriate by the Investigator, will be performed at the time points delineated in the Study Events Flow Chart (Section 6) by a licensed physician experienced in conducting the procedure. A 180 mL BAL will be performed in each subsegment of the right middle or lower lobe, as deemed appropriate by the Investigator, using 6 x 30 mL aliquots of normal saline warmed to room temperature. BAL fluid will be aspirated following each 30 mL instillation. The lavage material, which averages 25% return in COPD patients, typically yields 1-10 x 10^6 macrophages. The centrifuged cell pellet and supernatant will be kept cooled until processed or stored as indicated in the laboratory manual to be provided as a separate document.

Samples must be protected from UV light during collection, processing, and storage.

14.3.2.4 Biomarkers

BAL samples will be analyzed for:

- YPL-001 component levels in epithelial brushings;
- total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells
- total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers
- concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9.

14.3.3 Blood Biomarkers

Blood samples will be collected via direct venipuncture at the time points delineated in the Study Events Flow Chart (Section 6) for PD assessments of biomarkers. Biomarker assessments include:

- inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils, and lymphocytes)
- concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9.

Blood will be drawn into 4.5 mL pre-chilled evacuated tubes containing K_2EDTA and

stored in an ice bath until processing.

14.3.4 Quality of Life Questionnaires

14.3.4.1 Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI)

Dyspnea at baseline (Day -1 of the Treatment Period) will be assessed with the BDI. This instrument has 3 domains (functional impairment, magnitude of task, and magnitude of effort) with the values added for a combined focal score. Functional impairment determines the impact of breathlessness on the ability to carry out activities; magnitude of task determines the type of task that causes breathlessness, magnitude of effort establishes the level of effort that results in breathlessness. The BDI scores range from 0 (very severe impairment) to 4 (no impairment) for each domain with the baseline focal score consisting of the sum of each domain (0 to 12).

Dyspnea throughout the study will be performed at the time points delineated in the Study Events Flow Chart (Section 6). The change from baseline is measured by the TDI score which ranges from -3 (major deterioration) to +3 (major improvement) for each domain with the TDI focal score consisting in the sum of each domain (-9 to +9).

The same Investigator or designee will interview specifically the patients during the study.

A copy of the questionnaire to be used will be kept in the study binder.

14.3.4.2 COPD Assessment Test (CAT)

CAT is a short and simple questionnaire of 8 items completed by patients to be performed at the time points delineated in the Study Events Flow Chart (Section 6). Scores for each of the 8 items are summed to give a single, final score ranging from 0 (no impact on daily activities) to 40 (very high impact on daily activity). This is a measure of the overall impact of a patient's condition on their life. Scores for the individual items within the questionnaire will provide insight into the relative influence that the different components of COPD have on its overall impact on a patient's life.[7,8]

A copy of the questionnaire to be used will be kept in the study binder.

14.4 Pharmacokinetic Assessments

The sampling schedule and/or collection intervals delineated in the Study Events Flow Chart (Section 6) may be modified based on the results from previously dosed patients.

14.4.1 Blood Sampling and Processing

Samples must be protected from UV light during collection, processing, and storage.

Samples will be collected via direct venipuncture at the time points delineated in the Study Events Flow Chart (Section 6).

Blood will be drawn into 5 mL pre-chilled evacuated tubes containing K_2EDTA. A manual for blood sampling, collection, processing, and sample shipment will be provided in a separate document.

14.5 Blood Volume for Study Assessments

Table 5: Blood Volume during Study

Sample Type	Number of Time Points	Volume per Time Point*	Sample Volume Over Course of Study
Screening laboratory safety tests (including hematology, serum chemistry, serology), FSH (for postmenopausal female patients only) and serum pregnancy (for female patients only).	1	~ 17 mL	~ 17 mL
On-study serum chemistry and serum pregnancy (for female patients only) when scheduled at the same time	4	~ 8.5 mL	~ 34 mL
Additional on-study serum pregnancy (for female patients only)	2	~ 3.5 mL	~ 7 mL
On-study hematology	4	~ 4 mL	~ 16 mL
Blood samples for PD biomarkers	8	~ 4.5 mL	~ 36 mL
Blood samples for PK of verproside and picroside II	37	~ 5 mL	~ 185 mL
Total Blood Volume for males →			~ 288 mL
Total Blood Volume for females →			~ 295 mL

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

15. DATA ANALYSIS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCPs.

15.1 Statistical Analysis

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a SAP. The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP.

15.1.1 Sample Size Calculation

According to the exploratory nature of this study no formal statistical hypotheses will be tested. However, a sample size of 60 evaluable patients is deemed to be sufficient to assess the safety and tolerability and to provide an indication of the potential effect of YPL-001 on COPD exacerbation symptoms, selected biomarkers and pulmonary function parameters.

15.1.2 Patients to Analyze

Safety population: the safety population data set will include all available data for patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo. Safety data for all discontinued patients will be included in this set for the time points for which their data are available.

Symptom monitoring population: the symptom monitoring population data set will include all available data for patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo. Symptom monitoring data for all discontinued patients will be included in this set for the time points for which their data are available.

PK population:

- The PK full data set will include all patients receiving at least one dose of YPL-001 and having at least one measurable plasma concentration of verproside and picroside II.
- The PK per-protocol data set will include all patients receiving all scheduled doses of YPL-001 and having sufficient samples collected to determine PK parameters from plasma concentrations of verproside and picroside II on Days 1 and/or 56.

PD population:

- The PD full data set will include all patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo and provide at least 1 post-baseline PD measurement.
- The PD per-protocol data set will include all patients receiving all scheduled doses of

the investigational product (i.e., YPL-001) or placebo and having measurable PD data.

PK/PD population: All patients who receive at least one dose of YPL-001 and having any measurable concentration of verproside and picroside II and measurable PD data will be included in the PK/PD relationship assessment, as applicable.

15.1.3 Safety Analysis

The following analyses will be performed. Safety analyses will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data, when appropriate.

Medical History:

Medical history will be listed by patient.

Adverse Events:

AEs will be coded using the most current MedDRA® available at Celerion (e.g., 17.0 or higher) and data will be summarized by SOC and preferred term. The number of TEAEs will be reported. In addition, the number and percent of patients reporting each TEAE will be summarized separately for each treatment.

A by-patient AE data listing, including verbatim term, preferred term, treatment, severity, outcome, and relationship to treatment, will be provided.

Physical Examination:

Changes in physical examinations will be described in the text of the final report and significant findings will be reported as AEs.

Clinical Laboratory Tests, Electrocardiograms, Vital Signs and Pulse Oximetry:

All clinical laboratory tests, 12-lead ECGs, vital signs, and pulse oximetry measurements and their change from baseline, if applicable, will be summarized by treatment and time point of collection.

A shift table describing out-of-normal range shifts will be provided for clinical laboratory results.

A normal-abnormal shift table will be presented for ECGs.

Peak Expiratory Flow:

PEF measurements and its change from baseline, will be summarized by treatment and time point of collection.

Concomitant Medications:

Concomitant medications will be listed by patient and coded using the most current WHO drug dictionary available at Celerion (e.g., 01-MAR-2014 or later).

15.1.4 Symptom Monitoring Analysis

Symptom free days and overall symptom burden will be evaluated and compared across treatment groups. Secondary outcome analysis will be based on treatment actually

received by patients. Descriptive statistics will be calculated for quantitative data and frequency counts will be compiled for classification of qualitative data, when appropriate.

Peak Expiratory Flow and Symptoms of COPD Exacerbation:

PEF measurements and symptoms of COPD exacerbation and their change from baseline, will be summarized by treatment and time point of collection.

Dyspnea and Activity:

The Modified Borg Dyspnea Scale and DASI scores will be listed and presented descriptively.

Additional analysis may be performed if deemed appropriate.

15.1.5 Pharmacodynamic Analysis

15.1.5.1 Biomarkers

When applicable, the following PD biomarkers will be summarized by treatment group using descriptive statistics (arithmetic means, SD, CV, N, minimum, maximum, and median). Figures will be created to display mean and individual level or activity as a function of time, as appropriate:

- Pulmonary biomarker (i.e., Pulmonary Function measurements [Spirometry]): pre- and post-bronchodilator change in activity by time point will be calculated relative to the pre- and post-bronchodilator baseline activity;
- BAL biomarkers (i.e., total cell count [cells/mL] of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; total cell count [cells/mL] of neutrophils, macrophages, lymphocytes and eosinophils as absolute inflammatory cell numbers; and concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9): raw and % change from baseline levels; and
- Blood biomarkers (i.e., inflammatory markers [total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes] and concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9): raw and % change from baseline levels.

PK/PD relationship may be explored graphically using scatter plots and an appropriate regression model.

15.1.5.2 Quality of Life

The quality of life parameters reported from the BDI/TDI and CAT questionnaires will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.

15.1.6 Pharmacokinetic Analysis

15.1.6.1 Pharmacokinetic Parameters

15.1.6.1.1 Plasma

PK parameters will be computed from the individual plasma verproside and picroside II concentrations using a noncompartmental approach. Appropriate validated PK software (e.g., WinNonlin Professional) will be used. PK parameters for other components of YPL-001 and its metabolites may also be computed, as appropriate.

The following PK parameters will be computed following Day 1 morning dose:

AUC_{0-12}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to 12 hours.
AUC_{0-t}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (Ct). This parameter will be reported only if plasma concentrations fall below the lower limit of quantitation before the last time point prior to the evening drug administration on Day 1 for at least one patient. Otherwise, only AUC_{0-12} will be reported.
AUC_{0-inf}	Area under the drug concentration-time curve from time zero to infinity, $AUC_{0-inf} = AUC_{0-t} + Ct/k_{el}$, where k_{el} is the terminal elimination rate constant. †
C_{max}	Maximum observed drug concentration.
t_{max}	Time of the maximum drug concentration (obtained without interpolation).
k_{el}	Apparent terminal elimination rate constant, calculated by linear regression of the terminal linear portion of the log concentration vs. time curve. †
$t_{1/2}$	Apparent elimination half-life, calculated as $\ln(2)/k_{el}$. †
CL/F	Oral clearance [$Dose/AUC_{0-inf}$]. †
V_Z/F	Apparent volume of distribution at the terminal phase, calculated as $Dose/(k_{el} * AUC_{0-inf})$.†

† All k_{el} and related PK parameters (AUC_{0-inf}, $t_{1/2}$, CL/F, and V_z/F) will be reported only if the half-life of verproside or picroside II can be appropriately estimated from a 12-hour sampling period following dosing.

The following PK parameters will be computed following Day 56 morning dose:

AUC_{τ}	The area under the plasma concentration versus time curve over the final dosing interval, as calculated by the log-linear trapezoidal method (e.g., 0-12 hours).
AUC_{0-t}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (C_t).
C_{max_ss}	Maximum observed drug concentration at steady-state.
$C_{min,ss}$:	Minimum observed/measured non-zero concentration at steady-state.
C_{trough}	Concentration at the end of a dosing interval.
C_{avg}	Ratio of AUC_{τ} to the dosing interval, τ.
%Fluc:	Percent fluctuation will be calculated as follows: $$\frac{C_{\max\_ss} - C_{\min\_ss}}{C_{avg}} \; x \; 100$$
Swing:	Percent swing will be calculated as follows: $$\frac{C_{\max\_ss} - C_{\min\_ss}}{C_{\min\_ss}} \; x \; 100$$
t_{max_ss}	Time to reach the maximum drug concentration (obtained without interpolation) at steady-state.
CL_{ss}/F	Total body clearance estimated at steady-state after oral administration, calculated as Dose/AUC_{τ}.
V_{z_ss}/F	Apparent volume of distribution at steady-state, calculated as $(CL_{ss}/F)/k_{el}$.*

* All k_{el} and related PK parameters ($t_{1/2}$ or V_{z_ss}/F) will not be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

If metabolite data are available, metabolite to parent ratios may be calculated for AUC_{0-t}, AUC_{τ}, and C_{max_ss}.

15.1.6.1.2 Bronchoalveolar Lavage

Levels of YPL-001 components in epithelial brushing will be listed.

15.1.6.2 Statistical Methods for Pharmacokinetic Analyses

PK parameters will be summarized by treatment group using descriptive statistics (arithmetic means, SD, CV, N, minimum, maximum, and median). In addition, geometric means will be calculated for AUC_{τ} and C_{max_ss}, as appropriate. Figures will be created to display mean and individual verproside and picroside II concentration-time curves. Additional PK analyses may be performed if deemed appropriate.

No value for k_{el}, $t_{1/2}$, and V_{z_ss}/F, as appropriate, will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

An estimate of the relative systemic exposure of AUC_{τ} and C_{max_ss} will be performed by dose normalized ratio analysis expressing the geometric mean ratio and 90% CI of the geometric mean ratio.

Steady-state will be assessed by visual inspection of predose plasma C_{trough} values on Days 15, 29, 43, and 56 following multiple oral dose administration of YPL-001.

Additional analyses will be performed as deemed necessary upon review of the data.

15.1.7 Assessment of Efficacy

Efficacy will not be assessed in this study.

16. STUDY ADMINISTRATION

16.1 Ethics

16.1.1 Institutional Review Board

This protocol will be reviewed by an IRB and the study will not start until the Board has approved the protocol or a modification thereof. The Board is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The board is ICH compliant.

16.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, GCP, 21 CFR Parts 50, 56, and 312, the ethical princliples set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

16.1.3 Patient Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the patients in non-technical terms. Patients will be required to read, sign and date an informed consent form summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Patients will be given a copy of their informed consent form.

16.2 Termination of the Study

The Sponsor reserves the right to discontinue this study and the Investigator reserves the right to terminate their participation at any time.

16.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion relevant to the quality of this study. Designated personnel of Celerion will be responsible for maintaining quality assurance (QA) and quality control (QC) to ensure that the trial is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and Good Laboratory Practice requirements as well as applicable regulatory requirements.

The Clinical Study Report will be audited by the QA department and the quality assurance audit certificate will be included in the study report.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to statistical database lock.

Patient compliance will be monitored throughout the study via procedures such as questioning at check-in to review inclusion and exclusion criteria, urine drug screen at

check-in, mouth check following dosing, and confinement for all conduct procedures with clinical research staff on site at all times.

16.4 Direct Access to Source Data/Documents

The Investigator must maintain, at all times, the primary records (i.e., source documents) of each patient's data. Examples of source documents are laboratory reports, drug inventory, study drug label records, and eCRFs that are used as the source.

Celerion will ensure that the sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6] 5.1.2 & 6.10). In the event that other trial-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

16.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of YPL-001 80 mg tablets, and matching placebo tablets to allow completion of this study. The lot numbers and expiration dates (where available) of the drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the drugs supplied. At the conclusion of the study, any unused drugs (including placebo) will either be retained by the CRU, or returned to the Sponsor, depending on the specific requirements of the regulatory bodies to whom the study report will be submitted. If no supplies remain, this fact will be indicated in the Drug Accountability section of the final report.

16.6 Data Handling and Record Keeping

Celerion standard eCRFs will be used. Each eCRF is reviewed and signed off by the Investigator.

All raw data generated in connection with this study, together with the original copy of the final report, will be retained at each CRU in a designated storage facility, until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

16.7 Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be discussed between Sponsor and the Investigator. All revisions and/or amendments to the protocol in writing must be approved by the Sponsor, the Investigator, and the IRB before implementation.

16.8 Finance and Insurance

Finance and insurance will be addressed in a separate document.

16.9 Publication Policy

All unpublished information given to Celerion by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor's written consent to publish the article.

17. REFERENCES

[1] Yungjin Pharma Co., LTD.: YPL-001. Investigator's Brochure. Final 2.0; 3 June 2014.

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[3] FDA Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies-Small Entity Compliance Guide. December 2012. Available online: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM332846.pdf

[4] National Cancer Institute. Common Terminology Criteria for Adverse Events v4.0. NCI, NIH, DHHS. May 29, 2009. NIH publication # 09-7473. Available online at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm The quick reference guide is available online at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

[5] Busse WW, et al. Investigative bronchoprovocation and bronchoscopy in airway diseases. Am J Respir Crit Care Med. 2005;172(7):807-816

[6] Jarjour NN, Peters SP, Djukanović R, and Calhoun WJ. Investigative use of bronchoscopy in asthma. Am J Respir Crit Care Med. 1998;157(3 Pt 1):692-697.

[7] Jones PW, et al. Development and First Validation of the COPD Assessment Test. Eur Respir J. 2009;34:648-654.

[8] The COPD Assessment Test healthcare professional user guide: expert guidance on frequently asked questions (issue 3: February 2012). Jones PW, Jenkins C, Bauerle O (on behalf of the CAT Development Steering Group).

18. APPENDIXES

18.1 Appendix 1 - UGT Drug Interaction Table

The following list provides medications that are substrates or inhibitors of UGT. Adapted from Williams JA, et al. Drug-drug interactions for UDP-glucuronosyltransferase substrates: a pharmacokinetic explanation for typically observed low exposure (AUCi/AUC) ratios. Drug Metab Dispos. 2004;32(11):1201-8. Epub 2004 Aug 10.

Substrates	Inhibitors
17-beta-estradiol glucuronide Amitriptyline Carvedilol Clofibric acid Codeine Cyclobenzaprine Diclofenac DMXAA Fenofibrate Flavopiridol Furosemide Gemfibrozil Glipizide Irbesartan Lamotrigine Levothyroxine Metoclopramide Metronidazole Morphine Naloxone Naproxen Olanzapine Oxazepam Paracetamol Propofol Raloxifene Tramadol Valdecoxib Valproic acid Zidovudine	17-beta-estradiol glucuronide Flavonoids (citrus fruit) Silybin (herb supplement milk thistle)

18.2 Appendix 2 - SULT Drug Interaction Table

The following list provides medications that are substrates and inhibitors of sulfotransferase. Adapted from Zhang H, Cui D, Wang B, Han YH, et al. Pharmacokinetic drug interactions involving 17alpha-ethinylestradiol: a new look at an old drug. Clin Pharmacokinet. 2007;46(2):133-57; Coughtrie MW, Johnston LE. Interactions between dietary chemicals and human sulfotransferases-molecular mechanisms and clinical significance. Drug Metab Dispos. 2001;29(4 Pt 2):522-528; King RS, Ghosh AA, and Wu J Inhibition of human phenol and estrogen sulfotransferase by certain non-steroidal anti-inflammatory agents. Curr Drug Metab. 2006;7(7):745–753; Nagai M, et al. Inhibitory effects of herbal extracts on the activity of human sulfotransferase isoform sulfotransferase 1A3 (SULT1A3). Biol Pharm Bull. 2009;32(1):105-109; and Harris, R. M.; Waring, R. H. Sulfotransferase inhibition: potential impact of diet and environmental chemicals on steroid metabolism and drug. Current Drug Metabolism 2008;9(4):269-275.

Substrates	Inhibitors
17-beta-estradiol glucuronide Vitamin C Acetaminophen	17-beta-estradiol glucuronide Vitamin C Brown rice Beer Meclofenamate Nimesulide Salicylic acid Acetylsalicylic acid Naproxen Banaba extract Rafuma extract Grape seed extract Peanut seed coat extract Gingko extract Biloba leaf extract St. John’s wort Gymnema Milk thistle

Celerion Project No.: AA98497

Sponsor Project No.: YPL-001-YJP-130403

IND No.: 114903

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

1. PROTOCOL REVISION HISTORY

DATE/NAME	DESCRIPTION
20-Nov-2014 by Ziv Machnes	Final Protocol, Amendment 1 This protocol amendment is generated to update the study population with regards to smoking frequency, to update the handling procedures for BAL samples, and to clarify other study procedures as listed below. **Study Population:** Section 13.3.2 - Inclusion Criteria, bullet 11 was updated to indicate that the study population will consist only of current and ex-smokers with a history of >10 pack years. As such, the indications for 'packs/year' were replaced with 'pack years' and the allowance for current smokers with <10 pack/years was removed. Wording was added to indicate an approximately equal number of current and ex-smokers will be enrolled, and that each treatment group will consist of an approximetly equal number of smokers and ex-smokers. In addition, the stratification criteria for the randomization was updated to consist of either current or ex-smokers. The following sections were affected: • Section 5 – Synopsis (under Study Population and Number of Patients) • Section 13.1 - Overall Study Design and Plan (second paragraph) • Section 13.3.1 – Number of Patients. • Section 13.4.2 - Method of Assigning Patients to Treatment Groups. **BAL Sample Handling:** Section 14.3.2.3 - Bronchoalveolar Lavage (BAL) was updated to indicate that sample handling, processing and storage procedures will be provided in a separate document. **Follow-up Procedures:** The wording in regards to follow-up procedures to be conducted on 14 days (± 2 day), after the last study drug administration, was updated to indicated a phone-call and not a visit, as indicated correctly in Section 6 – Study Event Flow Chart. Study event were updated accordingly. The following sections were affected: • Section 5 – Synopsis (under Duration of Participation for Patients, and Exploratory Outcome Measures [under Blood Assessments, Pulmonary Assessment, and Quality of Life Assessments]) • Section 13.3.5.2 – Prohibitions (under Alcohol) • Section 14.1.8.2 – Monitoring (first paragraph).

	Study Duration: The total duration of the study indicated in Section 5 – Synopsis (under Duration of Participation for Patients) was corrected to 12 weeks to correspond with the actual study duration as indicated throughout the protocol. **Inflammatory Markers in Blood Samples:** The list of cell types to be evaluated as part of the inflammatory markers in the blood was updated to include monocytes instead of macrophages, as macrophages are not expected to be present in blood. The following sections were affected: • Section 5 – Synopsis (under Study Objectives, fourth exploratory objective, and under Exploratory Outcome Measures [under Pharmacodynamic Assesments, Blood Assessments, first bullet]) • Section 12.1 - Study Objectives (fourth exploratory objective) • Section 12.2 - Study Endpoints (third exploratory endpoint) • Section 14.3.3 - Blood Biomarkers (first bullet) • Section 15.1.5.1 - Biomarkers (third bullet) **Neutrophil Evaluation in BAL Samples** Neutrophils were added to the list of cell types to be evaluated as a percentage of the total cell count in BAL samples. The following sections were affected: • Section 5 – Synopsis (under Study Objectives, second exploratory objective and under Exploratory Outcome Measures [under Pharmacodynamic Assessments, Bronchoalveolar Lavage Assessments, second bullet]) • Section 12.1 - Study Objectives (second exploratory objective) • Section 12.2 - Study Endpoints (second exploratory endpoint) • Section 14.3.2.4 - Biomarkers (second bullet) • Section 15.1.5.1 – Biomarkers (second bullet) **Location of Study Drug Administration**: Wording was added in Section 6 – Study Events Flow Chart for Day 56, to clarify that the study drug will be administered at the CRU. **Meal Schedule**: The indication for fasting requirement in Section 13.2.4.1 – Meal Schedule, was corrected to indicate patients will fast overnight for at least 12 hours before bronchoscopy and BAL collection on Days -1 and 55 instead of Days -1 and 56, as correctly indicated in Section 6 – Study Events Flow Chart.

	ECG Monitoring: Following an update in Celerion's standard operating procedure, Section 14.1.5 – Electrocardiogram Monitoring was updated to include at least 5 minutes of rest prior to each ECG measurement (instead of at least 1 minute as previously indicated). **Hematology:** The tests included in the hematology panel Section 14.1.6.1 – Hematology were updated to indicate that the red blood cell (RBC) count will include a reticulocytes count, and that the white blood cell (WBC) count with differential will include monocytes but will not include reticulocytes. **Bronchoscopy and BAL:** Due to the sensitivity of YPL-001 components to UV light, a warning was added to protect all samples from exposure to UV light, as indicated for the PK blood samples. The following sections were affected: • Section 14.3.2.2 - Bronchial Brushings • Section 14.3.2.3 - Bronchoalveolar Lavage (BAL) **PK Population:** The indication for measurable concentration of verproside and picroside II in urine was removed from the definition of PK population in Section 15.1.2 - Patients to Analyze, as there is no urine PK sampling planned for this study. Minor typographic and editorial corrections were made where applicable.
18-Sep-2014 by Caroline Engel	Final Protocol

2. SPONSOR – SIGNATORIES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

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Signature

20/NOV/2014
Date

3. INVESTIGATORS SIGNATURES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

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Date

INVESTIGATORS SIGNATURES (*CONTINUED*)

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

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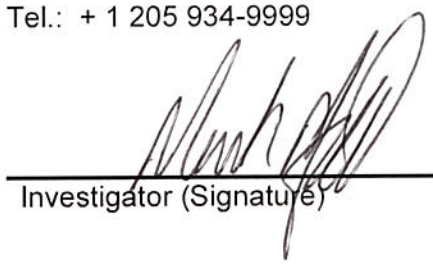

Investigator (Signature)

Date

4. ADDITIONAL KEY CONTACTS FOR THE STUDY

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5. SYNOPSIS

Compound:	YPL-001
Clinical Indication:	Treatment of inflammatory diseases of the respiratory tract such as asthma and chronic obstructive pulmonary disease (COPD)
Study Type	Phase 2a, proof of concept
Study Objectives	The **primary objective** of the study is to assess the safety and tolerability of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients. The **secondary objective** of the study is to assess the number and magnitude of daily respiratory symptoms of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients. The **exploratory objectives** of the study are to evaluate the following in moderate to severe COPD patients: 1. To assess bronchoalveolar lavage (BAL) epithelial brushings for YPL-001 component levels. 2. To compare BAL samples for total cell count (cells/mL) macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; neutrophil, macrophage, lymphocyte and eosinophil counts as absolute inflammatory cell numbers in YPL-001 groups versus placebo group. 3. To compare BAL samples for tumor necrosis factors alpha (TNF-α), interleukin (IL)-1β, IL-4, IL-5, IL-6, IL-8, IL-13, myeloperoxidase (MPO), neutrophil elastase, monocyte chemotactic protein (MCP)-1, and matrix metalloproteinase (MMP)-9 in YPL-001 groups versus placebo group. 4. To compare blood inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) and concentrations of C-reactive protein (CRP), fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9 in YPL-001 groups versus placebo group. 5. To compare spirometric functions (forced expiratory volume in one second [FEV_1], forced vital capacity [FVC], FEV_1/FVC, and inspiratory capacity [IC]) in YPL-001 groups versus placebo group. 6. To compare patient reported outcomes (Baseline Dyspnea Index [BDI]/Transition Dyspnea Index [TDI], COPD Assessment Test [CAT]) in YPL-001 groups versus placebo group. 7. To assess verproside and picroside II concentration in plasma and BAL and verproside and picroside II pharmacokinetics (PK) in plasma following multiple oral doses administration of two YPL-001 dose levels.

Summary of Study Design	This is a Phase 2a, proof-of-concept, multicenter, randomized, double-blind, double-dummy, 3-treatment, parallel study, with low and high YPL-001 doses (80 mg and 160 mg twice daily [BID]) and a placebo control in moderate to severe COPD patients. Sixty-nine (69) patients will be enrolled and randomized into 3 treatment groups (23 patients per group). Patients will participate only once. Safety and tolerability will be assessed throughout the study. Assessment of respiratory symptoms and symptom burden in YPL-001 and placebo treatments will be performed daily through patient self-report of peak expiratory flow (PEF), major and minor symptoms of COPD exacerbation, dyspnea, and activity in their electronic diary (e-diary). Spirometry measurement, bronchoalveolar lavage (BAL), and blood samples will be collected for the pharmacodynamic (PD) assessment of YPL-001 and placebo treatments. Serial blood samples will also be collected for PK assessment of verproside (the principal active ingredient of YPL-001) and picroside II. Other components of YPL-001 and its metabolites may also be analyzed in plasma. Following screening, eligible patients will discontinue non permitted respiratory drugs if already receiving them and enter a 14 ± 2 days Run-in Period during which patients will be given albuterol taken on an as required basis and daily tiotropium 18 µg (one capsule inhaled daily in the morning) to be administered at home. On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their daily symptoms throughout the Run-in Period. Patients will return to the clinical research unit (CRU) on the morning of Day -1 of the Treatment Period to confirm their eligibility and assess their health conditions. If they still meet all of the inclusion criteria and none of the exclusion criteria, they will undergo Day -1 scheduled study procedures. Patients will return to the CRU the next day (Day 1) to be randomized and receive one of the 3 treatments and undergo all scheduled study procedures. Patients will return on the morning of Days 15, 29, 43, 55, and 56 of the Treatment Period for study drug administration and procedures. Prior to each release from the CRU, patients will receive a properly labeled container with sufficient doses which will be self-administered by patients at home until the next morning visit at the CRU. Patients will continue recording their daily symptoms via the e-diary throughout the Treatment Period. Patients will return the e-diary device on Day 56 to CRU staff. The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any adverse event (AE) has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary. Patients will be instructed to call the Investigator if breathing worsens or if they need to take more than 8 puffs per day of albuterol for more than 2 consecutive days. If the Investigator determines that the patient is too unstable to continue in the study, he/she will be discontinued. Rescue medication will be used for any patient with an exacerbation of COPD and will be administered in accordance with the study center standard of care.

Study Population	Patients will be adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3) with a predominant bronchitic component and a history of frequent (>2/year) COPD exacerbations, between 40 and 80 years of age (inclusive). An approximately equal number of current and ex-smokers will be enrolled.
Number of Patients	The study is planned to enroll 69 patients to ensure completing the study with 60 patients. Patients will be divided in 3 treatment groups with 23 patients to receive one of the 3 treatments (i.e., low and high YPL-001 doses [80 mg and 160 mg BID] and a placebo control) as per the randomization schedule. Each treatment group will consist of an approximately equal number of current and ex-smokers.
Duration of Participation for Patients	The planned length of participation in the study for each patient is approximately 12 weeks (from Day 1 of the Run-in Period through completion of the follow-up procedures on Day 70 [± 2 day]).
Duration of Study Conduct	The study is planned to take place over approximately 12 to 24 months (from screening of the first patient through completion of all study procedures for the last patient). This time period may change in the event that the study is terminated early, additional time is required to review safety, or a decision is made to complete an unscheduled analysis for a group.
Study Products	YPL-001 will be supplied as 80 mg tablets for oral administration. Placebo will be supplied as YPL-001 80 mg matching placebo tablets for oral administration. An unblinded pharmacist will be responsible for providing YPL-001 or placebo to the blinded study personnel for administration.
Dosage, Dosage Form, Route, and Dose Regimen	Treatments are described as follows: Treatment A: Multiple oral YPL-001 80 mg doses (1 x 80 mg tablet + 1 x 1 YPL-001 80 mg matching placebo tablet) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56. Treatment B: Multiple oral YPL-001 160 mg doses (2 x 80 mg tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56. Treatment C: Multiple oral matching placebo (2 x 1 YPL-001 80 mg matching placebo tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56. In all treatments, one tiotropium (Spiriva® HandiHaler®) 18 µg capsule will also be administered QD every morning prior to study drugs administration. Albuterol will be administered on an as needed basis. Each dose of Treatments A, B and C will be administered orally with approximately 240 mL of water.

Stopping Rules	A decision to stop or suspend the study will be made jointly by the Sponsor and the Investigator following the review of all pertinent safety and tolerability. Together they will make one of the following determinations: 1. To continue with the study as planned. 2. To continue with the study and add additional safety evaluations. 3. To continue with the study by adjusting to a lower dose if 2 patients at any dose level meets any of the following criteria and the patient was determined to have received YPL-001 after unblinding: a. Has a drug–related, unexpected serious adverse event (SAE). b. Experiences drug-related grade ≥ 3 toxicity. 4. The study will be terminated if ≥ 3 patients at any dose level meet any of the following criteria and the patients were determined to have received YPL-001 after unblinding: a. Has a drug–related, unexpected SAE. b. Experience drug related grade ≥ 3 toxicity.
Primary Outcome Measures	Safety and tolerability will be monitored through physical examinations, vital signs, pulse oximetry, ECGs, clinical laboratory tests, and AEs.
Safety and Tolerability Analysis	The following analyses will be performed. Safety analyses will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data, when appropriate. **Medical History:** Medical history will be listed by patient. **Adverse Events:** AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion (e.g., 17.0 or higher) and data will be summarized by System organ class (SOC) and preferred term. The number of treatment-emergent AEs (TEAEs) will be reported. In addition, the number and percent of patients reporting each TEAE will be summarized separately for each treatment. A by-patient AE data listing, including verbatim term, preferred term, treatment, severity, outcome, and relationship to treatment, will be provided. **Physical Examination:** Changes in physical examinations will be described in the text of the final report and significant findings will be reported as AEs. **Clinical Laboratory Tests, Electrocardiograms, Vital Signs, and Pulse Oximetry Measurements:** All clinical laboratory tests, 12-lead ECGs, vital signs, and pulse oximetry measurements and their change from baseline, if applicable, will be summarized by treatment and time point of collection. A shift table describing out-of-normal range shifts will be provided for clinical laboratory results. A normal-abnormal shift table will be presented for ECGs.

Safety and Tolerability Analysis (continued)	**Concomitant Medications:** Concomitant medications will be listed by patient and coded using the most current World Health Organization (WHO) drug dictionary available at Celerion (e.g., 01-MAR-2014 or later).
Secondary Outcome Measures	PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (Duke Activity Status Index [DASI]) self-reported daily by the patients using an e-diary.
Symptom Monitoring Analysis	Symptom free days and overall symptom burden will be evaluated and compared across treatment groups. Secondary outcome analysis will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative data and frequency counts will be compiled for classification of qualitative data, when appropriate. **Peak Expiratory Flow and Symptoms of COPD Exacerbation:** PEF measurements and symptoms of COPD exacerbation and their change from baseline, will be summarized by treatment and time point of collection. **Dyspnea and Activity:** The Modified Borg Dyspnea Scale and DASI scores will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.
Exploratory Outcome Measures	**Pharmacodynamic Assessments:** <u>Bronchoalveolar Lavage Assessments:</u> BAL samples will be collected at baseline and again at the completion of the study for PD assessments of biomarkers. Biomarker assessments include: 1. epithelial brushings for YPL-001 component levels; 2. total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells 3. total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers 4. concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9. <u>Blood Assessments:</u> Blood samples will be collected at screening, and throughout the study for PD assessments of biomarkers. Biomarker assessments include: 1. inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) 2. concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9. <u>Pulmonary Assessment:</u> Pulmonary function measurements (spirometry [FEV_1, FVC, FEV_1/FVC, and IC) will be performed at screening, and throughout the study.

Exploratory Outcome Measures (continued)	Quality of Life Assessments: Patient reported outcomes (e-diary, BDI/TDI, CAT) will be performed at baseline, and throughout the study. **Pharmacokinetic Assessments:** Bronchoalveolar Lavage Assessments: BAL samples will be collected at baseline and again at the completion of the study to determine verproside and picroside II concentrations in BAL. Other components of YPL-001 and its metabolites may also be analyzed. Plasma Assessments: Serial blood samples will be collected prior to the initial dosing and through 12 hours following dosing on Days 1 and 56 to determine verproside and picroside II concentrations in plasma. Predose samples will also be collected in the morning of Days 15, 29, 43 and 56 for C_{trough} determination. Other components of YPL-001 and its metabolites may also be analyzed. The sampling schedule and/or collection intervals may be modified based on the results as the study progress.
Pharmacodynamic Analysis	**Blood, Plasma, and Pulmonary biomarkers:** When applicable, the raw data and % change from baseline or placebo, as appropriate, for PD markers (BAL biomarkers, blood biomarkers, and pulmonary biomarker) will be summarized by time point and treatment using descriptive statistics (arithmetic means, standard deviations [SD], coefficients of variation [CV], sample size [N], minimum, maximum, and median). Figures will be created to display mean and individual level or activity as a function of time. **Quality of Life:** The quality of life parameters will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.
Pharmacokinetic Parameters and Analysis	Noncompartmental PK parameters, including AUC_{0-t}, AUC_{0-inf}, AUC_{τ}, k_{el}, C_{max}, C_{max_ss}, C_{min_ss}, C_{trough}, t_{max}, t_{max_ss}, CL/F, CL_{ss}/F, V_z/F, V_{z_ss}/F, and $t_{1/2}$, as appropriate, will be calculated from plasma concentrations of verproside and picroside II from patients who received YPL-001 only. Additional PK parameters may be calculated if deemed appropriate. Plasma PK parameters may also be calculated for other components of YPL-001 and its metabolites. PK parameters will be summarized by treatment using descriptive statistics. Relative exposure of verproside and picroside II will be assessed between the two YPL-001 dose levels, and steady-state will be assessed by visual inspection in the active treatment groups. Verproside and picroside II concentration in BAL samples from patients who received YPL-001 only will be listed.

6. STUDY EVENTS FLOW CHART

Study Procedures[a]	Screen[b]	Run-in Period		Treatment Period																			
Days →		1	2-14 (±2)	-1	1																		
Hours →					Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12
Administrative Procedures																							
Informed Consent	X																						
Inclusion/Exclusion Criteria	X	X																					
Medical History	X																						
Randomization																							
Safety Evaluations																							
Physical Examination[c]	X			X[d]																			
Height	X																						
Weight	X			X[d]																			
Chest X-ray[e]	X																						
12-Lead Electrocardiogram	X			X[f]																			
Vital Signs[g]	X			X[f]	X						X		X						X				
Pulse Oximetry	X			X[f]																			
Hem, Chem, and UA[h]	X			X[d]																			
Serum Pregnancy Test (♀ only)	X			X[d]																			
Serum FSH (postmenopausal ♀ only)	X																						
Urine Alcohol & Drug Screen	X			X[d]																			
HIV/Hepatitis Screen	X																						
AE Inquiries																							
AE Monitoring										X													
ConMeds Monitoring	X									X													
Symptoms Monitoring																							
Diary Training		X																					
Diary Use[i]										X													
PEF, COPD exacerbation, dyspnea and activity[j]										X													
Study Drug Administration																							
Tiotropium Administration		X	X	X	X																		
Study Drug Administration at CRU[k]						X																	X
Pharmacodynamic																							
Pulmonary Function (Spirometry)[l]	X			X[d]																			

Study Procedures[a]	Screen[b]	Run-in Period		Treatment Period																		
Days →		1	2-14 (±2)	-1	1																	
Hours →					Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12
Pharmacodynamic																						
Bronchoscopy and BAL Biomarkers[m]				X																		
Blood Biomarkers	X				X						X											
BDI/TDI & CAT	X			X[d]																		
Pharmacokinetic																						
Blood for Verproside & Picroside II PK					X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]
Other Procedures																						
Visit & Return Visits[o]	X	X		X	X																	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.
b. Within 14 days of Day 1 (inclusive) of the Run-in Period.
c. A full physical examination will be performed at screening. Symptom-driven physical examinations will be performed at other scheduled times, and may be performed at other times at the Investigator's discretion.
d. To be performed prior to the bronchoscopy procedures.
e. To be performed at screening or within 3 months (inclusive) of screening.
f. ECGs, vital sign and pulse oximetry will be measured within 2 hours of bronchoscopy procedures. During the bronchoscopy procedures and BAL sample collection, patients will be continuously monitored for ECGs, vital signs (blood pressure, heart rate, respiration rate, and body temperature), and oxygen saturation.
g. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
h. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.
i. Patients will be provided with an e-diary device to record their self-administered doses and whether the dose was administered with food, concomitant medications and daily respiratory symptoms.
j. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).
k. Prior to release from the CRU, patients will receive a properly labeled container with sufficient study drug for their assigned treatment which will be self-administered by patients at home until the next morning visit at the CRU. Patients must return the container (empty or not) at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.
l. Pulmonary function will be performed prior to and 20 to 30 minutes after inhalation of approximately 400 µg albuterol.
m. Bronchoscopy and BAL sample collection will be performed following a 12-hour fast.
n. To be performed prior to dosing.
o. Patients will be admitted to the CRU at the time indicated by the CRU.

STUDY EVENTS FLOW CHART *(CONTINUED)*

Study Procedures[a]	Treatment Period											
Days →	2-14	15		16-28	29		30-42	43		44-54	55	
Hours →		AM	PM		AM	PM		AM	PM		AM	PM
Safety Evaluations												
Physical Examination[b]					X[c]						X[d]	
Weight					X[c]						X[d]	
12-Lead Electrocardiogram					X[c]						X[e]	
Vital Signs[f]		X[c]			X[c]			X[c]			X[e]	
Pulse Oximetry											X[e]	
Hem, Chem, and UA[g]					X[c]						X[d]	
Serum Pregnancy Test (♀ only)		X[c]			X[c]			X[c]			X[d]	
Urine Alcohol & Drug Screen		X[c]			X[c]			X[c]			X[d]	
AE Inquiries		X[c]			X[c]			X[c]			X[d]	
AE Monitoring	X											
ConMeds Monitoring	X											
Symptoms Monitoring												
Diary Use[h]	X											
PEF, COPD exacerbation, dyspnea and activity[i]	X											
Study Drug Administration												
Tiotropium Administration	X											
Study Drug Administration at CRU		X			X			X			X	
Study Drug Administration at Home[j]	X		X	X		X	X		X	X		X
Pharmacodynamic												
Pulmonary Function (Spirometry)[k]		X[c]			X[c]			X[c]			X[d]	
Bronchoscopy and BAL Biomarkers[l]											X[c]	
Blood Biomarkers		X[c]			X[c]			X[c]				
BDI/TDI & CAT		X[d]			X[d]			X[d]			X[d]	
Pharmacokinetic												
Blood for Verproside & Picroside II PK		X[c]			X[c]			X[c]				
Other Procedures												
Visit & Return Visits[m]		X			X			X			X	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.
b. Symptom-driven physical examinations will be performed at scheduled times, and may be performed at other times at the Investigator's discretion.
c. To be performed or completed prior to dosing.
d. To be performed or completed prior to bronchoscopy procedures and/or dosing.
e. ECGs, vital sign and pulse oximetry will be measured within 2 hours of bronchoscopy procedures. During the bronchoscopy procedures and BAL sample collection, patients will be continuously monitored for ECGs, vital signs (blood pressure, heart rate, respiration rate, and body temperature), and oxygen saturation.
f. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
g. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.
h. Patients will be provided with an e-diary device to record their self-administered doses and whether the dose was administered with food, concomitant medications and daily respiratory symptoms.
i. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).
j. Prior to release from the CRU, patients will receive a properly labeled container with sufficient study drug for their assigned treatment which will be self-administered by patients at home until the next morning visit at the CRU. Patients must return the container (empty or not) at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.
k. Pulmonary function will be performed prior to and 20 to 30 minutes after inhalation of approximately 400 µg albuterol.
l. Bronchoscopy and BAL sample collection will be performed following a 12-hour fast.
m. Patients will be admitted to the CRU at the time indicated by the CRU.

STUDY EVENTS FLOW CHART *(CONTINUED)*

Study Procedures[a]	Treatment Period																		EOT or ET[b]	FU[c]
Days →	56																			
Hours →	Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12		
Safety Evaluations																				
Physical Examination[d]																			X	
Weight																				
12-Lead Electrocardiogram																			X	
Vital Signs[e]	X						X		X						X				X	
Pulse Oximetry																				
Hem, Chem, and UA[f]																			X	
Serum Pregnancy Test (females only)																				
Urine Alcohol & Drug Screen	X																			
AE Inquiries	X																		X	
AE Monitoring									X											X
Concomitant Medication Monitoring									X											
Symptoms Monitoring																				
Diary Use[g]	X																			
PEF, COPD exacerbation, dyspnea and activity[h]	X																			
Study Drug Administration																				
Tiotropium Administration	X																			
Study Drug Administration at CRU		X																		
Pharmacodynamic																				
Blood Biomarkers	X[i]						X													
BDI/TDI & CAT	X[i]																			
Pharmacokinetic																				
Blood for Verproside Pharmacokinetics	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Other Procedures																				
Return Visits[j]								X											X	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.

b. To be performed at the end of the Treatment Period on Day 56 or prior to early termination from the study.

c. The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

d. Symptom-driven physical examinations will be performed at scheduled times, and may be performed at other times at the Investigator's discretion.

e. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.

f. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, Patients may not have fasted for 8 hours before the serum chemistry sample is taken.

g. Patients will return the e-diary device on Day 56 to CRU staff.

h. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

i. To be performed at predose on Day 56 or upon early termination.

j. Patients will be admitted to the CRU at the time indicated by the CRU.

Abbreviations: ♀ = Female, AE = Adverse events, AM = Morning, BAL = bronchoalveolar lavage, BDI/TDI = Baseline Dyspnea Index/Transition Dyspnea Index Test, CAT = COPD Assessment Test, Chem = Serum chemistry, COPD = chronic obstructive pulmonary disease, CRU = Clinical research unit, ConMeds = Concomitant medication monitoring, DASI = Duke Activity Status Index, ECG = Electrocardiogram, e-diary = electronic diary, EOT/ET = End-of-Treatment or early termination, FSH = Follicle-stimulating hormone, Hem = Hematology, HIV = Human immunodeficiency virus, IL= interleukin, PEF = Peak expiratory flow, PK = Pharmacokinetics, PM = Evening, Preg = Serum pregnancy, Screen = Screening, UA = Urinalysis.

7. TABLE OF CONTENTS

8. ABBREVIATIONS

Only those uncommon abbreviations specific to this study are listed. Pharmacokinetic (PK) parameter abbreviations and definitions may be found in Section 15.1.6.1.

AE	Adverse event
AHR	Airway hyper-responsiveness
ALD	Approximate lethal dose
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
BALF	Bronchoalveolar lavage fluid
BDI	Baseline Dyspnea Index
BID	Twice daily
BLQ	Below the lower limit of quantification
BMI	Body mass index
bpm	Beat per minute
BUN	Blood urea nitrogen
°C	Degrees Celsius
CAT	COPD Assessment Test
Chem	Chemistry
CFR	Code of Federal Regulations
CK	Creatine kinase
CNS	Central nervous system
CO_2	Carbon dioxide
Coag	Coagulation
COPD	Chronic obstructive pulmonary disease
CRO	Contract Research Organization
CRP	C-reactive protein
CRU	Clinical research unit

CS	Clinically significant abnormality
CSC	Cigarette smoking condensate
CXCL	Chemokine (C-X-C motif) ligand
CV	Coefficient of variation
DASI	Duke Activity Status Index
dL	Deciliter
DRF	Dose range finding
e-diary	Electronic diary
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
ERS	European Respiratory Society
F	Female
°F	Degrees Fahrenheit
FDA	Unites States Foods and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FU	Follow-up
FVC	Forced vital capacity
g	gram
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HBsAg	hepatitis B surface antigen
HCO_3	Bicarbonate
HCV	hepatitis C antibodies
HED	Human equivalent dose
Hem	Hematology
HIV	Human immunodeficiency virus
hr	Hour
IC	Inspiratory capacity
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroid

IgE	Immunoglobulin E
IL	Interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
kg	Kilogram
kg/m^2	Kilogram per meter squared
LABA	long acting beta agonist
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
LOQ	Limit of quantitation
LPS	Lipopolysaccharide
LSM	Least-squares means
µg	Microgram
m^2	Square meter
M	Male
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCO	Myeloperoxidase
MCP	Monocyte chemotactic protein
MCV	Mean Corpuscular Volume
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
MIP	Monocyte inhibitory protein
mL	Milliliter
mmHg	Millimetre of mercury
MMP	Matrix metalloproteinase
msec	Millisecond
MTD	Maximum Tolerated Dose
N	Sample size
NCS	Not clinically significant

ng	Nanogram
No.	Number
NOAEL	No observed adverse effect levels
OTC	Over-the-counter
OVA	Ovalbumin
PD	Pharmacodynamic(s)
PEF	Peak expiratory flow
PK	Pharmacokinetic(s)
QA	Quality Assurance
QC	Quality Control
QT	Interval between the Q and T waves on the electrocardiogram tracing
QTcF	Corrected QT interval with Fridericia's formula
RBC	Red blood cell
RDW	Red cell distribution width
Resp	Respiration
ROS	Reactive oxygen species
SABA	Short-acting β2-agonist
SAD	Single ascending dose
SAE	Serious adverse event
SAMA	Short-acting anticholinergic agent
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SULT	Sulfotranferase
TBIL	Total bilirubin
TDI	Transition Dyspnea Index
TEAE	Treatment-emergent adverse event
Th	T helper
TNF-α	Tumor necrosis factors alpha
UA	Urinalysis
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal

US	United States
WBC	White blood cell
WHO	World Health Organization

9. INTRODUCTION AND BACKGROUND

This study is being conducted as the third in a series of studies for the clinical development of YPL-001. The trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. The patient population will be comprised of moderate to severe (GOLD Stage 2-3) COPD patients.

9.1 YPL-001

YPL-001 drug product is an oral dosage form of an herbal extract from the aerial parts of the plant Speedwell (*Pseudolysimachion rotundum* subsp. *Subintegrum*). *Pseudolysimachion* (*Veronica*) is a perennial herb which has been used as a traditional medicine in Korea and China for the treatment of inflammatory diseases of the respiratory tract such as asthma and COPD.

As a botanical drug product, the drug substance is a mixture of chemical species (iridoids [including verproside] and other related compounds) and biological activity is considered to be from the mixture and not from an individual component. It is unknown if the total activity from individual components is additive or synergistic. Five active constituents, classified as iridoids, have been identified in the herbal extract: verproside, picroside II, catalpolside, isovanilloyl catalpol, and 6-*O*-veratroylcatalpol. Recent experimentation has revealed that the principal active ingredient in *Pseudolysimachion* is verproside, a dihydroxylated catalpol derivative.

YPL-001, containing verproside and other active ingredients, is being developed as a potential oral treatment for long term inflammatory diseases of the respiratory tract such as asthma or bronchitic COPD. Current long term control medications include corticosteroids, cromolyn sodium, immunomodulators, long acting beta agonists, (LABAs), methylxanthines, and leukotriene modifiers. YPL-001 belongs most closely with the leukotriene modifier class of drug.

A brief overview of available information regarding YPL-001 follows below. Details can be found in the YPL-001 Investigator's Brochure of March 1, 2013. [1]

9.1.1 Preclinical Trials

9.1.1.1 Pharmacology

Five *in vivo* primary pharmacology studies have been completed.

In ovalbumin-sensitized mice, an animal model for asthma, YPL-001 reduced elevated immunoglobulin E (IgE), IL-4, IL-5, IL-13, airway hyper-responsiveness, and mucus hyper-secretion.

In the lipopolysaccharide (LPS)- and cigarette smoking condensate (CSC)-induced COPD mice model, verproside and roflumilast treatment inhibited the accumulation of neutrophils in Bronchoalveolar lavage fluid (BALF) as well as the increase of several proinflammatory cytokines and chemokines. Neutrophil infiltration induced by LPS and CSC treatments was associated with a significant increase in BALF levels of the chemoattractants, TNF-α, chemokine (C-X-C motif) ligand (CXCL)-1, and monocyte inhibitory protein (MIP)-2. These data also demonstrated that the effect of YPL-001 and verproside involves down-regulation of the influx of neutrophils and production of TNF-α,

CXCL-1, and MIP-2 molecules which play a major role in tissue remodeling.

YPL-001 significantly suppressed the increase of inflammatory cell counts, particularly neutrophils in BALF and also effectively suppressed elevated levels of TNF-α, CXCL-1 and MIP-2 with the reduction in airway inflammatory responses in CSC- and LPS-induced COPD mice.

YPL-001 also effectively suppressed the increased inflammatory cell count, particularly neutrophils in BALF and also significantly inhibited elevated levels of TNF-α, IL-1β and IL-6 with the reduction in reactive oxygen species (ROS) production and elastase activity in cigarette smoke- and LPS-induced COPD mice.

In the LPS- and cigarette smoke-induced COPD rats model, YPL-001 significantly inhibited the increase of inflammatory cell count, particularly neutrophils in BALF and also effectively suppressed elevated levels of TNF-α, IL-1β, IL-6, MIP-2 and CRP.

YPL-001 effectively inhibited development of both T helper (Th)2 and Th1/Th17 type asthma in these murine models. These effects resulted from inhibition of cytokine and chemokine production by infiltrated inflammatory cells and antigen specific T cells in lymph nodes. YPL-001 did not inhibit development of COPD which was induced by *E.coli* extracellular vesicles.

9.1.1.2 Pharmacokinetics

After oral administration of YPL-001 at 12.5, 25, and 50 mg/kg doses (5.225, 10.45, and 20.9 mg/kg as verproside) in rats, verproside was rapidly absorbed; verproside was detected at the first blood sampling time (5 min) and absorbed rapidly, with the t_{max} achieved at 0.46-0.61 hour for all three doses. The post-absorption phase of the mean plasma verproside concentration-time profiles showed a poly-exponential decay.

The area under the plasma concentration-time curve (AUC) and the maximum plasma concentration (C_{max}) of verproside were linearly increased as the oral dose of YPL-001 increased. Alternately, the dose normalized (based on 12.5 mg/kg) AUCs and C_{max} of verproside were comparable among different doses studied. The elimination half-lives ($t_{1/2}$), 2.14 – 3.91 hours, and other PK parameters of verproside for all three doses were also comparable. These findings indicate that the PK parameters of verproside were independent of doses.

The fraction of dose of verproside excreted unchanged in urine at 24 hours was less than 0.10%. Verproside was not detected in the 24 hours feces sample for all three doses studied. These results indicate that verproside is almost completely eliminated by the first pass metabolism due to O-methylation, glucuronidation, sulfation, and intestinal microflora-mediated metabolism. Verproside is metabolized to verproside glucuronides (M1 and M2), verproside sulfates (M3 and M4), O-methylverproside such as picroside II (M5) and isovanilloylcatalpol (M6), 3,4-dihydroxybenzoic acid (M11), 3-methyoxy-4-hydroxybenzoic acid (M15) and 3-hydroxy-4-methoxybenzoic acid (M16), which are further metabolized to their glucuronides and sulfates including M5 glucuronide (M7), M5 sulfate (M9), M6 glucuronide (M8), M6 sulfate (M10), M11 glucuronide (M12), M11 sulfates (M13 and M14), M15 glucuronides (M17 and M18), M15 sulfate (M20), M16 glucuronide (M19), and M16 sulfate (M21). The O-methylation of verproside to picroside II (M5) and isovanilloylcatalpol (M6) followed by glucuronidation and sulfation

were identified as the major metabolic pathway in bile and urine samples.

Picroside II, a major metabolite of verproside, was detected in plasma samples but most plasma concentrations in 12.5 and 25 mg/kg YPL-001 treated groups were below the lower limit of quantification (LLOQ, 2.5 ng/mL) compared to 50 mg/kg YPL-001 treated group. The picroside II-to-verproside AUC ratios in the 50 mg/kg YPL-001 treated group were 13.9-65.1%, suggesting that picroside II may be one of the major YPL-001 metabolites. Plasma concentrations of isovanilloylcatalpol, a metabolite of verproside and isomer of picroside II, were below LLOQ (2.5 ng/mL) after oral administration of all three YPL-001doses tested.

Verproside, catalposide, and picroside II were not considerably bound to human plasma proteins; the binding values were 36.3-55.0% at verproside concentrations of 0.1, 1.0, and 10.0 μg/mL, 31.2-49.5% at catalposide concentrations of 0.5, 1, and 10 μg/mL, and 34.0-41.2% at picroside II concentrations of 0.5, 1, and 10 μg/mL.

9.1.1.3 Toxicology

Two single dose toxicity studies with YPL-001 have been completed in rat and dog. In the rat study, polyuria was observed in the 5,000 mg/kg dosing group of each sex between 2-4 hours after YPL-001 administration. Discolored stool was observed dose-dependently in the all dosing groups of each sex at 1-3 days post administration. Soft stool, mucous stool and soiled perineal region were observed at 1 day after administration in the 2,500 and 5,000 mg/kg dosing group of each gender. There were no notable changes of body weight in any study group. There were no notable gross necropsy findings in any of the study groups. Based on the results above, when YLP-001 is administered orally to Sprague-Dawley rats, the approximate lethal dose (ALD) is higher than 5,000 mg/kg. In the dog study, There were no changes with respect to the toxicity of the test article in the clinical signs, body weight change and necropsy findings after a single dose. Vomiting and discoloration of stool was noted. The Maximum Tolerated Dose (MTD) was determined to be 2,000 mg/kg for males and 1,000 mg/kg for females.

Two dose range finding (DRF) studies with YPL-001 have been completed in rat and dog, followed by two pivotal, 4-week, GLP repeated-dose toxicology studies in the same species. In the rat DRF study, YPL-001 induced anemia and hemolysis at 667 mg/kg/d and at higher doses. In addition, enlargement of cecum was observed at 667 mg/kg/d and at higher doses. The NOEL for this study was 74 mg/kg/d in both genders. In the dog DRF study, decreases in red blood cell (RBC) values were present in males at the high dose level (1000 mg/kg/d). In females the TBIL values were elevated at the 1000 mg/kg/d dose levels. Females had enlarged spleens at 125, 250 and 1000 mg/kg dose levels without dose relationship (trend was toward significance). The MTD for this study was 1000 mg/kg/d.

Primary results from the pivotal, 4-week rat study included:

There were no abnormal clinical signs observed in any group during dosing or the recovery periods and no mortality was reported.

Hematology: Compared to controls, there were decreases in values of RBC, hematocrit, and hemoglobin at all dose levels of both genders in a dose-dependent fashion. The

values of hemoglobin distribution width, red cell distribution width (RDW) and reticulocyte at all dose levels of both genders were higher or significantly higher than those of vehicle control.

Clinical Biochemistry: There were significant increases in the values of TBIL at all dose levels of both genders when compared with that of vehicle control. After the recovery period, there were no noticeable changes related to the test article.

Organ Weights: Slight increase in absolute & relative weights of the spleen at 540 mg/kg/d in males and notable increase in absolute & relative weights of the spleen at all dose levels of females were observed. Weights of left and right kidneys in female at 540 mg/kg/d were significantly higher than that of vehicle control. After the recovery period, the absolute weights of the spleen and both kidneys in both genders at 540 mg/kg/d were significantly higher than that of vehicle control.

Necropsy Findings: At necropsy, 6 cases of dark reddish discoloration of spleen were observed at 540 mg/kg/d in both genders, and 1 case of enlargement of cecum was observed at 540 mg/kg/d in female. After the recovery period, one case of dark reddish discoloration of spleen was observed at 540 mg/kg/d in the female. The histopathology examination revealed increased hematopoiesis of spleen at the high dose in both genders.

No Observed Adverse Effect Levels (NOAEL): The NOAEL for this study was 180 mg/kg/d for both genders.

Primary results from the pivotal, 4-week dog study included:

YPL-001 colored stool with/without soft stool or diarrhea was persistently observed in both sexes at 1000 mg/kg/d during the dosing period. It was not observed during the recovery period. No mortality was reported.

Hematology: There were no treatment-related changes.

Clinical Biochemistry: The TBIL increased in a dose-dependent manner in both genders at 111, 333 and 1000 mg/kg/d, and it was not recovered completely after the 2-week recovery period.

Organ Weights: There were no treatment-related changes.

Necropsy Findings: Slight red discoloration of mucous membranes in the stomach or duodenum was observed in female treatment groups but not observed after the 2-week recovery period.

NOAEL: The NOAEL for this study was 1000 mg/kg/d for both genders.

9.1.2 Clinical Experience

To date, 2 studies have been conducted in healthy subjects, a randomized, double-blind, placebo-controlled, sequential single ascending dose (SAD) clinical study (AA98496) and a randomized, double-blind, placebo-controlled, sequential multiple ascending dose (MAD) clinical study (AA98495).

9.1.2.1 SAD study

All 5 cohorts of 8 subjects (6 active and 2 placebo), with one cohort crossing over to assess food effect, were dosed and completed. All dosed levels (i.e., 40, 80, 160, 240, and 320 mg) were well tolerated with no SAEs reported during the conduct of the study. All 9 AEs reported in 7 subjects were mild in severity and the most frequent AE reported, regardless of causality, was headache. Of the 7 AEs experienced by subjects receiving the active drug, the Investigator considered 2 of these to be possibly related (nausea, and vomiting), 2 unlikely related, and 3 unrelated. Of the 2 AEs experienced by subjects receiving placebo, the Investigator considered 1 of these to be possibly related (headache), and 1 unrelated.

Plasma samples were analyzed using a validated bioanalytical method. Verproside concentrations were lower than concentrations observed from the animal PK data. The limit of quantitation (LOQ) was approximately 20% of the C_{max} after a single 160 mg dose and approximately 10% of the C_{max} after a single 320 mg dose. Therefore, the half-life could not be well characterized since only a few PK concentrations were available for the estimation.

Verproside appeared to be rapidly absorbed following oral administration and independent on dose, as suggested by median t_{max} values of approximately 0.5 to 0.67 hours under fasting conditions. Verproside appeared to be cleared rapidly from plasma, with mean $t_{1/2}$ values under 1 hour; plasma verproside concentrations were below the lower limit of quantification (BLQ) for all subjects by 6 hours postdose. Table 1 below summaries the PK parameters of verproside following single-dose administrations of YPL-001 at each dose level:

Table 1 Summary of PK Parameters

Pharmacokinetic Parameters	Dose Level Mean ± SD					
	40 mg (N = 1)[a]	80 mg (N = 6)[b]	160 mg (fasting) (N = 6)[c]	160 mg (fed) (N = 6)[d]	240 mg (N = 6)[e]	320 mg (N = 6)[f]
C_{max} (ng/mL)	1.19	1.14 ± 0.328	2.90 ± 1.76	1.08 ± 0.287	4.78 ± 5.66	4.49 ± 1.44
t_{max} (hr)[g]	0.4969	0.6682 (0.5158, 1.0025)	0.5074 (0.3331, 0.6700)	1.2538 (0.9994, 2.0008)	0.5867 (0.3486, 1.5022)	0.5057 (0.3419, 1.5014)
AUC_{0-t} (ng·hr/mL)	0.7422	0.7520 ± 0.3818	2.5616 ± 1.7947	1.2822 ± 0.3599	5.4567 ± 5.0158	5.3612 ± 0.8664
AUC_{0-inf} (ng·hr/mL)	·	·	3.8048 ± 1.8238	·	8.2199 ± 5.3327	6.2162 ± 0.7776
$t_{1/2}$ (hr)	·	·	0.677 ± 0.263	·	0.919 ± 0.176	0.713 ± 0.100

[a] Individual values are presented for the 40 mg dose level
[b] N=5 for AUC_{0-t}
[c] N=3 for AUC_{0-inf} and $t_{1/2}$,
[d] N=4 for AUC_{0-t}
[e] N=3 for AUC_{0-inf}, and $t_{1/2}$,
[f] N=5 for AUC_{0-inf}, and $t_{1/2}$,
[g] t_{max} is presented as Median (Minimum, Maximum)
· = Value missing or not reportable

9.1.2.2 MAD Study

In total, 2 cohorts of 8 subjects and 1 cohort of 10 subjects received multiple YPL-001 doses of 80, 160, or 240 mg BID. Each cohort was constituted of 2 subjects receiving placebo and the remaining subjects receiving the active drug. All dose levels were well tolerated. There were no deaths or SAEs in this study. One (1) subject was discontinued due to the AE of chest pain. Overall, TEAEs were experienced by 38% of subjects in this study. The Investigator considered 1 AE (chest pain) to be possibly related to study drug and the remaining AEs unlikely or unrelated. There were no treatment-related trends in physical examination, laboratory, vital sign, or ECG assessments in this study.

Verproside appeared to be rapidly absorbed following multiple-dose oral administration, as suggested by median t_{max} values of approximately 0.5 - 0.9 hours and independent of dose. Following a multiple oral doses of YPL-001, verproside appeared to be cleared rapidly from plasma, with mean $t_{½}$ values under 1.6 hours, and plasma verproside concentrations were BLQ for most subjects by 12 hours postdose.

Picroside II appeared to be also rapidly absorbed following single- and multiple-dose oral administration, as suggested by median t_{max} values of approximately 0.6 to 0.9 hours and independent of dose. Following a single oral dose of YPL-001, picroside II appeared to be cleared rapidly from plasma, with mean $t_{1/2}$ values under 1 hour, CL/F values of 14000 – 18500 L/hour, and plasma picroside II concentrations BLQ by 10 - 12 hours postdose. Following multiple oral doses, mean $t_{1/2}$ values were under 2.5 hours, and plasma picroside II concentrations were BLQ for most subjects by 12 hours postdose.

For all 3 dose levels, minimal to modest accumulation of verproside and picroside II was observed following BID administration of YPL-001 for 2 weeks. The mean peak and total exposure of verproside and picroside II in plasma appeared to increase in a dose-dependent manner between 80 and 160 mg of YPL-001, but no increase in plasma bioavailability was observed between 160 and 240 mg dose levels. Table 2 and Table 3 below summaries the PK parameters of verproside and picroside II, respectively, following multiple-dose administrations of YPL-001 at each dose level:

Table 2 Summary of Verproside PK Parameters

Pharmacokinetic Parameters	YPL-001 Dose Level Mean ± SD		
	80 mg	**160 mg**	**240 mg**
AUC_t (pg*hr/mL)	4709 ± 4080 (N=6)	10860 ± 11424 (N=6)	9658 ± 9246 (N=5)
AUC_{0t} (pg*hr/mL)	4596 ± 4127 (N=6)	10770 ± 11489 (N=6)	9566 ± 9298 (N=5)
C_{max_ss} (pg/mL)	2414 ± 1281 (N=6)	6737 ± 7342 (N=6)	5458 ± 4387 (N=5)
t_{max_ss} (hr)*	0.756 (0.252, 2.00) (N=6)	0.759 (0.329, 1.50) (N=6)	0.528 (0.272, 0.751) (N=5)
$t_{½}$ (hr)	1.47 ± 0.425 (N=6)	1.30 ± 0.406 (N=6)	1.57 ± 0.236 (N=5)

* = t_{max_ss} is presented as median (minimum, maximum)

Table 3 Summary of Picroside II PK Parameters

Pharmacokinetic Parameters	YPL-001 Dose Level Mean ± SD		
	80 mg	**160 mg**	**240 mg**
AUC_{τ} (pg*hr/mL)	2556 ± 599 (N=2)†	4287 ± 4369 (N=4)†	1985 ± 1024 (N=5)
AUC_{0t} (pg*hr/mL)	1124 ± 1044 (N=6)	3024 ± 3877 (N=6)	1804 ± 949 (N=5)
C_{max_ss} (pg/mL)	419 ± 240 (N=6)	1116 ± 1391 (N=6)	751 ± 490 (N=5)
t_{max_ss} (hr)*	0.756 (0.252, 2.00) (N=6)	0.759 (0.329, 1.50) (N=6)	0.748 (0.524, 0.751) (N=5)
$t_{½}$ (hr)	2.23 ± 0.254 (N=6)	1.84 ± 0.395 (N=6)	2.08 ± 0.793 (N=5)

* = t_{max_ss} is presented as median (minimum, maximum)
. = Value missing or not reportable

10. RATIONALE

10.1 Purpose of the Study

This study will be the initial exploration of multiple-dose administration of YPL-001 in COPD patients. The assessments of the safety, tolerability, COPD symptoms, PD, and PK of verproside and picroside II following administration of multiple doses of YPL-001 will guide decisions to further develop the drug and support the compound as a useful clinical candidate in the treatment of inflammatory diseases of the respiratory tract such as asthma and COPD and the data generated will support larger studies in patients with inflammatory diseases of the respiratory tract such as asthma and COPD to demonstrate safety and evidence of efficacy and clinical benefit.

10.2 Dose Selection

This will be the first COPD patient study of YPL-001.

YPL-001 appeared well tolerated in a panel of standard animal toxicology studies. In the initial studies in humans, the initial dose of YPL-001 was justified conservatively according to the United States (US) Food and Drug Administration (FDA) guidance document “Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers”.[2]

Accordingly, the single and multiple dose escalation study (AA98496) initiated single doses at the 40 mg and 80 mg level, respectively. Dose escalations up to 320 mg and 240 mg in the SAD and MAD studies, respectively, were reached. All cohorts have been completed and all doses administered were well tolerated in human subjects and no clear pattern of toxicity is apparent.

Based on the review of safety, tolerability, and PK data from Cohorts 1 to 5 of the SAD study (AA98496) and Cohorts 1 to 3 of the MAD study, and the in vivo efficacy data in rat and mouse models, it is predicted that the therapeutic range should be between 1.2 mg/kg and 4.8 mg/kg which is equivalent to 84 mg to 336 mg daily in a 70 kg patient. Therefore, a low YPL-001 dose of 80 mg BID and the high YPL-001 dose of 160 mg BID were selected for this proof-of-concept study.

The total strength (23.75 mg) of identified compounds in YPL-001 as a whole in the 40 mg starting dose administered in the first-time-in-human dose escalation study (AA98496) corresponded to approximately 35% of the dosages that have been used in the traditional medicine setting in China (68.65 mg). In this present proof-of-concept study the total strength (47.50 mg) of identified compounds in the initial starting dose of 80 mg is still lower than the dosages that have been used in the traditional medicine setting in China, as shown in Table 4, corresponding to 70% of the traditional Chinese medicine.

Table 4: Traditional Chinese Medicine Use Versus Proposed Clinical Starting Dose

Identified Compounds in YPL-001	1.40 g (Single Dose) Traditional Chinese Medicine[a] (mg)	2.80 g/day (Divided Dose) Traditional Chinese Medicine[a] (mg)	80 mg (Single Dose) for MAD Study[b] (mg)
Verproside	47.94	95.88	30.64
Veratric acid	2.10	4.20	1.08
Catalpolside	3.77	7.54	4.08
Picroside II	3.43	6.86	3.36
Isovanilloyl catalpol	3.53	7.06	4.72
6-*O*-veratroyl catalpol	7.88	15.76	3.62
Total	68.65	137.30	47.50

[a] Traditional medicine dosage from Chinese Medical Great Dictionary; Zhong Yao Da Ci Dian.
[b] Proposed dosage of YPL-001 in MAD study

11. RISK/BENEFIT

YPL-001 is being developed as a potential oral treatment for long term control of persistent asthma and COPD. YPL-001 belongs most closely with the leukotriene modifier class of drug and has the potential to inhibit the accumulation of neutrophils the increase of several proinflammatory cytokines and chemokines which play a major role in tissue remodeling. The development of a product to improve the treatment of asthma and COPD will be of benefit to the wider community/patients with respiratory disease.

The safety monitoring practices employed by this protocol (i.e., physical examination, vital signs, pulse oximetry, 12-lead ECG, hematology, serum chemistry, urinalysis, AE monitoring, and AE questioning) are deemed adequate to protect the patients' safety and should detect all expected TEAEs. The procedures employed in this study to assess efficacy are primarily non-invasive and present no undue risk to the patient.

The approximate volume of blood planned for collection from each patient over the course of the study (see Section 14.5), presents no undue risk to the patients nor does the possibility of collection (for wasting to ensure clean sample) of additional blood in the event an indwelling cannula is utilized (as a last resort solution when venipuncture becomes difficult for a patient) and the possibility of additional blood collection for recheck of safety labs if deemed necessary by the Investigator.

12. STUDY OBJECTIVES AND ENDPOINTS

12.1 Study Objectives

The primary objective of the study is to assess the safety and tolerability of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients.

The secondary objective of the study is to assess the number and magnitude of daily respiratory symptoms of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients.

The exploratory objectives of the study are to evaluate the following in moderate to severe COPD patients:

1. To assess BAL epithelial brushings for YPL-001 component levels.
2. To compare BAL samples for total cell count (cells/mL) macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; neutrophil, macrophage, lymphocyte, and eosinophil counts as absolute inflammatory cell numbers in YPL-001 groups versus placebo group.
3. To compare BAL samples for TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9 in YPL-001 groups versus placebo group.
4. To compare blood inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes) and concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9 in YPL-001 groups versus placebo group.
5. To compare spirometric functions (FEV_1, FVC, FEV_1/FVC, and IC) in YPL-001 groups versus placebo group.
6. To compare patient reported outcomes (BDI/TDI, CAT) in YPL-001 groups versus placebo group.
7. To assess verproside and picroside II concentration in plasma and BAL and verproside and picroside II PK in plasma following multiple oral doses administration of two YPL-001 dose levels.

12.2 Study Endpoints

The primary endpoint is the number and severity of TEAEs following multiple oral doses of YPL-001 or placebo.

The secondary endpoint is the number of symptom free days and overall symptom burden following multiple oral doses of YPL-001 or placebo, assessed by measuring:

- daily PEF;
- major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation;

- dyspnea (using the Modified Borg Dyspnea Scale); and
- activity (using the DASI).

The exploratory endpoints are:

1. YPL-001 component levels in epithelial brushings;
2. BAL biomarkers following multiple oral doses of YPL-001 or placebo, measuring:
   - total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells
   - total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers
   - concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9.
3. Blood biomarkers following multiple oral doses of YPL-001 or placebo, measuring:
   - inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils, and lymphocytes)
   - concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9.
4. Pulmonary function results (spirometry) following multiple oral doses of YPL-001 or placebo.
5. Quality of life scores using the BDI/TDI, CAT questionnaires.
6. Concentrations and PK of verproside and picroside II in plasma following multiple oral doses of YPL-001.
7. Concentrations of verproside and picroside II in BAL following multiple oral doses of YPL-001.

13. INVESTIGATIONAL PLAN

13.1 Overall Study Design and Plan

This is a Phase 2a, proof-of-concept, multicenter, randomized, double-blind, double-dummy, 3-treatment, parallel study, with low and high YPL-001 doses (80 mg and 160 mg BID) and a placebo control, in moderate to severe COPD patients.

Sixty-nine (69) patients will be enrolled and randomized into 3 treatment groups (23 patients per group) to ensure completing the study with 60 patients. Patients will participate only once. An approximately equal number of current and ex-smokers will be enrolled in the study.

Safety and tolerability will be assessed throughout the study. Assessment of respiratory symptoms and symptom burden in YPL-001 and placebo treatments will be performed daily through patient self-report of PEF, major and minor symptoms of COPD exacerbation, dyspnea, and activity in their e-diary. Spirometry measurement, BAL, and blood samples will be collected for the PD assessment of YPL-001 and placebo treatments. Serial blood samples will also be collected for PK assessment of verproside (the principal active ingredient of YPL-001) and picroside II. Other components of YPL-001 and its metabolites may also be analyzed in plasma.

Following screening, eligible patients will discontinue non permitted respiratory drugs if already receiving them and enter a 14 ± 2 days Run-in Period during which patients will be given albuterol taken on an as required basis and daily tiotropium 18 µg (one capsule inhaled daily in the morning) to be administered at home. On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their daily symptoms throughout the Run-in Period.

Patients will return to the CRU on the morning of Day -1 of the Treatment Period to confirm their eligibility and assess their health conditions. If they still meet all of the inclusion criteria and none of the exclusion criteria, they will undergo Day -1 scheduled study procedures. Patients will return to the CRU the next day (Day 1) to be randomized and receive one of the 3 treatments and undergo all scheduled study procedures. Patients will return on the morning of Days 15, 29, 43, 55, and 56 of the Treatment Period for study drug administration and procedures. Prior to each release from the CRU, patients will receive a properly labeled container with sufficient doses which will be self-administered by patients at home until the next morning visit at the CRU. Patients will continue recording their daily symptoms via the e-diary throughout the Treatment Period. Patients will return the e-diary device on Day 56 to CRU staff.

The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

Patients will be instructed to call the Investigator if breathing worsens or if they need to take more than 8 puffs per day of albuterol for more than 2 consecutive days. If the Investigator determines that the patient is too unstable to continue in the study, he/she will be discontinued. Rescue medication will be used for any patient with an

exacerbation of COPD and will be administered in accordance with the study center standard of care.

Discontinued patients may be replaced at the discretion of the Sponsor.

13.2 Study Conduct

Please see the Study Events Flow Chart for a summary of the schedule of study participation and procedures in Section 6.

13.2.1 Screening

Screening will begin within 14 days of Day 1 (inclusive) of the Run-in Period. Informed consent will be obtained at screening (see Section 16.1.3) and prior to any study procedures being performed. Patients will have to meet all eligibility criteria before being enrolled in the study (see Section 13.3). Patients will be informed of the study restrictions (see Section 13.3.5).

The following will be recorded at screening: medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI, and history of tobacco use (including number of pack-year and cigarette smoked per day).

Screening procedures are listed in Section 6.

13.2.2 Patient Confinement

Patients will be admitted to the CRU on the morning of each scheduled visit at a time designated by the CRU as delineated in the Study Events Flow Chart (Section 6). Patients will remain in the clinic through completion of all scheduled study procedures.

13.2.3 Run-In Period (Days 1 to 14 [± 2 days])

Eligible patients will be admitted to the CRU on the morning of Day 1 of the Run-in Period at a time designated by the CRU. Patients will discontinue all restricted concomitant medications as indicated in Section 13.3.5.1 and undergo the Run-in procedures as listed in Section 6.

During the Run-in Period, patients will self-administer tiotropium (Spiriva® HandiHaler®) daily for 14 ± 2 days before Day 1 of the Treatment Period. Patients will be instructed to inhale 1 capsule of tiotropium (Spiriva® HandiHaler®) every morning. Patients will also receive albuterol for as needed use. Patient will keep this rescue albuterol throughout the Run-in Period.

Prior to release from the CRU, patients will receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. They must return the container (empty or not) at the next schedule visit, which is scheduled after 14 ± 2 days.

Each patient will also be issued and trained on the use of the e-diary to record their self-administered doses, concomitant medications use, and their daily respiratory symptoms. Prior to each morning dose, patients will record at home their daily PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

13.2.4 Treatment Period (Days 1 to 56)

Patients who completed the Run-in Period and still meet all the inclusion criteria and none of the exclusion criteria will be randomized to receive one of the assigned treatments (80 mg or 160 mg YPL-001 BID, or placebo BID) on Day 1 through Day 56 (see Section 13.4.1 and Section 13.4.2).

Safety and tolerability will be monitored throughout the Treatment Period as listed in Section 6. Patients will continue to record their self-administered doses, concomitant medications use, and their daily respiratory symptoms on their e-diary. Prior to each morning dose, patients will record at home their daily PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

BAL samples for YPL-001 concentrations and PD assessments will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

Spirometry and quality of life questionnaires for PD assessments will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

Blood samples for PD and PK assessment will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

13.2.4.1 Meal Schedule

Patients will be required to fast overnight for at least 12 hours before bronchoscopy and BAL collection on Days -1 and 55. On Days 1 and 56, patients will be required to fast overnight for at least 8 hours before and for at least 4 hours after the morning dose. On all other days, patients will be asked to fast for at least 2 hours before and 2 hours after each morning dose. Patients will also be asked to fast for at least 2 hours before and after each evening dose.

Patients will also be required to fast for at least 8 hours before the scheduled serum chemistry tests at the time points delineated in the Study Events Flow Chart (Section 6).

During in-clinic dosing, water (except that administered with dosing) will not be permitted from 1 hour before until 1 hour after each dosing. Water will be allowed as desired at all other times. On all other days, patients will be informed to follow the same restrictions.

On Days 1 and 56, patients will fast from all food and drink except water between meals and snacks. Foods and beverages containing alcohol, xanthines, caffeine, vegetables from the mustard green family, mustard, tea (especially speedwell tea), or grapefruit/Seville oranges will not be served in the CRU. Across all CRUs, menus should be similar in content. The same menu and meal (except for snacks) schedule will be administered uniformly for all patients confined within the same CRU, across all treatment groups. Meals are not required to be completed by patients and all meals and snacks eaten by patients will be recorded on the CRFs.

13.2.4.2 End-of-Treatment or Early Termination (Day 56)

End-of-treatment evaluation will be performed on all patients before leaving the CRU or prior to early termination.

The end-of-treatment procedures are listed in Section 6.

13.2.5 Follow-up Call (14 ± 2 days)

The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

13.2.6 Scheduled End of Study

The end of the study is scheduled after completion of the evaluations in the 3 treatment groups or after dose-limiting clinical safety endpoints have been reached to preclude continuation of the study. The clinical conduct of the study is intended to last approximately 12 to 24 months.

This time period may change in the event that the study is terminated early, additional time is required to review safety, or a decision is made to complete an unscheduled analysis for a group.

13.3 Selection of Study Population

13.3.1 Number of Patients

The study is planned to enroll 69 patients to ensure completion of 60 patients. An approximately equal number of current and ex-smokers will be enrolled. Patients will be divided in 3 treatment groups with 23 patients to receive one of the 3 treatments (i.e., low and high YPL-001 doses [80 mg and 160 mg BID] and a placebo control) as per the randomization schedule. Each treatment group will consist of an approximately equal number of current and ex-smokers.

13.3.2 Inclusion Criteria

Patient candidates must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Adult males and/or females, 40 to 80 years of age (inclusive).
2. History of COPD for at least 12 months prior to screening.
3. Diagnosed with COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines with symptoms compatible with COPD for at least 12 months prior to screening.
4. Classified as moderate to severe COPD based on the current severity classification GOLD Stage 2-3 disease in terms of post-bronchodilator spirometry at screening:
   - Post-bronchodilator FEV_1/FVC ratio of <70%
   - Post-bronchodilator FEV_1 ≥30 % and <80 % of predicted normal values
5. Weigh at least 52 kg for males and 45 kg for females and within the normal range according to accepted normal values of the Body Mass Index (BMI) chart 18.5-32.0 kg/m^2 inclusive.
6. In the judgment of the Investigator, the patient is medically stable with no change in symptoms, medication, or with clinical laboratory results that in the Investigator's opinion are compatible with the diagnosis of either COPD or a complication thereof and are judged acceptable for inclusion with predominantly bronchitic symptoms at screening.
7. Must be on a stable medical regimen for COPD ≥ 30 days prior to screening.
8. In the Investigator's opinion patients should be able to withhold tiotropium 24h prior to Day 1 of the Run-in Period, if already receiving it and prior to each scheduled CRU visit.
9. Must have oxygen saturation on room air > 93%.
10. Hemoglobin must be equal to or above the lower limit of normal at screening and check-in.
11. Current or ex-smoker with a history of >10 pack years. Ten pack years are defined as: 20 cigarettes a day for 10 years; 10 cigarettes a day for 20 years; or 40 cigarettes a day for 5 years (i.e., [number of cigarettes smoked per day × number of years smoked]/20). Patients, who undergo smoking cessation therapy, must be completed 3 months prior to screening visit and smoking status should not change between the patient's screening visit and patient's last study visit.
12. For a female of childbearing potential: either be sexually inactive (abstinent) for 14 days prior to the first dose and throughout the study or be using one of the following acceptable birth control methods:
    a. non-hormone releasing intrauterine device in place for at least 3 months prior to the first dose.
    b. surgical sterilization of the partner (vasectomy for 4 months minimum).

c. physical barrier method (e.g., condom, diaphragm) with spermicide for at least 14 days prior to the first dose and throughout the study.

A female patient who claims to be sexually inactive, but becomes sexually active during the course of the study must agree to use a physical barrier method (e.g., condom, diaphragm) with spermicide from the time of the start of sexual activity through to the completion of the study.

13. For a female of non-childbearing potential: must have undergone one of the following sterilization procedures at least 6 months prior to the first dose:
    a. hysteroscopic sterilization;
    b. bilateral tubal ligation or bilateral salpingectomy;
    c. hysterectomy;
    d. bilateral oophorectomy;

    or be postmenopausal with amenorrhea for at least 1 year prior to the first dose and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status as per Investigator judgment.
14. Non-vasectomized males must agree to be sexually abstinent or to use a condom with spermicide when engaging in sexual activity from the first dose through completion of the end-of-treatment evaluations. Patients will be advised to use a condom with spermicide for 90 days following the last administration of the study drug, and to not donate sperm during this same period of time. In the event that the sexual partner is surgically sterile, use of a condom with spermicide is not necessary. No restrictions are required for vasectomized males provided their vasectomy has been performed 120 days or more prior to study start. Males who have been vasectomized less than 120 days prior to study start must follow the same restrictions as non-vasectomized males.
15. Understands study procedures and provides written informed consent for the trial.
16. Be able to comply with the protocol, such as all the study restrictions, and the assessments therein.

13.3.3 Exclusion Criteria

Patients will be excluded from the study if there is evidence of any of the following criteria at screening or check-in, as appropriate.

1. History of life-threatening COPD including respiratory arrest, intensive care unit admission and/or requiring intubation.
2. History of more than 2 hospitalizations for COPD within 12 months prior to screening.
3. Presentation of an acute exacerbation of COPD that will be associated with increase sputum volume or change in sputum color within 4 weeks before Day 1 of the Run-in Period.
4. Evidence of cor pulmonale, or clinically significant pulmonary hypertension.
5. Continuous use of more than 2L/day of oxygen.

6. History or presence of other respiratory disorders, such as asthma, α-1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis or other chronic pulmonary diseases.
7. A chest X-ray at screening (or within 3 months prior to screening) showing abnormalities, which in the opinion of the Investigator are clinically significant and unrelated to COPD.
8. A history of chronic disease including, but not limited to, unstable or uncontrolled hypertension (or been diagnosed with hypertension in the 6 months before screening), sleep apnea, cardiovascular, endocrine, neurological, hepatic, gastrointestinal, renal, hematological, urological, immunological or ophthalmic diseases that the Investigator believes are clinically significant e.g., unstable and could impact patient safety by participation in the study.
9. History or presence of:
    - significant cardiac arrhythmia;
    - prostatic hyperplasia;
    - bladder-neck obstruction;
    - urinary retention;
    - narrow-angle glaucoma.
10. Evidence of clinically relevant abnormal baseline hematology, serum chemistry, or urinalysis. Patients with an AST > 2 x ULN, ALT > 2 x ULN, bilirubin > 2 x ULN or creatinine > 2 x ULN (confirmation of results may be done once).
11. Evidence of hepatic impairment with a Child-Pugh class A score or higher.
12. Lung resection or lung reduction surgery within 12 months.
13. Positive urine drug/alcohol testing at screening or at each CRU visit.
14. Positive testing for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C antibodies (HCV).
15. History or presence of alcoholism or drug abuse within the 2 years prior to Day 1 of the Treatment Period.
16. Hypersensitivity or idiosyncratic reaction to compounds related to YPL-001, including Speedwell tea and herbal remedies.
17. Requires one (or more) routine therapies for COPD during the indicated restricted time period as listed in Section 13.3.5.1.1.
18. Use of any drugs or substances known to be significant inhibitors (strong or moderate) of UDP-glucuronosyltransferase (UGT) and/or sulfotransferases (SULT), within 12 hours prior to Day 1 of the Run-in Period (refer to Appendix 1 and Appendix 2).
19. Blood donation or significant blood loss within 56 days prior to Day 1 of the Treatment Period.

20. Plasma donation within 7 days prior to Day 1 of the Treatment Period.
21. Participation in another clinical trial within 30 days prior to Day 1 of the Run-in Period.
22. Females who are pregnant or lactating.
23. Surgery within the past 3 months prior to Day 1 of the Treatment Period determined by the Investigator to be clinically relevant.
24. Active or history of any disease or condition that would, in the opinion of the Investigator and/or medical monitor, place the patient at an unacceptable risk to participate in this study.

13.3.4 Removal of Patients from the Study

Patient participation in this trial may be discontinued for any of the following reasons:

1. Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol.
2. Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient.
3. The patient interrupts trial study drug administration for more than 7 consecutive days of dosing or missed a total of 17 doses (15%) throughout the Treatment Period.
4. Patient's decision to withdraw.
5. Requirement for prohibited concomitant medication.
6. Patient failure to comply with protocol requirements or study related procedures.
7. Termination of the study by the Investigator, Sponsor, FDA, Celerion, or other regulatory authorities.

The clinical report will include reason(s) for patient withdrawals as well as details relevant to the patient withdrawal. If a patient is withdrawn from the trial prior to study completion, the patient will undergo all procedures scheduled for study completion (end-of-treatment evaluations) as the situation allows (see Section 13.2.5). Any patient withdrawn due to an AE (whether serious or non-serious) or clinically significant abnormal laboratory test values will be evaluated by the Investigator and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

Patients withdrawn may be replaced at the Sponsor's discretion.

13.3.5 Study Restrictions

13.3.5.1 Concomitant Therapy

All medications taken during the 30 days prior to the first dose will be recorded and reviewed by the Investigator.

Any medication taken by patients during the course of the study will be recorded. Concomitant medication will be coded using the most current WHO drug dictionary available at Celerion (e.g., 01-MAR-2014 or later). If drug therapy other than that specified by the protocol is taken, a joint decision will be made by the Investigator and Sponsor to continue or discontinue the patient.

13.3.5.1.1 Prohibited Therapy

The following medications are not permitted within the time delineated below and during the study (from Day 1 of the Run-in Period to the completion of the end-of-treatment procedures). Intake of these medications during the Run-in Period constitutes a non-eligibility criterion and the patients will not be randomized into the study. If any of these medications are taken during the Treatment Period, the need for this patient to be withdrawn from the study will be carefully evaluated by the Investigator and the Sponsor on the basis of the potential impact on efficacy or safety evaluation and in the patient's best interest:

1. Any medications administered for the treatment of worsening of COPD within 4 weeks prior to Day 1 of the Run-in Period:
   - nebulized, inhaled, oral, IV, IM corticosteroids;
   - oral or parenteral β2 agonists;
   - Antibiotics.
2. Inhaled corticosteroids (ICS), LABA, and/or inhaled ICS/LABA fixed combinations within 12 hours prior to Day 1 of the Run-in Period;
3. Inhaled long acting anticholinergic agents other than tiotropium within 2 weeks prior to Day 1 of the Run-in Period;
4. Inhaled short-acting β2-agonists (SABA) other than albuterol (e.g., terbutaline, fenoterol) within 12 hours prior to Day 1 of the Run-in Period;
5. Inhaled short-acting anticholinergic agents (SAMA) (e.g., ipratropium) within 12 hours prior to Day 1 of the Run-in Period;
6. PDE inhibitors (including roflumilast) within 2 weeks prior to Day 1 of the Run-in Period.
7. Leukotriene modifiers and xanthines derivatives within 2 weeks prior to Day 1 of the Run-in Period.
8. Drugs or substances known to be significant inhibitors (strong or moderate) of UGT and/or SULT, within 12 hours prior to Day 1 of the Run-in Period and through collection of the final PK sample.
9. Acetaminophen will be prohibited 24 hours prior to Day 1 of the Treatment Period and through collection of the final PK sample.
10. Vitamin supplements and herbal products (especially Speedwell) will be prohibited 7 days prior Day 1 of the Treatment Period and through collection of the final PK sample.

13.3.5.1.2 Permitted Therapy

Throughout the study Period (from Day 1 of the Run-in Period to the completion of the end-of-treatment procedures) patients will be permitted to take the following medications in addition to the study drugs:

1. Albuterol, as required (except approximately 4 hours before schedule pulmonary function test);
2. Tiotropium (Spiriva® HandiHaler®) 18 µg once a day (except approximately 24 hours before schedule pulmonary function test);
3. Ibuprofen, as required, up to 1200 mg per day for intercurrent illness or AEs. Ibuprofen should not be taken for 2 hours before or after each dosing.
4. In the case of a concomitant disease, appropriate treatment will be permitted if it does not interfere with the study evaluation parameters and does not qualify under the section "Prohibited Therapy" (see Section 13.3.5.1.1)

13.3.5.2 Prohibitions

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/caffeine: 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Alcohol: 48 hours prior to each CRU visit, 48 hours prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts), and mustard: 14 days prior to Day 1 of the Treatment Period through collection of Day 56 last PK sample.
- Fruit Juice: 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Tea (especially Speedwell tea), Coffee and Red Wine: 7 days prior to Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Grapefruit/Seville orange and beer: 14 days prior to Day 1 of the Treatment Period through collection of Day 56 last PK sample.

13.3.5.3 Activity

Patients will remain ambulatory or seated upright for 1 hour following each study medication administration.

Patients will be advised to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

13.4 Treatments

13.4.1 Treatments administered

13.4.1.1 Drug Administration During Run-in Period

Tiotropium (Spiriva® HandiHaler®) will be supplied as 18 µg capsules for inhalation.

Albuterol will be supplied as 100 µg albuterol base (1 actuation = 100 µg albuterol base) for oral inhalation. Albuterol may be administered via a nebulizer or a metered-dose inhaler.

Multiple oral inhalation of tiotropium (Spiriva® HandiHaler®) 18 µg capsule will be administered QD every morning for 14 ± 2 days during the Run-in Period. Albuterol will be administered on an as needed basis.

13.4.1.2 Drug Administration During Treatment Period

YPL-001 will be supplied as 80 mg tablets for oral administration.

Placebo will be supplied as YPL-001 80 mg matching placebo tablets for oral administration.

Treatments A, B, and C are described as follows:

Treatment A: Multiple oral YPL-001 80 mg doses (1 x 80 mg tablet + 1 x 1 YPL-001 80 mg matching placebo tablet) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56.

Treatment B: Multiple oral YPL-001 160 mg doses (2 x 80 mg tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56.

Treatment C: Multiple oral matching placebo (2 x 1 YPL-001 80 mg matching placebo tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56.

Each dose of Treatments A, B and C will be administered with approximately 240 mL of water.

In all treatments, one tiotropium (Spiriva® HandiHaler®) 18 µg capsule will also be administered QD every morning prior to study drugs administration. Albuterol will be administered on an as needed basis.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each patient, as per the randomization scheme.

Prior to release from the CRU on Days 1, 15, 29, 43, and 55 of the Treatment Period, patients will receive a properly labeled container with the appropriate doses which will be self-administered by patients at home. Patients will record their self-administered doses

in their e-diary, and whether the dose was administered with food, and must return the container (empty or not) at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.

Patients will be instructed not to crush, split or chew the study drug.

The exact clock time of dosing will be recorded on on-site dosing days. Patients will be given instructions on recording of dosing times in their e-diary on home-dosing days.

Each dose will be administered under fasting conditions as described in Section 13.2.4.1.

13.4.1.3 Stopping Rules

A decision to stop or suspend the study will be made jointly by the Sponsor and the Investigator following the review of all pertinent safety and tolerability. Together they will make one of the following determinations:

1. To continue with the study as planned.
2. To continue with the study and add additional safety evaluations.
3. To continue with the study by adjusting to a lower dose if 2 patients at any dose level meets any of the following criteria and the patient was determined to have received YPL-001 after unblinding:
   a. Has a drug–related, unexpected SAE.
   b. Experiences drug-related grade ≥ 3 toxicity.
4. The study will be terminated if ≥ 3 patients at any dose level meet any of the following criteria and the patients were determined to have received YPL-001 after unblinding:
   a. Has a drug–related, unexpected SAE.
   b. Experience drug related grade ≥ 3 toxicity.

PK data will not be required for the dose-escalation decision.

When applicable, a written statement fully documenting the reasons for study termination will be provided to the Institutional Review Board (IRB).

13.4.2 Method of Assigning Patients to Treatment Groups

Each patient will be assigned a unique identification number upon screening. Patients who complete the study screening assessments, complete the Run-in Period, and meet all the eligibility criteria will receive the corresponding product, according to a randomization scheme generated at Celerion. Each treatment group will consist of an approximately equal number of current and ex-smokers.

Patients will receive one of the 3 treatments (Treatments A, B, or C) on one occasion.

If replacement patients are used, the replacement patient number will be 100 more than the original (e.g., Patient No. 0101 will replace Patient No. 0001).

13.4.3 Blinding

This is a double-blind, double-dummy, randomized study.

13.4.3.1 Maintenance of Randomization

A computerized randomization scheme will be created by a Celerion unblinded statistician (who is not otherwise involved in the study) and shall be considered blinded (per the following).

The randomization is available only to the clinic pharmacy staff preparing the drug who are not involved in any other aspect of the study including administration of the drug. It will not be made available to the Sponsor, patients, or members of the staff responsible for the monitoring and evaluation of safety assessments.

The bioanalytical department will also be blinded to the randomization scheme.

13.4.3.2 Procedures for Breaking the Blind Prior to Study Completion

One set of the sealed envelopes containing the randomization code will be available to the Investigator at the start of the trial

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the patient.

In the event of a medical emergency, it is requested that the Investigator make every effort to contact the study monitor or designee prior to breaking the blind. If breaking the blind is required because of a medical emergency, the treatment identity would be revealed by the qualified designee, for that patient only. In the event that the emergency is one, in which it appears that the other patients may be at imminent risk, the blind may be broken for all patients dosed at that dose level. The unblinding should be noted in the patient's electronic case report form (eCRF).

In all cases where the code is broken, the Investigator should record the date, reason for code breaking and his/her name for signature on the envelope.

At the end of the study, the envelopes will be reviewed by the Sponsor.

13.4.3.3 Revealing of Randomization

In the absence of a medical emergency, the blinded randomization for this entire trial will not be revealed until the following conditions are fulfilled:

- All data are entered in the database, edits checks are performed, queries closed, CRFs signed by the Investigator, and the database is officially locked.
- All PK/PD samples have been analyzed and quality checked by the responsible analytical associate.

13.4.4 Treatment Compliance

During in-clinic dosing, a qualified designate will be responsible for monitoring the administration of timed oral doses. When appropriate, a mouth check will be performed by the qualified designate to ensure that the patients have swallowed the study medication. Once a patient has finished the water, the qualified designate will use a flashlight and a tongue depressor to check the side of the mouth, the sides of the upper and lower gums and the area under the tongue. Patients' hands will also be verified to ensure that the medication was ingested.

Self-administration by patients at home will be monitored by the CRU via the e-diary and attempted phone calls will be performed to remind patients to take their medication, if they did not record their self-administration on the e-diary.

14. STUDY PROCEDURES

14.1 Safety Assessments

This study primarily assesses the safety and tolerability of YPL-001. Safety will be determined by evaluating physical examinations, vital signs, pulse oximetry, ECGs, clinical laboratory parameters, and AEs.

If deemed necessary, additional safety measurements will be performed at the discretion of the Investigator.

Study procedures should be completed as close to the prescribed/scheduled time as possible. The Quality of Life questionnaire should be performed prior to any other procedures. When the following procedures are scheduled at the same time, they will be performed in the following order:

1. Vital signs
2. ECG
3. Pulmonary function measurement
4. Bronchoscopy and BAL collection

All other procedures can be performed without specific order.

14.1.1 Body Height and Weight

Body height (centimeters) and body weight (kilograms) will be measured as outlined in the Study Events Flow Chart (Section 6).

14.1.2 Physical Examination

All full physical examinations will include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose and throat, respiratory system, cardiovascular system, gastrointestinal system, neurological condition, blood and lymphatic systems, and the musculoskeletal system.

A licensed physician will examine each patient as outlined in the Study Events Flow Chart (Section 6).

Medical history will be recorded at screening.

Physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator.

14.1.3 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate will be measured as outlined in the Study Events Flow Chart (Section 6).

Vital signs may be taken at any other times, if deemed necessary. Blood pressure and heart rate measurements will be performed with patients in a seated position for at least 1 minute, except when they are supine or semi-reclined because of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the Investigator.

When performed prior to the morning dose, blood pressure and heart rate will be measured within 2 hours prior to dosing. When scheduled postdose, vital signs readings will be performed within approximately 10 minutes of the scheduled time point. When performing the bronchoscopy, vital signs (body temperature, respiratory rate, blood pressure, and heart rate) will be monitored continuously until the end of the procedure.

14.1.4 Pulse Oximetry

Oxygen levels, saturation [%], and heart rate will be assessed using a pulse oximeter. All readings will be performed with a pulse oximeter (oxygen levels, saturation [%], and heart rate) as outlined in the Study Events Flow Chart in Section 6.

When performed prior to the morning dose, pulse oximetry monitoring will be measured within 2 hours prior to dosing. Readings may be taken at other times, if deemed necessary by the Investigator. When performing the bronchoscopy, oxygen saturation will be monitored continuously until the end of the procedure.

Any clinically relevant oxygen saturation reading below 93% will be documented as an AE, as per Investigator discretion.

14.1.5 Electrocardiogram Monitoring

When performed prior to the morning dose, ECG will be measured within 2 hours prior to dosing. When performing the bronchoscopy, ECG will be monitored continuously until the end of the procedure.

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6). Patients will be required to lie quietly in a supine position for at least 5 minute prior to ECG measurements. Single 12-lead ECGs may be performed at various unscheduled time points, if deemed necessary by the Investigator.

Single 12-lead ECGs will be interpreted and signed and dated by the Investigator. The ECGs will be classified as normal, having a non-clinically significant abnormality (NCS), or having a clinically significant abnormality (CS). In addition, ECG parameters of ventricular rate, PQ or PR interval, QRS duration, and QT interval (corrected according to Bazett's formula [QTcB] and uncorrected) will be noted on the CRF.

14.1.6 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 6). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator. The clinical laboratory tests include the following:

14.1.6.1 Hematology

- Hemoglobin
- Hematocrit
- RBC count (including a reticulocytes count)
- Platelet count
- Mean Corpuscular Hemoglobin (MCH)
- Mean Corpuscular Volume (MCV)
- Mean Corpuscular Hemoglobin Concentration (MCHC)
- RDW
- White blood cell (WBC) count with differential (including eosinophil, neutrophil, basophil, lymphocytes, and monocytes)

14.1.6.2 Serum Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.

- BUN
- Creatinine*
- Bilirubin (total and direct)
- Uric acid
- Albumin
- Alkaline phosphatase (ALP)
- Creatine kinase (CK)
- Lactate dehydrogenase (LDH)
- Estimated glomerular filtration rate
- Alpha-1 Antitrypsin**
- AST
- ALT
- Amylase
- Lipase
- Glucose (fasting)
- Carbon dioxide (CO_2)/Bicarbonate (HCO_3)
- Sodium
- Potassium
- Chloride

* Creatinine clearance will be calculated using Cockcroft-Gault formula at screening.

** To be performed at screening only.

14.1.6.3 Serology

- HIV
- HBsAg
- HCV

14.1.6.4 Human Chorionic Gonadotropin (Serum Pregnancy Test)

The test will be performed for females only.

14.1.6.5 Follicle-Stimulating Hormone

The test will be performed in postmenopausal females only.

14.1.6.6 Urinalysis

- pH
- Specific gravity
- Protein
- Glucose
- Ketones
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Leukocyte Esterase

If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination will be performed.

14.1.6.7 Urine Drug/Alcohol Screen

- Cannabinoids
- Alcohol
- Cocaine
- Amphetamines
- Barbiturates
- Benzodiazepines
- Opiates

14.1.7 Chest X-Ray

A baseline chest x-ray will be performed at the screening visit. If the patient has had an x-ray within the last 3 months prior to the screening visit, and the CRU has access to the report and images, this can be used as the baseline chest x-ray and does not need to be repeated.

14.1.8 Adverse Events

14.1.8.1 Adverse Event Definition

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.[3]

14.1.8.2 Monitoring

The patients will be instructed to inform the Investigator or clinic staff of any AEs and intercurrent illnesses experienced during the trial. Additionally, a specific inquiry regarding AEs will be conducted prior to each dosing at the CRU, at the end-of treatment (or upon early withdrawal), and at the follow-up phone call. The inquiry will be made in a non-specific manner using open-ended questions so as not to bias the response (e.g., How have you been feeling since your last visit?).

All symptoms will be evaluated by the Investigator.

Any patient who has a clinically significant AE (whether serious or non-serious) or clinically significant abnormal laboratory test value will be evaluated by the Investigator, or other monitoring physician, and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

Treatment of SAEs will be performed by a physician, either at the CRU or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal or unknown (lost to follow-up).

14.1.8.3 Reporting

AEs will be coded using the most current MedDRA® available at Celerion (e.g., 17.0 or higher). The Sponsor will inform the Celerion Global Project Manager which version is to be used prior to initiation of the study.

The Investigator will review each event and assess its relationship to drug treatment (unrelated, unlikely, possible, probable, definite). The severity of each sign or symptom reported will be graded based on the NIH NCI CTCAE toxicity grading scale 5-point severity scale (Grade 1, 2, 3, 4 and 5) [4] and the date and time of onset, time relationship to drug dosing, duration, and outcome (resolved, improved, unchanged, worse, fatal, or unknown/lost to follow-up) of each event will be noted.

The relationship of each AE will be assessed using the following definitions:

Unrelated	▪ Event occurring before dosing. ▪ Event or intercurrent illness due wholly to factors other than drug treatment.
Unlikely	▪ Poor temporal relationship with drug treatment. ▪ Event easily explained by patient's clinical state or other factors.
Possible	▪ Reasonable temporal relationship with drug treatment. ▪ Event could be explained by patient's clinical state or other factors.
Probable	▪ Reasonable temporal relationship with drug treatment. ▪ Likely to be known reaction to agent or chemical group, or predicted by known pharmacology. ▪ Event cannot easily be explained by patient's clinical state or other factors.
Definite	▪ Distinct temporal relationship with drug treatment. ▪ Known reaction to agent or chemical group, or predicted by known pharmacology. ▪ Event cannot be explained by patient's clinical state or other factors.

The following definitions for rating severity will be used:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**. Note**:** An experience may be severe but may not be serious, e.g., severe headache).
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

14.1.8.4 Serious Adverse Events

If any AEs are serious, as defined by the Food and Drug Administration (FDA) Code of Federal Regulations (CFR), Chapter 21, special procedures will be followed. All SAEs will be reported to the Sponsor via fax or e-mail within one working day of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012[3]. The institutional review board (IRB) will be notified of the Alert Reports as per FDA regulations.

If an SAE occurs to a patient on this study, the Sponsor's Medical Expert is to be contacted (see Section 3).

A SAE is any AE or suspected adverse reaction that in the view of either the Investigator or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or patient and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the investigator or sponsor, its occurrence places the patient at immediate risk of death. It

does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

14.2 Symptom Assessments

14.2.1 Electronic Diary

On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their self-administered doses and whether the dose was administered with food, concomitant medications and daily respiratory symptoms throughout the Run-in and Treatment Periods. Patients will return the e-diary device on Day 56 to CRU staff.

Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

14.2.2 Peak Expiratory Flow

PEF assessments will be made daily prior to each dose from Day 1 of the Run-in Period to Day 56 of the Treatment Period. Three measurements will be made at each time point using a hand held PEF meter. Readings not performed in the CRU will be recorded in the patient e-diary. All PEF assessments should be performed before administration of a bronchodilator where possible.

14.2.3 Symptoms of Chronic Obstructive Pulmonary Disease Exacerbation

Patient will be asked to record the major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation via the e-diary before each dosing.

14.2.4 Dyspnea (Modified Borg Dyspnea Scale)

Severity level of patient's dyspnea will be assessed via the modified Borg dyspnea scale programmed within the e-diary. The modified Borg dyspnea scale is a self-administered categorical scale with a score from 0 to 10, where 0 (as a measure of dyspnea) corresponds to the sensation of normal breathing (absence of dyspnea) and 10 corresponds to the patient's maximum possible sensation of dyspnea.

14.2.5 Activity (Duke Activity Status Index)

Patient's functional capacity and activity status will be assessed via the DASI programmed within the e-diary. DASI is a self-administered 12-item questionnaire that assesses daily activities such as personal care, ambulation, household tasks, sexual function and recreation with respective metabolic costs. Each item has a specific weight

based on the metabolic cost. The final score ranges between 0 and 58.2 points. The higher the score, the better the functional capacity.

14.3 Pharmacodynamic Assessments

14.3.1 Pulmonary Function (Spirometry)

Spirometry measures will be taken at the time points delineated in the Study Events Flow Chart (Section 6) using a standard calibrated spirometer to determine the parameters detailed below.

- FEV_1;
- FVC (forced vital capacity);
- FEV_1/FVC;
- IC.

Short acting β2-agonist and anticholinergic bronchodilators (e.g., albuterol, ipratropium bromide) and long acting β2-agonist and anticholinergic bronchodilators (e.g., salmeterol, tiotropium) agents will be withheld approximately 4 and 12 hours, respectively, before each pre-bronchodilator spirometry.

Every effort will be made to perform all assessments for a given patient on the same instrument throughout the study and all sites should be using the same brand and model of spirometer for this study.

At screening, baseline pre-bronchodilator spirometry will be performed (prior to albuterol administration) for a minimum of 3 times and a maximum of 8 times in order to obtain 3 manoeuvers with FEV_1 values within 150 mL of each other, using the manoeuver with the highest value of FEV_1 and FVC as the basis for comparison.

Patients shall receive 4 inhalations of albuterol, (100 µg/inhalation), for a total dose of 400 µg via metered-dose inhaler using a spacer. Within approximately 20 to 30 minutes after albuterol administration, the baseline post-bronchodilator spirometry will be performed.

Assessment of FEV_1 stability will take place:

1. Prior to Day 1 dosing of the Treatment Period (Day -1 measurement): Predose FEV_1 is defined as the time-point prior to Day 1 dosing in the Treatment Period and will be performed pre- and post-bronchodilatator administration. Predose FEV_1 will be compared to the corresponding baseline measurement. If the best FEV_1 measurement at predose on Day -1 of the Treatment Period has declined by greater than 20% from the best FEV_1 at screening, the visit may be rescheduled up to 3 times, at the discretion of the Investigator.

2. Following Day 1 dosing: At all other spirometry time point, measurements will be performed once. If the value shows a difference of greater than 150 mL decline than the best FEV_1 value collected predose on Day -1, up to 3 measures will be performed.

Consideration should be given, if a patient experiences any change in post Day 1 dose FEV_1 from the Day 1 predose FEV_1 value (measured following dosing with albuterol) equal to or greater than 20 % and should alert the Investigator to consider whether individual patients should continue to dose. The pulmonary function manoeuver(s) used to make this assessment must be valid and meet acceptable quality spirometry standards.

The Investigator may also use his or her discretion as to the completion of dosing for any period in which an FEV_1 decline and/or respiratory symptoms occur(s).

14.3.2 Bronchoscopy and Bronchoalveolar Lavage (BAL) Biomarkers

Patients will be asked to refrain from smoking approximately 48 hours before the bronchoscopy procedures and will be fasted for 12 hours before. If required, blood pressure medications can be taken with small sip of water based on preapproval of local Investigator.

14.3.2.1 Bronchoscopy

The bronchoscopy with bronchial brushings will be performed at the time points delineated in the Study Events Flow Chart (Section 6) by a licensed physician experienced in conducting the procedure according to guidelines published on the use of bronchoscopy for research on airway diseases such as COPD.[5,6]

Albuterol will be administered 20 minutes prior to the beginning of the bronchoscopy. An intravenous line will also be established to administer conscious sedation, and to administer emergency medications if the need were to arise. During the procedure, oxygen saturation (S_PO_2), blood pressure, and heart rate and rhythm (continuous electrocardiogram) will be monitored. Oxygen 2-4 L via nasal canula will be administered during bronchoscopy and oxygen saturation will be maintained at ≥95%. Conscious sedation will be achieved with incremental doses of 1–4 mg midazolam and 50-100 µg fentanyl. Local upper and lower airway topical anesthesia will be achieved with 1% or 2% lidocaine. The dose of lidocaine administered during the procedure will not exceed a total of 450 mg. The bronchoscope will usually be inserted preferably through the nares into trachea. The bronchoscope will be wedged into 2 subsegments of the right middle or lower lobe, as deemed appropriate by the Investigator. Emergency treatments for cardiopulmonary arrest and pneumothorax will be immediately available in the bronchoscopy room. The patient will remain in the recovery suite for observation for a minimum of 2 hours after the procedure.

14.3.2.2 Bronchial Brushings

Prior to BAL, a cytology brush is inserted into the bronchoscope channel and brushings are collected twice from each of 4 quadrants of visible subsegments of the right middle or lower lobe, as deemed appropriate by the Investigator, under direct visualization. The cellular material is washed off in saline following each brushing. The brushing is performed a total of 8 times. The liquid is centrifuged and the cell pellet is stored at -70°C.

Samples must be protected from UV light during collection, processing, and storage.

14.3.2.3 Bronchoalveolar Lavage (BAL)

BAL in the right middle or lower lobe, as deemed appropriate by the Investigator, will be performed at the time points delineated in the Study Events Flow Chart (Section 6) by a licensed physician experienced in conducting the procedure. A 180 mL BAL will be performed in each subsegment of the right middle or lower lobe, as deemed appropriate by the Investigator, using 6 x 30 mL aliquots of normal saline warmed to room temperature. BAL fluid will be aspirated following each 30 mL instillation. The lavage material, which averages 25% return in COPD patients, typically yields 1-10 x 10^6 macrophages. The centrifuged cell pellet and supernatant will be kept cooled until processed or stored as indicated in the laboratory manual to be provided as a separate document.

Samples must be protected from UV light during collection, processing, and storage.

14.3.2.4 Biomarkers

BAL samples will be analyzed for:

- YPL-001 component levels in epithelial brushings;
- total cell count (cells/mL) of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells
- total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers
- concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9.

14.3.3 Blood Biomarkers

Blood samples will be collected via direct venipuncture at the time points delineated in the Study Events Flow Chart (Section 6) for PD assessments of biomarkers. Biomarker assessments include:

- inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils, and lymphocytes)
- concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9.

Blood will be drawn into 4.5 mL pre-chilled evacuated tubes containing K_2EDTA and stored in an ice bath until processing.

14.3.4 Quality of Life Questionnaires

14.3.4.1 Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI)

Dyspnea at baseline (Day 1 of the Treatment Period) will be assessed with the BDI. This instrument has 3 domains (functional impairment, magnitude of task and magnitude of effort) with the values added for a combined focal score. Functional impairment determines the impact of breathlessness on the ability to carry out activities; magnitude of task determines the type of task that causes breathlessness, magnitude of effort

establishes the level of effort that results in breathlessness. The BDI scores range from 0 (very severe impairment) to 4 (no impairment) for each domain with the baseline focal score consisting of the sum of each domain (0 to 12).

Dyspnea throughout the study will be performed at the time points delineated in the Study Events Flow Chart (Section 6). The change from baseline is measured by the TDI score which ranges from -3 (major deterioration) to +3 (major improvement) for each domain with the TDI focal score consisting in the sum of each domain (-9 to +9).

The same Investigator or designee will interview specifically the patients during the study.

A copy of the questionnaire to be used will be kept in the study binder.

14.3.4.2 COPD Assessment Test (CAT)

CAT is a short and simple questionnaire of 8 items completed by patients to be performed at the time points delineated in the Study Events Flow Chart (Section 6). Scores for each of the 8 items are summed to give a single, final score ranging from 0 (no impact on daily activities) to 40 (very high impact on daily activity). This is a measure of the overall impact of a patient's condition on their life. Scores for the individual items within the questionnaire will provide insight into the relative influence that the different components of COPD have on its overall impact on a patient's life.[7,8]

A copy of the questionnaire to be used will be kept in the study binder.

14.4 Pharmacokinetic Assessments

The sampling schedule and/or collection intervals delineated in the Study Events Flow Chart (Section 6) may be modified based on the results from previously dosed patients.

14.4.1 Blood Sampling and Processing

Samples must be protected from UV light during collection, processing, and storage.

Samples will be collected via direct venipuncture at the time points delineated in the Study Events Flow Chart (Section 6).

Blood will be drawn into 5 mL pre-chilled evacuated tubes containing K_2EDTA. A manual for blood sampling, collection, processing, and sample shipment will be provided in a separate document.

14.5 Blood Volume for Study Assessments

Table 5: Blood Volume during Study

Sample Type	Number of Time Points	Volume per Time Point*	Sample Volume Over Course of Study
Screening laboratory safety tests (including hematology, serum chemistry, serology), FSH (for postmenopausal female patients only) and serum pregnancy (for female patients only).	1	~ 17 mL	~ 17 mL
On-study serum chemistry and serum pregnancy (for female patients only) when scheduled at the same time	4	~ 8.5 mL	~ 34 mL
Additional on-study serum pregnancy (for female patients only)	2	~ 3.5 mL	~ 7 mL
On-study hematology	4	~ 4 mL	~ 16 mL
Blood samples for PD biomarkers	8	~ 4.5 mL	~ 36 mL
Blood samples for PK of verproside and picroside II	37	~ 5 mL	~ 185 mL
Total Blood Volume for males →			~ 288 mL
Total Blood Volume for females →			~ 295 mL

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

15. DATA ANALYSIS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCPs.

15.1 Statistical Analysis

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a SAP. The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP.

15.1.1 Sample Size Calculation

According to the exploratory nature of this study no formal statistical hypotheses will be tested. However, a sample size of 60 evaluable patients is deemed to be sufficient to assess the safety and tolerability and to provide an indication of the potential effect of YPL-001 on COPD exacerbation symptoms, selected biomarkers and pulmonary function parameters. An additional 9 patients will be enrolled to account for a 15% drop-out rate.

15.1.2 Patients to Analyze

Safety population: the safety population data set will include all available data for patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo. Safety data for all discontinued patients will be included in this set for the time points for which their data are available.

Symptom monitoring population: the symptom monitoring population data set will include all available data for patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo. Symptom monitoring data for all discontinued patients will be included in this set for the time points for which their data are available.

PK population:

- The PK full data set will include all patients receiving at least one dose of YPL-001 and having at least one measurable plasma concentration of verproside and picroside II.
- The PK per-protocol data set will include all patients receiving all scheduled doses of YPL-001 and having sufficient samples collected to determine PK parameters from plasma concentrations of verproside and picroside II on Days 1 and/or 56.

PD population:

- The PD full data set will include all patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo and provide at least 1 post-baseline PD measurement.

- The PD per-protocol data set will include all patients receiving all scheduled doses of the investigational product (i.e., YPL-001) or placebo and having measurable PD data.

PK/PD population: All patients who receive at least one dose of YPL-001 and having any measurable concentration of verproside and picroside II and measurable PD data will be included in the PK/PD relationship assessment, as applicable.

15.1.3 Safety Analysis

The following analyses will be performed. Safety analyses will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data, when appropriate.

Medical History:

Medical history will be listed by patient.

Adverse Events:

AEs will be coded using the most current MedDRA® available at Celerion (e.g., 17.0 or higher) and data will be summarized by SOC and preferred term. The number of TEAEs will be reported. In addition, the number and percent of patients reporting each TEAE will be summarized separately for each treatment.

A by-patient AE data listing, including verbatim term, preferred term, treatment, severity, outcome, and relationship to treatment, will be provided.

Physical Examination:

Changes in physical examinations will be described in the text of the final report and significant findings will be reported as AEs.

Clinical Laboratory Tests, Electrocardiograms, Vital Signs and Pulse Oximetry:

All clinical laboratory tests, 12-lead ECGs, vital signs, and pulse oximetry measurements and their change from baseline, if applicable, will be summarized by treatment and time point of collection.

A shift table describing out-of-normal range shifts will be provided for clinical laboratory results.

A normal-abnormal shift table will be presented for ECGs.

Peak Expiratory Flow:

PEF measurements and its change from baseline, will be summarized by treatment and time point of collection.

Concomitant Medications:

Concomitant medications will be listed by patient and coded using the most current WHO drug dictionary available at Celerion (e.g., 01-MAR-2014 or later).

15.1.4 Symptom Monitoring Analysis

Symptom free days and overall symptom burden will be evaluated and compared across treatment groups. Secondary outcome analysis will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative data and frequency counts will be compiled for classification of qualitative data, when appropriate.

Peak Expiratory Flow and Symptoms of COPD Exacerbation:

PEF measurements and symptoms of COPD exacerbation and their change from baseline, will be summarized by treatment and time point of collection.

Dyspnea and Activity:

The Modified Borg Dyspnea Scale and DASI scores will be listed and presented descriptively.

Additional analysis may be performed if deemed appropriate.

15.1.5 Pharmacodynamic Analysis

15.1.5.1 Biomarkers

When applicable, the following PD biomarkers will be summarized by treatment group using descriptive statistics (arithmetic means, SD, CV, N, minimum, maximum, and median). Figures will be created to display mean and individual level or activity as a function of time, as appropriate:

- Pulmonary biomarker (i.e., Pulmonary Function measurements [Spirometry]): pre- and post-bronchodilator change in activity by time point will be calculated relative to the pre- and post-bronchodilator baseline activity;
- BAL biomarkers (i.e., total cell count [cells/mL] of macrophages, lymphocytes, neutrophils, and eosinophils as a percentage of total cells; total cell count [cells/mL] of neutrophils, macrophages, lymphocytes and eosinophils as absolute inflammatory cell numbers; and concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9): raw and % change from baseline levels; and
- Blood biomarkers (i.e., inflammatory markers [total and differential cell counts as absolute and percentage for neutrophils, monocytes, eosinophils and lymphocytes] and concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9): raw and % change from baseline levels.

PK/PD relationship may be explored graphically using scatter plots and an appropriate regression model.

15.1.5.2 Quality of Life

The quality of life parameters reported from the BDI/TDI and CAT questionnaires will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.

15.1.6 Pharmacokinetic Analysis

15.1.6.1 Pharmacokinetic Parameters

15.1.6.1.1 Plasma

PK parameters will be computed from the individual plasma verproside and picroside II concentrations using a noncompartmental approach. Appropriate validated PK software (e.g., WinNonlin Professional) will be used. PK parameters for other components of YPL-001 and its metabolites may also be computed, as appropriate.

The following PK parameters will be computed following Day 1 morning dose:

AUC_{0-12}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to 12 hours.
AUC_{0-t}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (Ct). This parameter will be reported only if plasma concentrations fall below the lower limit of quantitation before the last time point prior to the evening drug administration on Day 1 for at least one patient. Otherwise, only AUC_{0-12} will be reported.
AUC_{0-inf}	Area under the drug concentration-time curve from time zero to infinity, $AUC_{0-inf} = AUC_{0-t} + Ct/k_{el}$, where k_{el} is the terminal elimination rate constant. †
C_{max}	Maximum observed drug concentration.
t_{max}	Time of the maximum drug concentration (obtained without interpolation).
k_{el}	Apparent terminal elimination rate constant, calculated by linear regression of the terminal linear portion of the log concentration vs. time curve. †
$t_{1/2}$	Apparent elimination half-life, calculated as $\ln(2)/k_{el}$. †
CL/F	Oral clearance [$Dose/AUC_{0-inf}$]. †
V_Z/F	Apparent volume of distribution at the terminal phase, calculated as $Dose/(k_{el} * AUC_{0-inf})$.†

† All k_{el} and related PK parameters (AUC_{0-inf}, $t_{1/2}$, CL/F, and V_z/F) will be reported only if the half-life of verproside or picroside II can be appropriately estimated from a 12-hour sampling period following dosing.

The following PK parameters will be computed following Day 56 morning dose:

AUC_{τ}	The area under the plasma concentration versus time curve over the final dosing interval, as calculated by the log-linear trapezoidal method (e.g., 0-12 hours).
AUC_{0-t}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (C_t).
C_{max_ss}	Maximum observed drug concentration at steady-state.
$C_{min,ss}$:	Minimum observed/measured non-zero concentration at steady-state.
C_{trough}	Concentration at the end of a dosing interval.
C_{avg}	Ratio of AUC_{τ} to the dosing interval, τ.
%Fluc:	Percent fluctuation will be calculated as follows: $$\frac{C_{\max\_ss} - C_{\min\_ss}}{C_{avg}} \; x \; 100$$
Swing:	Percent swing will be calculated as follows: $$\frac{C_{\max\_ss} - C_{\min\_ss}}{C_{\min\_ss}} \; x \; 100$$
t_{max_ss}	Time to reach the maximum drug concentration (obtained without interpolation) at steady-state.
CL_{ss}/F	Total body clearance estimated at steady-state after oral administration, calculated as Dose/AUC_{τ}.
V_{z_ss}/F	Apparent volume of distribution at steady-state, calculated as $(CL_{ss}/F)/k_{el}$.*

* All k_{el} and related PK parameters ($t_{1/2}$ or V_{z_ss}/F) will not be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

If metabolite data are available, metabolite to parent ratios may be calculated for AUC_{0-t}, AUC_{τ}, and C_{max_ss}.

15.1.6.1.2 Bronchoalveolar Lavage

Levels of YPL-001 components in epithelial brushing will be listed.

15.1.6.2 Statistical Methods for Pharmacokinetic Analyses

PK parameters will be summarized by treatment group using descriptive statistics (arithmetic means, SD, CV, N, minimum, maximum, and median). In addition, geometric means will be calculated for AUC_{τ} and C_{max_ss}, as appropriate. Figures will be created to display mean and individual verproside and picroside II concentration-time curves. Additional PK analyses may be performed if deemed appropriate.

No value for k_{el}, $t_{1/2}$, and V_{z_ss}/F, as appropriate, will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

An estimate of the relative systemic exposure of AUC_{τ} and C_{max_ss} will be performed by dose normalized ratio analysis expressing the geometric mean ratio and 90% CI of the geometric mean ratio.

Steady-state will be assessed by visual inspection of predose plasma C_{trough} values on Days 15, 29, 43, and 56 following multiple oral dose administration of YPL-001.

Additional analyses will be performed as deemed necessary upon review of the data.

15.1.7 Assessment of Efficacy

Efficacy will not be assessed in this study.

16. STUDY ADMINISTRATION

16.1 Ethics

16.1.1 Institutional Review Board

This protocol will be reviewed by an IRB and the study will not start until the Board has approved the protocol or a modification thereof. The Board is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The board is ICH compliant.

16.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, GCP, 21 CFR Parts 50, 56, and 312, the ethical princliples set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

16.1.3 Patient Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the patients in non-technical terms. Patients will be required to read, sign and date an informed consent form summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Patients will be given a copy of their informed consent form.

16.2 Termination of the Study

The Sponsor reserves the right to discontinue this study and the Investigator reserves the right to terminate their participation at any time.

16.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion relevant to the quality of this study. Designated personnel of Celerion will be responsible for maintaining quality assurance (QA) and quality control (QC) to ensure that the trial is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and Good Laboratory Practice requirements as well as applicable regulatory requirements.

The Clinical Study Report will be audited by the QA department and the quality assurance audit certificate will be included in the study report.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® to check for missing data, data inconsistencies, data ranges, etc. Corrections are made prior to statistical database lock.

Patient compliance will be monitored throughout the study via procedures such as questioning at check-in to review inclusion and exclusion criteria, urine drug screen at

check-in, mouth check following dosing, and confinement for all conduct procedures with clinical research staff on site at all times.

16.4 Direct Access to Source Data/Documents

The Investigator must maintain, at all times, the primary records (i.e., source documents) of each patient's data. Examples of source documents are laboratory reports, drug inventory, study drug label records, and eCRFs that are used as the source.

Celerion will ensure that the sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6] 5.1.2 & 6.10). In the event that other trial-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

16.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of YPL-001 80 mg tablets, and matching placebo tablets to allow completion of this study. The lot numbers and expiration dates (where available) of the drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the drugs supplied. At the conclusion of the study, any unused drugs (including placebo) will either be retained by the CRU, or returned to the Sponsor, depending on the specific requirements of the regulatory bodies to whom the study report will be submitted. If no supplies remain, this fact will be indicated in the Drug Accountability section of the final report.

16.6 Data Handling and Record Keeping

Celerion standard eCRFs will be used. Each eCRF is reviewed and signed off by the Investigator.

All raw data generated in connection with this study, together with the original copy of the final report, will be retained at each CRU in a designated storage facility, until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

16.7 Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be discussed between Sponsor and the Investigator. All revisions and/or amendments to the protocol in writing must be approved by the Sponsor, the Investigator, and the IRB before implementation.

16.8 Finance and Insurance

Finance and insurance will be addressed in a separate document.

16.9 Publication Policy

All unpublished information given to Celerion by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor's written consent to publish the article.

17. REFERENCES

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[7] Jones PW, et al. Development and First Validation of the COPD Assessment Test. Eur Respir J. 2009;34:648-654.

[8] The COPD Assessment Test healthcare professional user guide: expert guidance on frequently asked questions (issue 3: February 2012). Jones PW, Jenkins C, Bauerle O (on behalf of the CAT Development Steering Group).

18. APPENDIXES

18.1 Appendix 1 - UGT Drug Interaction Table

The following list provides medications that are substrates or inhibitors of UGT. Adapted from Williams JA, et al. Drug-drug interactions for UDP-glucuronosyltransferase substrates: a pharmacokinetic explanation for typically observed low exposure (AUCi/AUC) ratios. Drug Metab Dispos. 2004;32(11):1201-8. Epub 2004 Aug 10.

Substrates	Inhibitors
17-beta-estradiol glucuronide Amitriptyline Carvedilol Clofibric acid Codeine Cyclobenzaprine Diclofenac DMXAA Fenofibrate Flavopiridol Furosemide Gemfibrozil Glipizide Irbesartan Lamotrigine Levothyroxine Metoclopramide Metronidazole Morphine Naloxone Naproxen Olanzapine Oxazepam Paracetamol Propofol Raloxifene Tramadol Valdecoxib Valproic acid Zidovudine	17-beta-estradiol glucuronide Flavonoids (citrus fruit) Silybin (herb supplement milk thistle)

18.2 Appendix 2 - SULT Drug Interaction Table

The following list provides medications that are substrates and inhibitors of sulfotransferase. Adapted from Zhang H, Cui D, Wang B, Han YH, et al. Pharmacokinetic drug interactions involving 17alpha-ethinylestradiol: a new look at an old drug. Clin Pharmacokinet. 2007;46(2):133-57; Coughtrie MW, Johnston LE. Interactions between dietary chemicals and human sulfotransferases-molecular mechanisms and clinical significance. Drug Metab Dispos. 2001;29(4 Pt 2):522-528; King RS, Ghosh AA, and Wu J Inhibition of human phenol and estrogen sulfotransferase by certain non-steroidal anti-inflammatory agents. Curr Drug Metab. 2006;7(7):745–753; Nagai M, et al. Inhibitory effects of herbal extracts on the activity of human sulfotransferase isoform sulfotransferase 1A3 (SULT1A3). Biol Pharm Bull. 2009;32(1):105-109; and Harris, R. M.; Waring, R. H. Sulfotransferase inhibition: potential impact of diet and environmental chemicals on steroid metabolism and drug. Current Drug Metabolism 2008;9(4):269-275.

Substrates	Inhibitors
17-beta-estradiol glucuronide Vitamin C Acetaminophen	17-beta-estradiol glucuronide Vitamin C Brown rice Beer Meclofenamate Nimesulide Salicylic acid Acetylsalicylic acid Naproxen Banaba extract Rafuma extract Grape seed extract Peanut seed coat extract Gingko extract Biloba leaf extract St. John’s wort Gymnema Milk thistle

Celerion Project No.: AA98497

Sponsor Project No.: YPL-001-YJP-130403

IND No.: 114903

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

1. PROTOCOL REVISION HISTORY

DATE/NAME	DESCRIPTION
18-Sep-2014 by Caroline Engel	Final Protocol

2. SPONSOR – SIGNATORIES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

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Signature _____ Date 18/Sep/2014

3. INVESTIGATORS SIGNATURES

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

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10/6/14
Date

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Date

INVESTIGATORS SIGNATURES (*CONTINUED*)

A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate-to-Severe Chronic Obstructive Pulmonary Disease

I agree with the content of this protocol and the confidential nature of the documentation made as part of this study. I also acknowledge that the Sponsor of the study has the right to discontinue the study at any time. I have read the protocol and understand it and will work according to it and according to the principles of Good Clinical Practices, applicable laws and regulations, and the Declaration of Helsinki.

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14 Oct 2014
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4. ADDITIONAL KEY CONTACTS FOR THE STUDY

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5. SYNOPSIS

Compound:	YPL-001
Clinical Indication:	Treatment of inflammatory diseases of the respiratory tract such as asthma and chronic obstructive pulmonary disease (COPD)
Study Type	Phase 2a, proof of concept
Study Objectives	The **primary objective** of the study is to assess the safety and tolerability of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients. The **secondary objective** of the study is to assess the number and magnitude of daily respiratory symptoms of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients. The **exploratory objectives** of the study are to evaluate the following in moderate to severe COPD patients: 1. To assess bronchoalveolar lavage (BAL) epithelial brushings for YPL-001 component levels. 2. To compare BAL samples for total cell count (cells/mL) macrophages, lymphocytes and eosinophils as a percentage of total cells; neutrophil, macrophage, lymphocyte and eosinophil counts as absolute inflammatory cell numbers in YPL-001 groups versus placebo group. 3. To compare BAL samples for tumor necrosis factors alpha (TNF-α), interleukin (IL)-1β, IL-4, IL-5, IL-6, IL-8, IL-13, myeloperoxidase (MPO), neutrophil elastase, monocyte chemotactic protein (MCP)-1, and matrix metalloproteinase (MMP)-9 in YPL-001 groups versus placebo group. 4. To compare blood inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, macrophages, eosinophils and lymphocytes) and concentrations of C-reactive protein (CRP), fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9 in YPL-001 groups versus placebo group. 5. To compare spirometric functions (forced expiratory volume in one second [FEV_1], forced vital capacity [FVC], FEV_1/FVC, and inspiratory capacity [IC]) in YPL-001 groups versus placebo group. 6. To compare patient reported outcomes (Baseline Dyspnea Index [BDI]/Transition Dyspnea Index [TDI], COPD Assessment Test [CAT]) in YPL-001 groups versus placebo group. 7. To assess verproside and picroside II concentration in plasma and BAL and verproside and picroside II pharmacokinetics (PK) in plasma following multiple oral doses administration of two YPL-001 dose levels.

Summary of Study Design	This is a Phase 2a, proof-of-concept, multicenter, randomized, double-blind, double-dummy, 3-treatment, parallel study, with low and high YPL-001 doses (80 mg and 160 mg twice daily [BID]) and a placebo control in moderate to severe COPD patients. Sixty-nine (69) patients will be enrolled and randomized into 3 treatment groups (23 patients per group). Patients will participate only once. Safety and tolerability will be assessed throughout the study. Assessment of respiratory symptoms and symptom burden in YPL-001 and placebo treatments will be performed daily through patient self-report of peak expiratory flow (PEF), major and minor symptoms of COPD exacerbation, dyspnea, and activity in their electronic diary (e-diary). Spirometry measurement, bronchoalveolar lavage (BAL), and blood samples will be collected for the pharmacodynamic (PD) assessment of YPL-001 and placebo treatments. Serial blood samples will also be collected for PK assessment of verproside (the principal active ingredient of YPL-001) and picroside II. Other components of YPL-001 and its metabolites may also be analyzed in plasma. Following screening, eligible patients will discontinue non permitted respiratory drugs if already receiving them and enter a 14 ± 2 days Run-in Period during which patients will be given albuterol taken on an as required basis and daily tiotropium 18 µg (one capsule inhaled daily in the morning) to be administered at home. On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their daily symptoms throughout the Run-in Period. Patients will return to the clinical research unit (CRU) on the morning of Day -1 of the Treatment Period to confirm their eligibility and assess their health conditions. If they still meet all of the inclusion criteria and none of the exclusion criteria, they will undergo Day -1 scheduled study procedures. Patients will return to the CRU the next day (Day 1) to be randomized and receive one of the 3 treatments and undergo all scheduled study procedures. Patients will return on the morning of Days 15, 29, 43, 55, and 56 of the Treatment Period for study drug administration and procedures. Prior to each release from the CRU, patients will receive a properly labeled container with sufficient doses which will be self-administered by patients at home until the next morning visit at the CRU. Patients will continue recording their daily symptoms via the e-diary throughout the Treatment Period. Patients will return the e-diary device on Day 56 to CRU staff. The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any adverse event (AE) has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary. Patients will be instructed to call the Investigator if breathing worsens or if they need to take more than 8 puffs per day of albuterol for more than 2 consecutive days. If the Investigator determines that the patient is too unstable to continue in the study, he/she will be discontinued. Rescue medication will be used for any patient with an exacerbation of COPD and will be administered in accordance with the study center standard of care.

Study Population	Patients will be adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3) with a predominant bronchitic component and a history of frequent (>2/year) COPD exacerbations, between 40 and 80 years of age (inclusive).
Number of Patients	The study is planned to enroll 69 patients to ensure completing the study with 60 patients. Patients will be divided in 3 treatment groups with 23 patients to receive one of the 3 treatments (i.e., low and high YPL-001 doses [80 mg and 160 mg BID] and a placebo control) as per the randomization schedule.
Duration of Participation for Patients	The planned length of participation in the study for each patient is approximately 10 weeks (from Day 1 of the Run-in Period through completion of the follow-up clinical procedures on Day 70 [± 2 day]).
Duration of Study Conduct	The study is planned to take place over approximately 12 to 24 months (from screening of the first patient through completion of all study procedures for the last patient). This time period may change in the event that the study is terminated early, additional time is required to review safety, or a decision is made to complete an unscheduled analysis for a group.
Study Products	YPL-001 will be supplied as 80 mg tablets for oral administration. Placebo will be supplied as YPL-001 80 mg matching placebo tablets for oral administration. An unblinded pharmacist will be responsible for providing YPL-001 or placebo to the blinded study personnel for administration.
Dosage, Dosage Form, Route, and Dose Regimen	Treatments are described as follows: Treatment A: Multiple oral YPL-001 80 mg doses (1 x 80 mg tablet + 1 x 1 YPL-001 80 mg matching placebo tablet) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56. Treatment B: Multiple oral YPL-001 160 mg doses (2 x 80 mg tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56. Treatment C: Multiple oral matching placebo (2 x 1 YPL-001 80 mg matching placebo tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56. In all treatments, one tiotropium (Spiriva® HandiHaler®) 18 µg capsule will also be administered QD every morning prior to study drugs administration. Albuterol will be administered on an as needed basis. Each dose of Treatments A, B and C will be administered orally with approximately 240 mL of water.

Stopping Rules	A decision to stop or suspend the study will be made jointly by the Sponsor and the Investigator following the review of all pertinent safety and tolerability. Together they will make one of the following determinations: 1. To continue with the study as planned. 2. To continue with the study and add additional safety evaluations. 3. To continue with the study by adjusting to a lower dose if 2 patients at any dose level meets any of the following criteria and the patient was determined to have received YPL-001 after unblinding: a. Has a drug–related, unexpected serious adverse event (SAE). b. Experiences drug-related grade ≥ 3 toxicity. 4. The study will be terminated if ≥ 3 patients at any dose level meet any of the following criteria and the patients were determined to have received YPL-001 after unblinding: a. Has a drug–related, unexpected SAE. b. Experience drug related grade ≥ 3 toxicity.
Primary Outcome Measures	Safety and tolerability will be monitored through physical examinations, vital signs, pulse oximetry, ECGs, clinical laboratory tests, and AEs.
Safety and Tolerability Analysis	The following analyses will be performed. Safety analyses will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data, when appropriate. **Medical History:** Medical history will be listed by patient. **Adverse Events:** AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®) available at Celerion (e.g., 17.0 or higher) and data will be summarized by System organ class (SOC) and preferred term. The number of treatment-emergent AEs (TEAEs) will be reported. In addition, the number and percent of patients reporting each TEAE will be summarized separately for each treatment. A by-patient AE data listing, including verbatim term, preferred term, treatment, severity, outcome, and relationship to treatment, will be provided. **Physical Examination:** Changes in physical examinations will be described in the text of the final report and significant findings will be reported as AEs. **Clinical Laboratory Tests, Electrocardiograms, Vital Signs, and Pulse Oximetry Measurements:** All clinical laboratory tests, 12-lead ECGs, vital signs, and pulse oximetry measurements and their change from baseline, if applicable, will be summarized by treatment and time point of collection. A shift table describing out-of-normal range shifts will be provided for clinical laboratory results. A normal-abnormal shift table will be presented for ECGs.

Safety and Tolerability Analysis (continued)	**Concomitant Medications:** Concomitant medications will be listed by patient and coded using the most current World Health Organization (WHO) drug dictionary available at Celerion (e.g., 01-MAR-2014 or later).
Secondary Outcome Measures	PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (Duke Activity Status Index [DASI]) self-reported daily by the patients using an e-diary.
Symptom Monitoring Analysis	Symptom free days and overall symptom burden will be evaluated and compared across treatment groups. Secondary outcome analysis will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative data and frequency counts will be compiled for classification of qualitative data, when appropriate. **Peak Expiratory Flow and Symptoms of COPD Exacerbation:** PEF measurements and symptoms of COPD exacerbation and their change from baseline, will be summarized by treatment and time point of collection. **Dyspnea and Activity:** The Modified Borg Dyspnea Scale and DASI scores will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.
Exploratory Outcome Measures	**Pharmacodynamic Assessments:** <u>Bronchoalveolar Lavage Assessments:</u> BAL samples will be collected at baseline and again at the completion of the study for PD assessments of biomarkers. Biomarker assessments include: 1. epithelial brushings for YPL-001 component levels; 2. total cell count (cells/mL) of macrophages, lymphocytes, and eosinophils as a percentage of total cells 3. total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers 4. concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9. <u>Blood Assessments:</u> Blood samples will be collected at screening, throughout the study, and at the follow-up visit (Day 70 [± 2 days]), for PD assessments of biomarkers. Biomarker assessments include: 1. inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, macrophages, eosinophils and lymphocytes) 2. concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9.

Exploratory Outcome Measures (continued)	Pulmonary Assessment: Pulmonary function measurements (spirometry [FEV_1, FVC, FEV_1/FVC, and IC) will be performed at screening, throughout the study and at the follow-up visit (Day 70 [± 2 days]). Quality of Life Assessments: Patient reported outcomes (e-diary, BDI/TDI, CAT) will be performed at baseline, throughout the study and at the follow-up visit (Day 70 [± 2 days]). **Pharmacokinetic Assessments:** Bronchoalveolar Lavage Assessments: BAL samples will be collected at baseline and again at the completion of the study to determine verproside and picroside II concentrations in BAL. Other components of YPL-001 and its metabolites may also be analyzed. Plasma Assessments: Serial blood samples will be collected prior to the initial dosing and through 12 hours following dosing on Days 1 and 56 to determine verproside and picroside II concentrations in plasma. Predose samples will also be collected in the morning of Days 15, 29, 43 and 56 for C_{trough} determination. Other components of YPL-001 and its metabolites may also be analyzed. The sampling schedule and/or collection intervals may be modified based on the results as the study progress.
Pharmacodynamic Analysis	**Blood, Plasma, and Pulmonary biomarkers:** When applicable, the raw data and % change from baseline or placebo, as appropriate, for PD markers (BAL biomarkers, blood biomarkers, and pulmonary biomarker) will be summarized by time point and treatment using descriptive statistics (arithmetic means, standard deviations [SD], coefficients of variation [CV], sample size [N], minimum, maximum, and median). Figures will be created to display mean and individual level or activity as a function of time. **Quality of Life:** The quality of life parameters will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.
Pharmacokinetic Parameters and Analysis	Noncompartmental PK parameters, including AUC_{0-t}, AUC_{0-inf}, AUC_{τ}, k_{el}, C_{max}, C_{max_ss}, C_{min_ss}, C_{trough}, t_{max}, t_{max_ss}, CL/F, CL_{ss}/F, V_z/F, V_{z_ss}/F, and $t_{1/2}$, as appropriate, will be calculated from plasma concentrations of verproside and picroside II from patients who received YPL-001 only. Additional PK parameters may be calculated if deemed appropriate. Plasma PK parameters may also be calculated for other components of YPL-001 and its metabolites. PK parameters will be summarized by treatment using descriptive statistics. Relative exposure of verproside and picroside II will be assessed between the two YPL-01 dose levels, and steady-state will be assessed by visual inspection in the active treatment groups. Verproside and picroside II concentration in BAL samples from patients who received YPL-001 only will be listed.

6. STUDY EVENTS FLOW CHART

Study Procedures[a]	Screen[b]	Run-in Period		Treatment Period																		
Days →		1	2-14 (±2)	-1	1																	
Hours →					Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12
Administrative Procedures																						
Informed Consent	X																					
Inclusion/Exclusion Criteria	X	X																				
Medical History	X																					
Randomization																						
Safety Evaluations																						
Physical Examination[c]	X			X[d]																		
Height	X																					
Weight	X			X[d]																		
Chest X-ray[e]	X																					
12-Lead Electrocardiogram	X			X[f]																		
Vital Signs[g]	X			X[f]	X						X		X						X			
Pulse Oximetry	X			X[f]																		
Hem, Chem, and UA[h]	X			X[d]																		
Serum Pregnancy Test (♀ only)	X			X[d]																		
Serum FSH (postmenopausal ♀ only)	X																					
Urine Alcohol & Drug Screen	X			X[d]																		
HIV/Hepatitis Screen	X																					
AE Inquiries																						
AE Monitoring										X												
ConMeds Monitoring	X									X												
Symptoms Monitoring																						
Diary Training		X																				
Diary Use[i]										X												
PEF, COPD exacerbation, dyspnea and activity[j]										X												
Study Drug Administration																						
Tiotropium Administration		X	X	X	X																	
Study Drug Administration at CRU[k]						X																X
Pharmacodynamic																						
Pulmonary Function (Spirometry)[l]	X			X[d]																		

Study Procedures[a]	**Screen**[b]	**Run-in Period**		**Treatment Period**																		
Days →		1	2-14 (±2)	-1	1																	
Hours →					Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12
Pharmacodynamic																						
Bronchoscopy and BAL Biomarkers[m]				X																		
Blood Biomarkers	X				X						X											
BDI/TDI & CAT	X			X[d]																		
Pharmacokinetic																						
Blood for Verproside & Picroside II PK					X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[n]
Other Procedures																						
Visit & Return Visits[o]	X	X		X	X																	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.
b. Within 14 days of Day 1 (inclusive) of the Run-in Period.
c. A full physical examination will be performed at screening. Symptom-driven physical examinations will be performed at other scheduled times, and may be performed at other times at the Investigator's discretion.
d. To be performed prior to the bronchoscopy procedures.
e. To be performed at screening or within 3 months (inclusive) of screening.
f. ECGs, vital sign and pulse oximetry will be measured within 2 hours of bronchoscopy procedures. During the bronchoscopy procedures and BAL sample collection, patients will be continuously monitored for ECGs, vital signs (blood pressure, heart rate, respiration rate, and body temperature), and oxygen saturation.
g. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
h. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.
i. Patients will be provided with an e-diary device to record their self-administered doses and whether the dose was administered with food, concomitant medications and daily respiratory symptoms.
j. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).
k. Prior to release from the CRU, patients will receive a properly labeled container with sufficient study drug for their assigned treatment which will be self-administered by patients at home until the next morning visit at the CRU. Patients must return the container (empty or not) at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.
l. Pulmonary function will be performed prior to and 20 to 30 minutes after inhalation of approximately 400 µg albuterol.
m. Bronchoscopy and BAL sample collection will be performed following a 12-hour fast.
n. To be performed prior to dosing.
o. Patients will be admitted to the CRU at the time indicated by the CRU.

STUDY EVENTS FLOW CHART *(CONTINUED)*

Study Procedures[a]	**Treatment Period**											
Days →	2-14	15		16-28	29		30-42	43		44-54	55	
Hours →		AM	PM		AM	PM		AM	PM		AM	PM
Safety Evaluations												
Physical Examination[b]					X[c]						X[d]	
Weight					X[c]						X[d]	
12-Lead Electrocardiogram					X[c]						X[e]	
Vital Signs[f]		X[c]			X[c]			X[c]			X[e]	
Pulse Oximetry											X[e]	
Hem, Chem, and UA[g]					X[c]						X[d]	
Serum Pregnancy Test (♀ only)		X[c]			X[c]			X[c]			X[d]	
Urine Alcohol & Drug Screen		X[c]			X[c]			X[c]			X[d]	
AE Inquiries		X[c]			X[c]			X[c]			X[d]	
AE Monitoring	X											
ConMeds Monitoring	X											
Symptoms Monitoring												
Diary Use[h]	X											
PEF, COPD exacerbation, dyspnea and activity[i]	X											
Study Drug Administration												
Tiotropium Administration	X											
Study Drug Administration at CRU		X			X			X			X	
Study Drug Administration at Home[j]	X		X	X		X	X		X	X		X
Pharmacodynamic												
Pulmonary Function (Spirometry)[k]		X[c]			X[c]			X[c]			X[d]	
Bronchoscopy and BAL Biomarkers[l]											X[c]	
Blood Biomarkers		X[c]			X[c]			X[c]				
BDI/TDI & CAT		X[d]			X[d]			X[d]			X[d]	
Pharmacokinetic												
Blood for Verproside & Picroside II PK		X[c]			X[c]			X[c]				
Other Procedures												
Visit & Return Visits[m]		X			X			X			X	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.
b. Symptom-driven physical examinations will be performed at scheduled times, and may be performed at other times at the Investigator's discretion.
c. To be performed or completed prior to dosing.
d. To be performed or completed prior to bronchoscopy procedures and/or dosing.
e. ECGs, vital sign and pulse oximetry will be measured within 2 hours of bronchoscopy procedures. During the bronchoscopy procedures and BAL sample collection, patients will be continuously monitored for ECGs, vital signs (blood pressure, heart rate, respiration rate, and body temperature), and oxygen saturation.
f. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.
g. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.
h. Patients will be provided with an e-diary device to record their self-administered doses and whether the dose was administered with food, concomitant medications and daily respiratory symptoms.
i. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).
j. Prior to release from the CRU, patients will receive a properly labeled container with sufficient study drug for their assigned treatment which will be self-administered by patients at home until the next morning visit at the CRU. Patients must return the container (empty or not) at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.
k. Pulmonary function will be performed prior to and 20 to 30 minutes after inhalation of approximately 400 µg albuterol.
l. Bronchoscopy and BAL sample collection will be performed following a 12-hour fast.
m. Patients will be admitted to the CRU at the time indicated by the CRU.

STUDY EVENTS FLOW CHART *(CONTINUED)*

Study Procedures[a]	**Treatment Period**																		**EOT or ET**[b]	**FU**[c]
Days →	56																			
Hours →	Predose	0	0.167	0.25	0.5	0.75	1	1.5	2	2.5	3	3.5	4	5	6	8	10	12		
Safety Evaluations																				
Physical Examination[d]																			X	
Weight																				
12-Lead Electrocardiogram																			X	
Vital Signs[e]	X						X		X						X				X	
Pulse Oximetry																				
Hem, Chem, and UA[f]																			X	
Serum Pregnancy Test (females only)																				
Urine Alcohol & Drug Screen	X																			
AE Inquiries	X																		X	
AE Monitoring									X											X
Concomitant Medication Monitoring									X											
Symptoms Monitoring																				
Diary Use[g]	X																			
PEF, COPD exacerbation, dyspnea and activity[h]	X																			
Study Drug Administration																				
Tiotropium Administration	X																			
Study Drug Administration		X																		
Pharmacodynamic																				
Blood Biomarkers	X[i]						X													
BDI/TDI & CAT	X[i]																			
Pharmacokinetic																				
Blood for Verproside Pharmacokinetics	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Other Procedures																				
Return Visits[j]								X											X	

Refer to the footnotes on the next page

a. For details on Procedures, refer to Section 14.

b. To be performed at the end of the Treatment Period on Day 56 or prior to early termination from the study.

c. The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

d. Symptom-driven physical examinations will be performed at scheduled times, and may be performed at other times at the Investigator's discretion.

e. Vital signs include blood pressure, heart rate, respiration rate, and body temperature.

f. Samples for serum chemistry will be obtained following a fast of approximately 8 hours, however, in case of dropouts or rechecks, Patients may not have fasted for 8 hours before the serum chemistry sample is taken.

g. Patients will return the e-diary device on Day 56 to CRU staff.

h. Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

i. To be performed at predose on Day 56 or upon early termination.

j. Patients will be admitted to the CRU at the time indicated by the CRU.

Abbreviations: ♀ = Female, AE = Adverse events, AM = Morning, BAL = bronchoalveolar lavage, BDI/TDI = Baseline Dyspnea Index/Transition Dyspnea Index Test, CAT = COPD Assessment Test, Chem = Serum chemistry, COPD = chronic obstructive pulmonary disease, CRU = Clinical research unit, ConMeds = Concomitant medication monitoring, DASI = Duke Activity Status Index, ECG = Electrocardiogram, e-diary = electronic diary, EOT/ET = End-of-Treatment or early termination, FSH = Follicle-stimulating hormone, Hem = Hematology, HIV = Human immunodeficiency virus, IL= interleukin, PEF = Peak expiratory flow, PK = Pharmacokinetics, PM = Evening, Preg = Serum pregnancy, Screen = Screening, UA = Urinalysis.

7. TABLE OF CONTENTS

8. ABBREVIATIONS

Only those uncommon abbreviations specific to this study are listed. Pharmacokinetic (PK) parameter abbreviations and definitions may be found in Section 15.1.6.1.

AE	Adverse event
AHR	Airway hyper-responsiveness
ALD	Approximate lethal dose
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANOVA	Analysis of variance
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATS	American Thoracic Society
BAL	Bronchoalveolar lavage
BALF	Broncheoalveolar lavage fluid
BDI	Baseline Dyspnea Index
BID	Twice daily
BLQ	Below the lower limit of quantification
BMI	Body mass index
bpm	Beat per minute
BUN	Blood urea nitrogen
°C	Degrees Celsius
CAT	COPD Assessment Test
Chem	Chemistry
CFR	Code of Federal Regulations
CK	Creatine kinase
CNS	Central nervous system
CO_2	Carbon dioxide
Coag	Coagulation
COPD	Chronic obstructive pulmonary disease
CRO	Contract Research Organization
CRP	C-reactive protein
CRU	Clinical research unit

CS	Clinically significant abnormality
CSC	Cigarette smoking condensate
CXCL	Chemokine (C-X-C motif) ligand
CV	Coefficient of variation
DASI	Duke Activity Status Index
dL	Deciliter
DRF	Dose range finding
e-diary	Electronic diary
ECG	Electrocardiogram
eCRF	Electronic case report form
EDTA	Ethylenediaminetetraacetic acid
ERS	European Respiratory Society
F	Female
°F	Degrees Fahrenheit
FDA	Unites States Foods and Drug Administration
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FU	Follow-up
FVC	Forced vital capacity
g	gram
GCP	Good Clinical Practice
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HBsAg	hepatitis B surface antigen
HCO_3	Bicarbonate
HCV	hepatitis C antibodies
HED	Human equivalent dose
Hem	Hematology
HIV	Human immunodeficiency virus
hr	Hour
IC	Inspiratory capacity
ICH	International Conference on Harmonization
ICS	Inhaled corticosteroid

IgE	Immunoglobulin E
IL	Interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
K_2EDTA	Dipotassium ethylenediaminetetraacetic acid
kg	Kilogram
kg/m^2	Kilogram per meter squared
LABA	long acting beta agonist
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantitation
LOQ	Limit of quantitation
LPS	Lipopolysaccharide
LSM	Least-squares means
µg	Microgram
m^2	Square meter
M	Male
MAD	Multiple ascending dose
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCO	Myeloperoxidase
MCP	Monocyte chemotactic protein
MCV	Mean Corpuscular Volume
MedDRA®	Medical Dictionary for Regulatory Activities
mg	Milligram
MIP	Monocyte inhibitory protein
mL	Milliliter
mmHg	Millimetre of mercury
MMP	Matrix metalloproteinase
msec	Millisecond
MTD	Maximum Tolerated Dose
N	Sample size
NCS	Not clinically significant

ng	Nanogram
No.	Number
NOAEL	No observed adverse effect levels
OTC	Over-the-counter
OVA	Ovalbumin
PD	Pharmacodynamic(s)
PEF	Peak expiratory flow
PK	Pharmacokinetic(s)
QA	Quality Assurance
QC	Quality Control
QT	Interval between the Q and T waves on the electrocardiogram tracing
QTcF	Corrected QT interval with Fridericia's formula
RBC	Red blood cell
RDW	Red cell distribution width
Resp	Respiration
ROS	Reactive oxygen species
SABA	Short-acting β2-agonist
SAD	Single ascending dose
SAE	Serious adverse event
SAMA	Short-acting anticholinergic agent
SAP	Statistical analysis plan
SD	Standard deviation
SOC	System organ class
SULT	Sulfotranferase
TBIL	Total bilirubin
TDI	Transition Dyspnea Index
TEAE	Treatment-emergent adverse event
Th	T helper
TNF-α	Tumor necrosis factors alpha
UA	Urinalysis
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal

US	United States
WBC	White blood cell
WHO	World Health Organization

9. INTRODUCTION AND BACKGROUND

This study is being conducted as the third in a series of studies for the clinical development of YPL-001. The trial will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and applicable regulatory requirements. The patient population will be comprised of moderate to severe (GOLD Stage 2-3) COPD patients.

9.1 YPL-001

YPL-001 drug product is an oral dosage form of an herbal extract from the aerial parts of the plant Speedwell (*Pseudolysimachion rotundum* subsp. *Subintegrum*). *Pseudolysimachion* (*Veronica*) is a perennial herb which has been used as a traditional medicine in Korea and China for the treatment of inflammatory diseases of the respiratory tract such as asthma and COPD.

As a botanical drug product, the drug substance is a mixture of chemical species (iridoids [including verproside] and other related compounds) and biological activity is considered to be from the mixture and not from an individual component. It is unknown if the total activity from individual components is additive or synergistic. Five active constituents, classified as iridoids, have been identified in the herbal extract: verproside, picroside II, catalpolside, isovanilloyl catalpol, and 6-*O*-veratroylcatalpol. Recent experimentation has revealed that the principal active ingredient in *Pseudolysimachion* is verproside, a dihydroxylated catalpol derivative.

YPL-001, containing verproside and other active ingredients, is being developed as a potential oral treatment for long term inflammatory diseases of the respiratory tract such as asthma or bronchitic COPD. Current long term control medications include corticosteroids, cromolyn sodium, immunomodulators, long acting beta agonists, (LABAs), methylxanthines, and leukotriene modifiers. YPL-001 belongs most closely with the leukotriene modifier class of drug.

A brief overview of available information regarding YPL-001 follows below. Details can be found in the YPL-001 Investigator's Brochure of March 1, 2013. [1]

9.1.1 Preclinical Trials

9.1.1.1 Pharmacology

Five *in vivo* primary pharmacology studies have been completed.

In ovalbumin-sensitized mice, an animal model for asthma, YPL-001 reduced elevated immunoglobulin E (IgE), IL-4, IL-5, IL-13, airway hyper-responsiveness, and mucus hyper-secretion.

In the lipopolysaccharide (LPS)- and cigarette smoking condensate (CSC)-induced COPD mice model, verproside and roflumilast treatment inhibited the accumulation of neutrophils in Broncheoalveolar lavage fluid (BALF) as well as the increase of several proinflammatory cytokines and chemokines. Neutrophil infiltration induced by LPS and CSC treatments was associated with a significant increase in BALF levels of the chemoattractants, TNF-α, chemokine (C-X-C motif) ligand (CXCL)-1, and monocyte inhibitory protein (MIP)-2. These data also demonstrated that the effect of YPL-001 and verproside involves down-regulation of the influx of neutrophils and production of TNF-α,

CXCL-1, and MIP-2 molecules which play a major role in tissue remodeling.

YPL-001 significantly suppressed the increase of inflammatory cell counts, particularly neutrophils in BALF and also effectively suppressed elevated levels of TNF-α, CXCL-1 and MIP-2 with the reduction in airway inflammatory responses in CSC- and LPS-induced COPD mice.

YPL-001 also effectively suppressed the increased inflammatory cell count, particularly neutrophils in BALF and also significantly inhibited elevated levels of TNF-α, IL-1β and IL-6 with the reduction in reactive oxygen species (ROS) production and elastase activity in cigarette smoke- and LPS-induced COPD mice.

In the LPS- and cigarette smoke-induced COPD rats model, YPL-001 significantly inhibited the increase of inflammatory cell count, particularly neutrophils in BALF and also effectively suppressed elevated levels of TNF-α, IL-1β, IL-6, MIP-2 and CRP.

YPL-001 effectively inhibited development of both T helper (Th)2 and Th1/Th17 type asthma in these murine models. These effects resulted from inhibition of cytokine and chemokine production by infiltrated inflammatory cells and antigen specific T cells in lymph nodes. YPL-001 did not inhibit development of COPD which was induced by *E.coli* extracellular vesicles.

9.1.1.2 Pharmacokinetics

After oral administration of YPL-001 at 12.5, 25, and 50 mg/kg doses (5.225, 10.45, and 20.9 mg/kg as verproside) in rats, verproside was rapidly absorbed; verproside was detected at the first blood sampling time (5 min) and absorbed rapidly, with the t_{max} achieved at 0.46-0.61 hour for all three doses. The post-absorption phase of the mean plasma verproside concentration-time profiles showed a poly-exponential decay.

The area under the plasma concentration-time curve (AUC) and the maximum plasma concentration (C_{max}) of verproside were linearly increased as the oral dose of YPL-001 increased. Alternately, the dose normalized (based on 12.5 mg/kg) AUCs and C_{max} of verproside were comparable among different doses studied. The elimination half-lives ($t_{1/2}$), 2.14 – 3.91 hours, and other PK parameters of verproside for all three doses were also comparable. These findings indicate that the PK parameters of verproside were independent of doses.

The fraction of dose of verproside excreted unchanged in urine at 24 hours was less than 0.10%. Verproside was not detected in the 24 hours feces sample for all three doses studied. These results indicate that verproside is almost completely eliminated by the first pass metabolism due to O-methylation, glucuronidation, sulfation, and intestinal microflora-mediated metabolism. Verproside is metabolized to verproside glucuronides (M1 and M2), verproside sulfates (M3 and M4), O-methylverproside such as picroside II (M5) and isovanilloylcatalpol (M6), 3,4-dihydroxybenzoic acid (M11), 3-methyoxy-4-hydroxybenzoic acid (M15) and 3-hydroxy-4-methoxybenzoic acid (M16), which are further metabolized to their glucuronides and sulfates including M5 glucuronide (M7), M5 sulfate (M9), M6 glucuronide (M8), M6 sulfate (M10), M11 glucuronide (M12), M11 sulfates (M13 and M14), M15 glucuronides (M17 and M18), M15 sulfate (M20), M16 glucuronide (M19), and M16 sulfate (M21). The O-methylation of verproside to picroside II (M5) and isovanilloylcatalpol (M6) followed by glucuronidation and sulfation

were identified as the major metabolic pathway in bile and urine samples.

Picroside II, a major metabolite of verproside, was detected in plasma samples but most plasma concentrations in 12.5 and 25 mg/kg YPL-001 treated groups were below the lower limit of quantification (LLOQ, 2.5 ng/mL) compared to 50 mg/kg YPL-001 treated group. The picroside II-to-verproside AUC ratios in the 50 mg/kg YPL-001 treated group were 13.9-65.1%, suggesting that picroside II may be one of the major YPL-001 metabolites. Plasma concentrations of isovanilloylcatalpol, a metabolite of verproside and isomer of picroside II, were below LLOQ (2.5 ng/mL) after oral administration of all three YPL-001doses tested.

Verproside, catalposide, and picroside II were not considerably bound to human plasma proteins; the binding values were 36.3-55.0% at verproside concentrations of 0.1, 1.0, and 10.0 μg/mL, 31.2-49.5% at catalposide concentrations of 0.5, 1, and 10 μg/mL, and 34.0-41.2% at picroside II concentrations of 0.5, 1, and 10 μg/mL.

9.1.1.3 Toxicology

Two single dose toxicity studies with YPL-001 have been completed in rat and dog. In the rat study, polyuria was observed in the 5,000 mg/kg dosing group of each sex between 2-4 hours after YPL-001 administration. Discolored stool was observed dose-dependently in the all dosing groups of each sex at 1-3 days post administration. Soft stool, mucous stool and soiled perineal region were observed at 1 day after administration in the 2,500 and 5,000 mg/kg dosing group of each gender. There were no notable changes of body weight in any study group. There were no notable gross necropsy findings in any of the study groups. Based on the results above, when YLP-001 is administered orally to Sprague-Dawley rats, the approximate lethal dose (ALD) is higher than 5,000 mg/kg. In the dog study, There were no changes with respect to the toxicity of the test article in the clinical signs, body weight change and necropsy findings after a single dose. Vomiting and discoloration of stool was noted. The Maximum Tolerated Dose (MTD) was determined to be 2,000 mg/kg for males and 1,000 mg/kg for females.

Two dose range finding (DRF) studies with YPL-001 have been completed in rat and dog, followed by two pivotal, 4-week, GLP repeated-dose toxicology studies in the same species. In the rat DRF study, YPL-001 induced anemia and hemolysis at 667 mg/kg/d and at higher doses. In addition, enlargement of cecum was observed at 667 mg/kg/d and at higher doses. The NOEL for this study was 74 mg/kg/d in both genders. In the dog DRF study, decreases in red blood cell (RBC) values were present in males at the high dose level (1000 mg/kg/d). In females the TBIL values were elevated at the 1000 mg/kg/d dose levels. Females had enlarged spleens at 125, 250 and 1000 mg/kg dose levels without dose relationship (trend was toward significance). The MTD for this study was 1000 mg/kg/d.

Primary results from the pivotal, 4-week rat study included:

There were no abnormal clinical signs observed in any group during dosing or the recovery periods and no mortality was reported.

Hematology: Compared to controls, there were decreases in values of RBC, hematocrit, and hemoglobin at all dose levels of both genders in a dose-dependent fashion. The

values of hemoglobin distribution width, red cell distribution width (RDW) and reticulocyte at all dose levels of both genders were higher or significantly higher than those of vehicle control.

Clinical Biochemistry: There were significant increases in the values of TBIL at all dose levels of both genders when compared with that of vehicle control. After the recovery period, there were no noticeable changes related to the test article.

Organ Weights: Slight increase in absolute & relative weights of the spleen at 540 mg/kg/d in males and notable increase in absolute & relative weights of the spleen at all dose levels of females were observed. Weights of left and right kidneys in female at 540 mg/kg/d were significantly higher than that of vehicle control. After the recovery period, the absolute weights of the spleen and both kidneys in both genders at 540 mg/kg/d were significantly higher than that of vehicle control.

Necropsy Findings: At necropsy, 6 cases of dark reddish discoloration of spleen were observed at 540 mg/kg/d in both genders, and 1 case of enlargement of cecum was observed at 540 mg/kg/d in female. After the recovery period, one case of dark reddish discoloration of spleen was observed at 540 mg/kg/d in the female. The histopathology examination revealed increased hematopoiesis of spleen at the high dose in both genders.

No Observed Adverse Effect Levels (NOAEL): The NOAEL for this study was 180 mg/kg/d for both genders.

Primary results from the pivotal, 4-week dog study included:

YPL-001 colored stool with/without soft stool or diarrhea was persistently observed in both sexes at 1000 mg/kg/d during the dosing period. It was not observed during the recovery period. No mortality was reported.

Hematology: There were no treatment-related changes.

Clinical Biochemistry: The TBIL increased in a dose-dependent manner in both genders at 111, 333 and 1000 mg/kg/d, and it was not recovered completely after the 2-week recovery period.

Organ Weights: There were no treatment-related changes.

Necropsy Findings: Slight red discoloration of mucous membranes in the stomach or duodenum was observed in female treatment groups but not observed after the 2-week recovery period.

NOAEL: The NOAEL for this study was 1000 mg/kg/d for both genders.

9.1.2 Clinical Experience

To date, 2 studies have been conducted in healthy subjects, a randomized, double-blind, placebo-controlled, sequential single ascending dose (SAD) clinical study (AA98496) and a randomized, double-blind, placebo-controlled, sequential multiple ascending dose (MAD) clinical study (AA98495).

9.1.2.1 SAD study

All 5 cohorts of 8 subjects (6 active and 2 placebo), with one cohort crossing over to assess food effect, were dosed and completed. All dosed levels (i.e., 40, 80, 160, 240, and 320 mg) were well tolerated with no SAEs reported during the conduct of the study. All 9 AEs reported in 7 subjects were mild in severity and the most frequent AE reported, regardless of causality, was headache. Of the 7 AEs experienced by subjects receiving the active drug, the Investigator considered 2 of these to be possibly related (nausea, and vomiting), 2 unlikely related, and 3 unrelated. Of the 2 AEs experienced by subjects receiving placebo, the Investigator considered 1 of these to be possibly related (headache), and 1 unrelated.

Plasma samples were analyzed using a validated bioanalytical method. Verproside concentrations were lower than concentrations observed from the animal PK data. The limit of quantitation (LOQ) was approximately 20% of the C_{max} after a single 160 mg dose and approximately 10% of the C_{max} after a single 320 mg dose. Therefore, the half-life could not be well characterized since only a few PK concentrations were available for the estimation.

Verproside appeared to be rapidly absorbed following oral administration and independent on dose, as suggested by median t_{max} values of approximately 0.5 to 0.67 hours under fasting conditions. Verproside appeared to be cleared rapidly from plasma, with mean $t_{1/2}$ values under 1 hour; plasma verproside concentrations were below the lower limit of quantification (BLQ) for all subjects by 6 hours postdose. Table 1 below summaries the PK parameters of verproside following single-dose administrations of YPL-001 at each dose level:

Table 1 Summary of PK Parameters

Pharmacokinetic Parameters	Dose Level Mean ± SD					
	40 mg (N = 1)[a]	80 mg (N = 6)[b]	160 mg (fasting) (N = 6)[c]	160 mg (fed) (N = 6)[d]	240 mg (N = 6)[e]	320 mg (N = 6)[f]
C_{max} (ng/mL)	1.19	1.14 ± 0.328	2.90 ± 1.76	1.08 ± 0.287	4.78 ± 5.66	4.49 ± 1.44
t_{max} (hr)[g]	0.4969	0.6682 (0.5158, 1.0025)	0.5074 (0.3331, 0.6700)	1.2538 (0.9994, 2.0008)	0.5867 (0.3486, 1.5022)	0.5057 (0.3419, 1.5014)
AUC_{0-t} (ng·hr/mL)	0.7422	0.7520 ± 0.3818	2.5616 ± 1.7947	1.2822 ± 0.3599	5.4567 ± 5.0158	5.3612 ± 0.8664
AUC_{0-inf} (ng·hr/mL)	·	·	3.8048 ± 1.8238	·	8.2199 ± 5.3327	6.2162 ± 0.7776
$t_{1/2}$ (hr)	·	·	0.677 ± 0.263	·	0.919 ± 0.176	0.713 ± 0.100

[a] Individual values are presented for the 40 mg dose level
[b] N=5 for AUC_{0-t}
[c] N=3 for AUC_{0-inf} and $t_{1/2}$,
[d] N=4 for AUC_{0-t}
[e] N=3 for AUC_{0-inf}, and $t_{1/2}$,
[f] N=5 for AUC_{0-inf}, and $t_{1/2}$,
[g] t_{max} is presented as Median (Minimum, Maximum)
· = Value missing or not reportable

9.1.2.2 MAD Study

In total, 2 cohorts of 8 subjects and 1 cohort of 10 subjects received multiple YPL-001 doses of 80, 160, or 240 mg BID. Each cohort was constituted of 2 subjects receiving placebo and the remaining subjects receiving the active drug. All dose levels were well tolerated. There were no deaths or SAEs in this study. One (1) subject was discontinued due to the AE of chest pain. Overall, TEAEs were experienced by 38% of subjects in this study. The Investigator considered 1 AE (chest pain) to be possibly related to study drug and the remaining AEs unlikely or unrelated. There were no treatment-related trends in physical examination, laboratory, vital sign, or ECG assessments in this study.

Verproside appeared to be rapidly absorbed following multiple-dose oral administration, as suggested by median t_{max} values of approximately 0.5 - 0.9 hours and independent of dose. Following a multiple oral doses of YPL-001, verproside appeared to be cleared rapidly from plasma, with mean $t_{½}$ values under 1.6 hours, and plasma verproside concentrations were BLQ for most subjects by 12 hours postdose.

Picroside II appeared to be also rapidly absorbed following single- and multiple-dose oral administration, as suggested by median t_{max} values of approximately 0.6 to 0.9 hours and independent of dose. Following a single oral dose of YPL-001, picroside II appeared to be cleared rapidly from plasma, with mean $t_{1/2}$ values under 1 hour, CL/F values of 14000 – 18500 L/hour, and plasma picroside II concentrations BLQ by 10 - 12 hours postdose. Following multiple oral doses, mean $t_{1/2}$ values were under 2.5 hours, and plasma picroside II concentrations were BLQ for most subjects by 12 hours postdose.

For all 3 dose levels, minimal to modest accumulation of verproside and picroside II was observed following BID administration of YPL-001 for 2 weeks. The mean peak and total exposure of verproside and picroside II in plasma appeared to increase in a dose-dependent manner between 80 and 160 mg of YPL-001, but no increase in plasma bioavailability was observed between 160 and 240 mg dose levels. Table 2 and Table 3 below summaries the PK parameters of verproside and picroside II, respectively, following multiple-dose administrations of YPL-001 at each dose level:

Table 2 Summary of Verproside PK Parameters

Pharmacokinetic Parameters	YPL-001 Dose Level Mean ± SD		
	80 mg	**160 mg**	**240 mg**
AUC_t (pg*hr/mL)	4709 ± 4080 (N=6)	10860 ± 11424 (N=6)	9658 ± 9246 (N=5)
AUC_{0-t}(pg*hr/mL)	4596 ± 4127 (N=6)	10770 ± 11489 (N=6)	9566 ± 9298 (N=5)
$C_{max\ ss}$ (pg/mL)	2414 ± 1281 (N=6)	6737 ± 7342 (N=6)	5458 ± 4387 (N=5)
t_{max_ss} (hr)*	0.756 (0.252, 2.00) (N=6)	0.759 (0.329, 1.50) (N=6)	0.528 (0.272, 0.751) (N=5)
$t_{½}$ (hr)	1.47 ± 0.425 (N=6)	1.30 ± 0.406 (N=6)	1.57 ± 0.236 (N=5)

* = t_{max_ss} is presented as median (minimum, maximum)

Table 3 Summary of Picroside II PK Parameters

Pharmacokinetic Parameters	YPL-001 Dose Level Mean ± SD		
	80 mg	160 mg	240 mg
AUC_t (pg*hr/mL)	2556 ± 599 (N=2)†	4287 ± 4369 (N=4)†	1985 ± 1024 (N=5)
AUC_{0t} (pg*hr/mL)	1124 ± 1044 (N=6)	3024 ± 3877 (N=6)	1804 ± 949 (N=5)
$C_{max\ ss}$ (pg/mL)	419 ± 240 (N=6)	1116 ± 1391 (N=6)	751 ± 490 (N=5)
$t_{max\ ss}$ (hr)*	0.756 (0.252, 2.00) (N=6)	0.759 (0.329, 1.50) (N=6)	0.748 (0.524, 0.751) (N=5)
$t_{½}$ (hr)	2.23 ± 0.254 (N=6)	1.84 ± 0.395 (N=6)	2.08 ± 0.793 (N=5)

* = t_{max_ss} is presented as median (minimum, maximum)
. = Value missing or not reportable

10. RATIONALE

10.1 Purpose of the Study

This study will be the initial exploration of multiple-dose administration of YPL-001 in COPD patients. The assessments of the safety, tolerability, COPD symptoms, PD, and PK of verproside and picroside II following administration of multiple doses of YPL-001 will guide decisions to further develop the drug and support the compound as a useful clinical candidate in the treatment of inflammatory diseases of the respiratory tract such as asthma and COPD and the data generated will support larger studies in patients with inflammatory diseases of the respiratory tract such as asthma and COPD to demonstrate safety and evidence of efficacy and clinical benefit.

10.2 Dose Selection

This will be the first COPD patient study of YPL-001.

YPL-001 appeared well tolerated in a panel of standard animal toxicology studies. In the initial studies in humans, the initial dose of YPL-001 was justified conservatively according to the United States (US) Food and Drug Administration (FDA) guidance document “Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers”.[2]

Accordingly, the single and multiple dose escalation study (AA98496) initiated single doses at the 40 mg and 80 mg level, respectively. Dose escalations up to 320 mg and 240 mg in the SAD and MAD studies, respectively, were reached. All cohorts have been completed and all doses administered were well tolerated in human subjects and no clear pattern of toxicity is apparent.

Based on the review of safety, tolerability, and PK data from Cohorts 1 to 5 of the SAD study (AA98496) and Cohorts 1 to 3 of the MAD study, and the in vivo efficacy data in rat and mouse models, it is predicted that the therapeutic range should be between 1.2 mg/kg and 4.8 mg/kg which is equivalent to 84 mg to 336 mg daily in a 70 kg patient. Therefore, a low YPL-001 dose of 80 mg BID and the high YPL-001 dose of 160 mg BID were selected for this proof-of-concept study.

The total strength (23.75 mg) of identified compounds in YPL-001 as a whole in the 40 mg starting dose administered in the first-time-in-human dose escalation study (AA98496) corresponded to approximately 35% of the dosages that have been used in the traditional medicine setting in China (68.65 mg). In this present proof-of-concept study the total strength (47.50 mg) of identified compounds in the initial starting dose of 80 mg is still lower than the dosages that have been used in the traditional medicine setting in China, as shown in Table 4, corresponding to 70% of the traditional Chinese medicine.

Table 4: Traditional Chinese Medicine Use Versus Proposed Clinical Starting Dose

Identified Compounds in YPL-001	1.40 g (Single Dose) Traditional Chinese Medicine[a] (mg)	2.80 g/day (Divided Dose) Traditional Chinese Medicine[a] (mg)	80 mg (Single Dose) for MAD Study[b] (mg)
Verproside	47.94	95.88	30.64
Veratric acid	2.10	4.20	1.08
Catalpolside	3.77	7.54	4.08
Picroside II	3.43	6.86	3.36
Isovanilloyl catalpol	3.53	7.06	4.72
6-*O*-veratroyl catalpol	7.88	15.76	3.62
Total	68.65	137.30	47.50

[a] Traditional medicine dosage from Chinese Medical Great Dictionary; Zhong Yao Da Ci Dian.
[b] Proposed dosage of YPL-001 in MAD study

11. RISK/BENEFIT

YPL-001 is being developed as a potential oral treatment for long term control of persistent asthma and COPD. YPL-001 belongs most closely with the leukotriene modifier class of drug and has the potential to inhibit the accumulation of neutrophils the increase of several proinflammatory cytokines and chemokines which play a major role in tissue remodeling. The development of a product to improve the treatment of asthma and COPD will be of benefit to the wider community/patients with respiratory disease.

The safety monitoring practices employed by this protocol (i.e., physical examination, vital signs, pulse oximetry, 12-lead ECG, hematology, serum chemistry, urinalysis, AE monitoring, and AE questioning) are deemed adequate to protect the patients' safety and should detect all expected TEAEs. The procedures employed in this study to assess efficacy are primarily non-invasive and present no undue risk to the patient.

The approximate volume of blood planned for collection from each patient over the course of the study (see Section 14.5), presents no undue risk to the patients nor does the possibility of collection (for wasting to ensure clean sample) of additional blood in the event an indwelling cannula is utilized (as a last resort solution when venipuncture becomes difficult for a patient) and the possibility of additional blood collection for recheck of safety labs if deemed necessary by the Investigator.

12. STUDY OBJECTIVES AND ENDPOINTS

12.1 Study Objectives

The primary objective of the study is to assess the safety and tolerability of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients.

The secondary objective of the study is to assess the number and magnitude of daily respiratory symptoms of two multiple oral YPL-001 dose levels versus placebo in moderate to severe COPD patients.

The exploratory objectives of the study are to evaluate the following in moderate to severe COPD patients:

1. To assess BAL epithelial brushings for YPL-001 component levels.
2. To compare BAL samples for total cell count (cells/mL) macrophages, lymphocytes and eosinophils as a percentage of total cells; neutrophil, macrophage, lymphocyte, and eosinophil counts as absolute inflammatory cell numbers in YPL-001 groups versus placebo group.
3. To compare BAL samples for TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9 in YPL-001 groups versus placebo group.
4. To compare blood inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, macrophages, eosinophils and lymphocytes) and concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9 in YPL-001 groups versus placebo group.
5. To compare spirometric functions (FEV_1, FVC, FEV_1/FVC, and IC) in YPL-001 groups versus placebo group.
6. To compare patient reported outcomes (BDI/TDI, CAT) in YPL-001 groups versus placebo group.
7. To assess verproside and picroside II concentration in plasma and BAL and verproside and picroside II PK in plasma following multiple oral doses administration of two YPL-001 dose levels.

12.2 Study Endpoints

The primary endpoint is the number and severity of TEAEs following multiple oral doses of YPL-001 or placebo.

The secondary endpoint is the number of symptom free days and overall symptom burden following multiple oral doses of YPL-001 or placebo, assessed by measuring:

- daily PEF;
- major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation;

- dyspnea (using the Modified Borg Dyspnea Scale); and
- activity (using the DASI).

The exploratory endpoints are:

1. YPL-001 component levels in epithelial brushings;
2. BAL biomarkers following multiple oral doses of YPL-001 or placebo, measuring:
   - total cell count (cells/mL) of macrophages, lymphocytes, and eosinophils as a percentage of total cells
   - total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers
   - concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9.
3. Blood biomarkers following multiple oral doses of YPL-001 or placebo, measuring:
   - inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, macrophages, eosinophils and lymphocytes)
   - concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9.
4. Pulmonary function results (spirometry) following multiple oral doses of YPL-001 or placebo.
5. Quality of life scores using the BDI/TDI, CAT questionnaires.
6. Concentrations and PK of verproside and picroside II in plasma following multiple oral doses of YPL-001.
7. Concentrations of verproside and picroside II in BAL following multiple oral doses of YPL-001.

13. INVESTIGATIONAL PLAN

13.1 Overall Study Design and Plan

This is a Phase 2a, proof-of-concept, multicenter, randomized, double-blind, double-dummy, 3-treatment, parallel study, with low and high YPL-001 doses (80 mg and 160 mg BID) and a placebo control, in moderate to severe COPD patients.

Sixty-nine (69) patients will be enrolled and randomized into 3 treatment groups (23 patients per group) to ensure completing the study with 60 patients. Patients will participate only once.

Safety and tolerability will be assessed throughout the study. Assessment of respiratory symptoms and symptom burden in YPL-001 and placebo treatments will be performed daily through patient self-report of PEF, major and minor symptoms of COPD exacerbation, dyspnea, and activity in their e-diary. Spirometry measurement, BAL, and blood samples will be collected for the PD assessment of YPL-001 and placebo treatments. Serial blood samples will also be collected for PK assessment of verproside (the principal active ingredient of YPL-001) and picroside II. Other components of YPL-001 and its metabolites may also be analyzed in plasma.

Following screening, eligible patients will discontinue non permitted respiratory drugs if already receiving them and enter a 14 ± 2 days Run-in Period during which patients will be given albuterol taken on an as required basis and daily tiotropium 18 µg (one capsule inhaled daily in the morning) to be administered at home. On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their daily symptoms throughout the Run-in Period.

Patients will return to the CRU on the morning of Day -1 of the Treatment Period to confirm their eligibility and assess their health conditions. If they still meet all of the inclusion criteria and none of the exclusion criteria, they will undergo Day -1 scheduled study procedures. Patients will return to the CRU the next day (Day 1) to be randomized and receive one of the 3 treatments and undergo all scheduled study procedures. Patients will return on the morning of Days 15, 29, 43, 55, and 56 of the Treatment Period for study drug administration and procedures. Prior to each release from the CRU, patients will receive a properly labeled container with sufficient doses which will be self-administered by patients at home until the next morning visit at the CRU. Patients will continue recording their daily symptoms via the e-diary throughout the Treatment Period. Patients will return the e-diary device on Day 56 to CRU staff.

The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

Patients will be instructed to call the Investigator if breathing worsens or if they need to take more than 8 puffs per day of albuterol for more than 2 consecutive days. If the Investigator determines that the patient is too unstable to continue in the study, he/she will be discontinued. Rescue medication will be used for any patient with an exacerbation of COPD and will be administered in accordance with the study center

standard of care.

Discontinued patients may be replaced at the discretion of the Sponsor.

13.2 Study Conduct

Please see the Study Events Flow Chart for a summary of the schedule of study participation and procedures in Section 6.

13.2.1 Screening

Screening will begin within 14 days of Day 1 (inclusive) of the Run-in Period. Informed consent will be obtained at screening (see Section 16.1.3) and prior to any study procedures being performed. Patients will have to meet all eligibility criteria before being enrolled in the study (see Section 13.3). Patients will be informed of the study restrictions (see Section 13.3.5).

The following will be recorded at screening: medical history and demographic data, including name, sex, age, race, ethnicity, body weight (kg), height (cm), BMI, and history of tobacco use (including number of pack-year and cigarette smoked per day).

Screening procedures are listed in Section 6.

13.2.2 Patient Confinement

Patients will be admitted to the CRU on the morning of each scheduled visit at a time designated by the CRU as delineated in the Study Events Flow Chart (Section 6). Patients will remain in the clinic through completion of all scheduled study procedures.

13.2.3 Run-In Period (Days 1 to 14 [± 2 days])

Eligible patients will be admitted to the CRU on the morning of Day 1 of the Run-in Period at a time designated by the CRU. Patients will discontinue all restricted concomitant medications as indicated in Section 13.3.5.1 and undergo the Run-in procedures as listed in Section 6.

During the Run-in Period, patients will self-administer tiotropium (Spiriva® HandiHaler®) daily for 14 ± 2 days before Day 1 of the Treatment Period. Patients will be instructed to inhale 1 capsule of tiotropium (Spiriva® HandiHaler®) every morning. Patients will also receive albuterol for as needed use. Patient will keep this rescue albuterol throughout the Run-in Period.

Prior to release from the CRU, patients will receive a properly labeled container with the appropriate doses of tiotropium and albuterol for home dosing. They must return the container (empty or not) at the next schedule visit, which is scheduled after 14 ± 2 days.

Each patient will also be issued and trained on the use of the e-diary to record their self-administered doses, concomitant medications use, and their daily respiratory symptoms. Prior to each morning dose, patients will record at home their daily PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

13.2.4 Treatment Period (Days 1 to 56)

Patients who completed the Run-in Period and still meet all the inclusion criteria and none of the exclusion criteria will be randomized to receive one of the assigned treatments (80 mg or 160 mg YPL-001 BID, or placebo BID) on Day 1 through Day 56 (see Section 13.4.1 and Section 13.4.2).

Safety and tolerability will be monitored throughout the Treatment Period as listed in Section 6. Patients will continue to record their self-administered doses, concomitant medications use, and their daily respiratory symptoms on their e-diary. Prior to each morning dose, patients will record at home their daily PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

BAL samples for YPL-001 concentrations and PD assessments will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

Spirometry and quality of life questionnaires for PD assessments will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

Blood samples for PD and PK assessment will be collected at the time points delineated in the Study Events Flow Chart (Section 6).

13.2.4.1 Meal Schedule

Patients will be required to fast overnight for at least 12 hours before bronchoscopy and BAL collection on Days -1 and 56. On Days 1 and 56, patients will be required to fast overnight for at least 8 hours before and for at least 4 hours after the morning dose. On all other days, patients will be asked to fast for at least 2 hours before and 2 hours after each morning dose. Patients will also be asked to fast for at least 2 hours before and after each evening dose.

Patients will also be required to fast for at least 8 hours before the scheduled serum chemistry tests at the time points delineated in the Study Events Flow Chart (Section 6).

During in-clinic dosing, water (except that administered with dosing) will not be permitted from 1 hour before until 1 hour after each dosing. Water will be allowed as desired at all other times. On all other days, patients will be informed to follow the same restrictions.

On Days 1 and 56, patients will fast from all food and drink except water between meals and snacks. Foods and beverages containing alcohol, xanthines, caffeine, vegetables from the mustard green family, mustard, tea (especially speedwell tea), or grapefruit/Seville oranges will not be served in the CRU. Across all CRUs, menus should be similar in content. The same menu and meal (except for snacks) schedule will be administered uniformly for all patients confined within the same CRU, across all treatment groups. Meals are not required to be completed by patients and all meals and snacks eaten by patients will be recorded on the CRFs.

13.2.4.2 End-of-Treatment or Early Termination (Day 56)

End-of-treatment evaluation will be performed on all patients before leaving the CRU or prior to early termination.

The end-of-treatment procedures are listed in Section 6.

13.2.5 Follow-up Call (14 ± 2 days)

The CRU will attempt to contact patients using their standard procedures approximately 14 days (± 2 days) after the last study drug administration to determine if any AE has occurred since the last dose of study drug. Patients who terminate the study early will be contacted or asked to return to the CRU for monitoring if the Investigator deems necessary.

13.2.6 Scheduled End of Study

The end of the study is scheduled after completion of the evaluations in the 3 treatment groups or after dose-limiting clinical safety endpoints have been reached to preclude continuation of the study. The clinical conduct of the study is intended to last approximately 12 to 24 months.

This time period may change in the event that the study is terminated early, additional time is required to review safety, or a decision is made to complete an unscheduled analysis for a group.

13.3 Selection of Study Population

13.3.1 Number of Patients

The study is planned to enroll 69 patients to ensure completion of 60 patients. Patients will be divided in 3 treatment groups with 23 patients to receive one of the 3 treatments (i.e., low and high YPL-001 doses [80 mg and 160 mg BID] and a placebo control) as per the randomization schedule.

13.3.2 Inclusion Criteria

Patient candidates must fulfill all of the following inclusion criteria to be eligible for participation in the study:

1. Adult males and/or females, 40 to 80 years of age (inclusive).
2. History of COPD for at least 12 months prior to screening.
3. Diagnosed with COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines with symptoms compatible with COPD for at least 12 months prior to screening.
4. Classified as moderate to severe COPD based on the current severity classification GOLD Stage 2-3 disease in terms of post-bronchodilator spirometry at screening:
   - Post-bronchodilator FEV_1/FVC ratio of <70%
   - Post-bronchodilator FEV_1 ≥30 % and <80 % of predicted normal values
5. Weigh at least 52 kg for males and 45 kg for females and within the normal range according to accepted normal values of the Body Mass Index (BMI) chart 18.5-32.0 kg/m^2 inclusive.
6. In the judgment of the Investigator, the patient is medically stable with no change in

symptoms, medication, or with clinical laboratory results that in the Investigator's opinion are compatible with the diagnosis of either COPD or a complication thereof and are judged acceptable for inclusion with predominantly bronchitic symptoms at screening.

7. Must be on a stable medical regimen for COPD ≥ 30 days prior to screening.
8. In the Investigator's opinion patients should be able to withhold tiotropium 24h prior to Day 1 of the Run-in Period, if already receiving it and prior to each scheduled CRU visit.
9. Must have oxygen saturation on room air > 93%.
10. Hemoglobin must be equal to or above the lower limit of normal at screening and check-in.
11. Current or ex-smoker with a history of >10 pack/years. Ten pack/years are defined as: 20 cigarettes a day for 10 years; 10 cigarettes a day for 20 years; or 40 cigarettes a day for 5 years (i.e., [number of cigarettes smoked per day × number of years smoked]/20). Current smokers with <10 pack/years can be included. Patients, who undergo smoking cessation therapy, must be completed 3 months prior to screening visit and smoking status should not change between the patients screening visit and patients last study visit.
12. For a female of childbearing potential: either be sexually inactive (abstinent) for 14 days prior to the first dose and throughout the study or be using one of the following acceptable birth control methods:
    a. non-hormone releasing intrauterine device in place for at least 3 months prior to the first dose.
    b. surgical sterilization of the partner (vasectomy for 4 months minimum).
    c. physical barrier method (e.g., condom, diaphragm) with spermicide for at least 14 days prior to the first dose and throughout the study.

    A female patient who claims to be sexually inactive, but becomes sexually active during the course of the study must agree to use a physical barrier method (e.g., condom, diaphragm) with spermicide from the time of the start of sexual activity through to the completion of the study.
13. For a female of non-childbearing potential: must have undergone one of the following sterilization procedures at least 6 months prior to the first dose:
    a. hysteroscopic sterilization;
    b. bilateral tubal ligation or bilateral salpingectomy;
    c. hysterectomy;
    d. bilateral oophorectomy;

    or be postmenopausal with amenorrhea for at least 1 year prior to the first dose and follicle-stimulating hormone (FSH) serum levels consistent with postmenopausal status as per Investigator judgment.

14. Non-vasectomized males must agree to be sexually abstinent or to use a condom with spermicide when engaging in sexual activity from the first dose through completion of the end-of-treatment evaluations. Patients will be advised to use a condom with spermicide for 90 days following the last administration of the study drug, and to not donate sperm during this same period of time. In the event that the sexual partner is surgically sterile, use of a condom with spermicide is not necessary. No restrictions are required for vasectomized males provided their vasectomy has been performed 120 days or more prior to study start. Males who have been vasectomized less than 120 days prior to study start must follow the same restrictions as non-vasectomized males.
15. Understands study procedures and provides written informed consent for the trial.
16. Be able to comply with the protocol, such as all the study restrictions, and the assessments therein.

13.3.3 Exclusion Criteria

Patients will be excluded from the study if there is evidence of any of the following criteria at screening or check-in, as appropriate.

1. History of life-threatening COPD including respiratory arrest, intensive care unit admission and/or requiring intubation.
2. History of more than 2 hospitalizations for COPD within 12 months prior to screening.
3. Presentation of an acute exacerbation of COPD that will be associated with increase sputum volume or change in sputum color within 4 weeks before Day 1 of the Run-in Period.
4. Evidence of cor pulmonale, or clinically significant pulmonary hypertension.
5. Continuous use of more than 2L/day of oxygen.
6. History or presence of other respiratory disorders, such as asthma, α-1 antitrypsin deficiency, active tuberculosis, lung cancer, bronchiectasis, sarcoidosis, lung fibrosis or other chronic pulmonary diseases.
7. A chest X-ray at screening (or within 3 months prior to screening) showing abnormalities, which in the opinion of the Investigator are clinically significant and unrelated to COPD.
8. A history of chronic disease including, but not limited to, unstable or uncontrolled hypertension (or been diagnosed with hypertension in the 6 months before screening), sleep apnea, cardiovascular, endocrine, neurological, hepatic, gastrointestinal, renal, hematological, urological, immunological or ophthalmic diseases that the Investigator believes are clinically significant e.g., unstable and could impact patient safety by participation in the study.

9. History or presence of:
    - significant cardiac arrhythmia;
    - prostatic hyperplasia;
    - bladder-neck obstruction;
    - urinary retention;
    - narrow-angle glaucoma.
10. Evidence of clinically relevant abnormal baseline hematology, serum chemistry, or urinalysis. Patients with an AST > 2 x ULN, ALT > 2 x ULN, bilirubin > 2 x ULN or creatinine > 2 x ULN (confirmation of results may be done once).
11. Evidence of hepatic impairment with a Child-Pugh class A score or higher.
12. Lung resection or lung reduction surgery within 12 months.
13. Positive urine drug/alcohol testing at screening or at each CRU visit.
14. Positive testing for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), or hepatitis C antibodies (HCV).
15. History or presence of alcoholism or drug abuse within the 2 years prior to Day 1 of the Treatment Period.
16. Hypersensitivity or idiosyncratic reaction to compounds related to YPL-001, including Speedwell tea and herbal remedies.
17. Requires one (or more) routine therapies for COPD during the indicated restricted time period as listed in Section 13.3.5.1.1.
18. Use of any drugs or substances known to be significant inhibitors (strong or moderate) of UDP-glucuronosyltransferase (UGT) and/or sulfotransferases (SULT), within 12 hours prior to Day 1 of the Run-in Period (refer to Appendix 1 and Appendix 2).
19. Blood donation or significant blood loss within 56 days prior to Day 1 of the Treatment Period.
20. Plasma donation within 7 days prior to Day 1 of the Treatment Period.
21. Participation in another clinical trial within 30 days prior to Day 1 of the Run-in Period.
22. Females who are pregnant or lactating.
23. Surgery within the past 3 months prior to Day 1 of the Treatment Period determined by the Investigator to be clinically relevant.
24. Active or history of any disease or condition that would, in the opinion of the Investigator and/or medical monitor, place the patient at an unacceptable risk to participate in this study.

13.3.4 Removal of Patients from the Study

Patient participation in this trial may be discontinued for any of the following reasons:

1. Occurrence of any medical condition or circumstance that exposes the patient to substantial risk and/or does not allow the patient to adhere to the requirements of the protocol.
2. Any SAE, clinically significant AE, severe laboratory abnormality, intercurrent illness, or other medical condition that indicates to the Investigator that continued participation is not in the best interest of the patient.
3. The patient interrupts trial study drug administration for more than 7 consecutive days of dosing or missed a total of 17 doses (15%) throughout the Treatment Period.
4. Patient's decision to withdraw.
5. Requirement for prohibited concomitant medication.
6. Patient failure to comply with protocol requirements or study related procedures.
7. Termination of the study by the Investigator, Sponsor, FDA, Celerion, or other regulatory authorities.

The clinical report will include reason(s) for patient withdrawals as well as details relevant to the patient withdrawal. If a patient is withdrawn from the trial prior to study completion, the patient will undergo all procedures scheduled for study completion (end-of-treatment evaluations) as the situation allows (see Section 13.2.5). Any patient withdrawn due to an AE (whether serious or non-serious) or clinically significant abnormal laboratory test values will be evaluated by the Investigator and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

Patients withdrawn may be replaced at the Sponsor's discretion.

13.3.5 Study Restrictions

13.3.5.1 Concomitant Therapy

All medications taken during the 30 days prior to the first dose will be recorded and reviewed by the Investigator.

Any medication taken by patients during the course of the study will be recorded. Concomitant medication will be coded using the most current WHO drug dictionary available at Celerion (e.g., 01-MAR-2014 or later). If drug therapy other than that specified by the protocol is taken, a joint decision will be made by the Investigator and Sponsor to continue or discontinue the patient.

13.3.5.1.1 Prohibited Therapy

The following medications are not permitted within the time delineated below and during the study (from Day 1 of the Run-in Period to the completion of the end-of-treatment procedures). Intake of these medications during the Run-in Period constitutes a non-eligibility criterion and the patients will not be randomized into the study. If any of these medications are taken during the Treatment Period, the need for this patient to be

withdrawn from the study will be carefully evaluated by the Investigator and the Sponsor on the basis of the potential impact on efficacy or safety evaluation and in the patient's best interest:

1. Any medications administered for the treatment of worsening of COPD within 4 weeks prior to Day 1 of the Run-in Period:
   - nebulized, inhaled, oral, IV, IM corticosteroids;
   - oral or parenteral β2 agonists;
   - Antibiotics.
2. Inhaled corticosteroids (ICS), LABA, and/or inhaled ICS/LABA fixed combinations within 12 hours prior to Day 1 of the Run-in Period;
3. Inhaled long acting anticholinergic agents other than tiotropium within 2 weeks prior to Day 1 of the Run-in Period;
4. Inhaled short-acting β2-agonists (SABA) other than albuterol (e.g., terbutaline, fenoterol) within 12 hours prior to Day 1 of the Run-in Period;
5. Inhaled short-acting anticholinergic agents (SAMA) (e.g., ipratropium) within 12 hours prior to Day 1 of the Run-in Period;
6. PDE inhibitors (including roflumilast) within 2 weeks prior to Day 1 of the Run-in Period.
7. Leukotriene modifiers and xanthines derivatives within 2 weeks prior to Day 1 of the Run-in Period.
8. Drugs or substances known to be significant inhibitors (strong or moderate) of UGT and/or SULT, within 12 hours prior to Day 1 of the Run-in Period and through collection of the final PK sample.
9. Acetaminophen will be prohibited 24 hours prior to Day 1 of the Treatment Period and through collection of the final PK sample.
10. Vitamin supplements and herbal products (especially Speedwell) will be prohibited 7 days prior Day 1 of the Treatment Period and through collection of the final PK sample.

13.3.5.1.2 Permitted Therapy

Throughout the study Period (from Day 1 of the Run-in Period to the completion of the end-of-treatment procedures) patients will be permitted to take the following medications in addition to the study drugs:

1. Albuterol, as required (except approximately 4 hours before schedule pulmonary function test);
2. Tiotropium (Spiriva® HandiHaler®) 18 µg once a day (except approximately 24 hours before schedule pulmonary function test);
3. Ibuprofen, as required, up to 1200 mg per day for intercurrent illness or AEs. Ibuprofen should not be taken for 2 hours before or after each dosing.
4. In the case of a concomitant disease, appropriate treatment will be permitted if it does not interfere with the study evaluation parameters and does not qualify under the section "Prohibited Therapy" (see Section 13.3.5.1.1)

13.3.5.2 Prohibitions

Consumption of foods and beverages containing the following substances will be prohibited as indicated:

- Xanthines/caffeine: 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Alcohol: 48 hours prior to each CRU visit, 48 hours prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample, and 24 hours before the follow-up visit.
- Vegetables from the mustard green family (e.g., kale, broccoli, watercress, collard greens, kohlrabi, Brussels sprouts), and mustard: 14 days prior to Day 1 of the Treatment Period through collection of Day 56 last PK sample.
- Fruit Juice: 24 hours prior to each CRU visit and prior to dosing on Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Tea (especially Speedwell tea), Coffee and Red Wine: 7 days prior to Days 1 and 56 of the Treatment Period through collection of Days 1 and 56 last PK sample.
- Grapefruit/Seville orange and beer: 14 days prior to Day 1 of the Treatment Period through collection of Day 56 last PK sample.

13.3.5.3 Activity

Patients will remain ambulatory or seated upright for 1 hour following each study medication administration.

Patients will be advised to refrain from strenuous physical activity which could cause muscle aches or injury, including contact sports at any time from screening until completion of the study.

13.4 Treatments

13.4.1 Treatments administered

13.4.1.1 Drug Administration During Run-in Period

Tiotropium (Spiriva® HandiHaler®) will be supplied as 18 µg capsules for inhalation.

Albuterol will be supplied as 100 µg albuterol base (1 actuation = 100 µg albuterol base) for oral inhalation. Albuterol may be administered via a nebulizer or a metered-dose inhaler.

Multiple oral inhalation of tiotropium (Spiriva® HandiHaler®) 18 µg capsule will be administered QD every morning for 14 ± 2 days during the Run-in Period. Albuterol will be administered on an as needed basis.

13.4.1.2 Drug Administration During Treatment Period

YPL-001 will be supplied as 80 mg tablets for oral administration.

Placebo will be supplied as YPL-001 80 mg matching placebo tablets for oral administration.

Treatments A, B, and C are described as follows:

Treatment A: Multiple oral YPL-001 80 mg doses (1 x 80 mg tablet + 1 x 1 YPL-001 80 mg matching placebo tablet) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56.

Treatment B: Multiple oral YPL-001 160 mg doses (2 x 80 mg tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56.

Treatment C: Multiple oral matching placebo (2 x 1 YPL-001 80 mg matching placebo tablets) will be administered approximately every 12 hours under fasting conditions for 55 consecutive days. Only the morning dose will be administered on Day 56.

Each dose of Treatments A, B and C will be administered with approximately 240 mL of water.

In all treatments, one tiotropium (Spiriva® HandiHaler®) 18 µg capsule will also be administered QD every morning prior to study drugs administration. Albuterol will be administered on an as needed basis.

The pharmacy at the CRU will provide each dose in individual unit dose containers for each patient, as per the randomization scheme.

Prior to release from the CRU on Days 1, 15, 29, 43, and 55 of the Treatment Period, patients will receive a properly labeled container with the appropriate doses which will be self-administered by patients at home. Patients will record their self-administered doses in their e-diary, and whether the dose was administered with food, and must return the container (empty or not) at the next morning visit. Home dosing will be monitored via attempted phone calls where patients will be reminded to take their medication, if they did not record their self-administration on the e-diary, and queried about the occurrence of AEs.

Patients will be instructed not to crush, split or chew the study drug.

The exact clock time of dosing will be recorded on on-site dosing days. Patients will be given instructions on recording of dosing times in their e-diary on home-dosing days.

Each dose will be administered under fasting conditions as described in Section 13.2.4.1.

13.4.1.3 Stopping Rules

A decision to stop or suspend the study will be made jointly by the Sponsor and the Investigator following the review of all pertinent safety and tolerability. Together they will make one of the following determinations:

1. To continue with the study as planned.
2. To continue with the study and add additional safety evaluations.
3. To continue with the study by adjusting to a lower dose if 2 patients at any dose level meets any of the following criteria and the patient was determined to have received YPL-001 after unblinding:
   a. Has a drug–related, unexpected SAE.
   b. Experiences drug-related grade ≥ 3 toxicity.
4. The study will be terminated if ≥ 3 patients at any dose level meet any of the following criteria and the patients were determined to have received YPL-001 after unblinding:
   a. Has a drug–related, unexpected SAE.
   b. Experience drug related grade ≥ 3 toxicity.

PK data will not be required for the dose-escalation decision.

When applicable, a written statement fully documenting the reasons for study termination will be provided to the Institutional Review Board (IRB).

13.4.2 Method of Assigning Patients to Treatment Groups

Each patient will be assigned a unique identification number upon screening. Patients who complete the study screening assessments, complete the Run-in Period, and meet all the eligibility criteria will receive the corresponding product, according to a randomization scheme generated at Celerion. Patients will be randomized according to their daily consumption of smoked cigarettes per day. The 4 levels (strata) of cigarette smoked/day to be used in the randomization scheme are non-smokers (i.e., 0 cigarette/day), less than (<) 15 cigarettes/day, between 15 and 30 cigarettes/day, and more than (>) 30 cigarettes/day.

Patients will receive one of the 3 treatments (Treatments A, B, or C) on one occasion.

If replacement patients are used, the replacement patient number will be 100 more than the original (e.g., Patient No. 0101 will replace Patient No. 0001).

13.4.3 Blinding

This is a double-blind, double-dummy, randomized study.

13.4.3.1 Maintenance of Randomization

A computerized randomization scheme will be created by a Celerion unblinded statistician (who is not otherwise involved in the study) and shall be considered blinded (per the following).

The randomization is available only to the clinic pharmacy staff preparing the drug who are not involved in any other aspect of the study including administration of the drug. It will not be made available to the Sponsor, patients, or members of the staff responsible for the monitoring and evaluation of safety assessments.

The bioanalytical department will also be blinded to the randomization scheme.

13.4.3.2 Procedures for Breaking the Blind Prior to Study Completion

One set of the sealed envelopes containing the randomization code will be available to the Investigator at the start of the trial

Breaking of the blind is expressly forbidden except in the event of a medical emergency where the identity of the drug must be known in order to properly treat the patient.

In the event of a medical emergency, it is requested that the Investigator make every effort to contact the study monitor or designee prior to breaking the blind. If breaking the blind is required because of a medical emergency, the treatment identity would be revealed by the qualified designee, for that patient only. In the event that the emergency is one, in which it appears that the other patients may be at imminent risk, the blind may be broken for all patients dosed at that dose level. The unblinding should be noted in the patient's electronic case report form (eCRF).

In all cases where the code is broken, the Investigator should record the date, reason for code breaking and his/her name for signature on the envelope.

At the end of the study, the envelopes will be reviewed by the Sponsor.

13.4.3.3 Revealing of Randomization

In the absence of a medical emergency, the blinded randomization for this entire trial will not be revealed until the following conditions are fulfilled:

- All data are entered in the database, edits checks are performed, queries closed, CRFs signed by the Investigator, and the database is officially locked.
- All PK/PD samples have been analyzed and quality checked by the responsible analytical associate.

13.4.4 Treatment Compliance

During in-clinic dosing, a qualified designate will be responsible for monitoring the administration of timed oral doses. When appropriate, a mouth check will be performed by the qualified designate to ensure that the patients have swallowed the study medication. Once a patient has finished the water, the qualified designate will use a flashlight and a tongue depressor to check the side of the mouth, the sides of the upper and lower gums and the area under the tongue. Patients' hands will also be verified to ensure that the medication was ingested.

Self-administration by patients at home will be monitored by the CRU via the e-diary and attempted phone calls will be performed to remind patients to take their medication, if they did not record their self-administration on the e-diary.

14. STUDY PROCEDURES

14.1 Safety Assessments

This study primarily assesses the safety and tolerability of YPL-001. Safety will be determined by evaluating physical examinations, vital signs, pulse oximetry, ECGs, clinical laboratory parameters, and AEs.

If deemed necessary, additional safety measurements will be performed at the discretion of the Investigator.

Study procedures should be completed as close to the prescribed/scheduled time as possible. The Quality of Life questionnaire should be performed prior to any other procedures. When the following procedures are scheduled at the same time, they will be performed in the following order:

1. Vital signs
2. ECG
3. Pulmonary function measurement
4. Bronchoscopy and BAL collection

All other procedures can be performed without specific order.

14.1.1 Body Height and Weight

Body height (centimeters) and body weight (kilograms) will be measured as outlined in the Study Events Flow Chart (Section 6).

14.1.2 Physical Examination

All full physical examinations will include, at a minimum, assessment of the following systems: skin, head, ears, eyes, nose and throat, respiratory system, cardiovascular system, gastrointestinal system, neurological condition, blood and lymphatic systems, and the musculoskeletal system.

A licensed physician will examine each patient as outlined in the Study Events Flow Chart (Section 6).

Medical history will be recorded at screening.

Physical examinations may be performed at various unscheduled time points if deemed necessary by the Investigator.

14.1.3 Vital Signs

Single measurements of body temperature, respiratory rate, blood pressure, and heart rate will be measured as outlined in the Study Events Flow Chart (Section 6).

Vital signs may be taken at any other times, if deemed necessary. Blood pressure and heart rate measurements will be performed with patients in a seated position for at least 1 minute, except when they are supine or semi-reclined because of study procedures and/or AEs (e.g., nausea, dizziness) or if deemed necessary by the Investigator.

When performed prior to the morning dose, blood pressure and heart rate will be measured within 2 hours prior to dosing. When scheduled, postdose vital signs readings will be performed within approximately 10 minutes of the scheduled time point. When performing the bronchoscopy, vital signs (body temperature, respiratory rate, blood pressure, and heart rate) will be monitored continuously until the end of the procedure.

14.1.4 Pulse Oximetry

Oxygen levels, saturation [%], and heart rate will be assessed using a pulse oximeter. All readings will be performed with a pulse oximeter (oxygen levels, saturation [%], and heart rate) as outlined in the Study Events Flow Chart in Section 6.

When performed prior to the morning dose, pulse oximetry monitoring will be measured within 2 hours prior to dosing. Readings may be taken at other times, if deemed necessary by the Investigator. When performing the bronchoscopy, oxygen saturation will be monitored continuously until the end of the procedure.

Any clinically relevant oxygen saturation reading below 93% will be documented as an AE, as per Investigator discretion.

14.1.5 Electrocardiogram Monitoring

When performed prior to the morning dose, ECG will be measured within 2 hours prior to dosing. When performing the bronchoscopy, ECG will be monitored continuously until the end of the procedure.

Single 12-lead ECGs will be performed as outlined in the Study Events Flow Chart (Section 6). Patients will be required to lie quietly in a supine position for at least 1 minute prior to ECG measurements. Single 12-lead ECGs may be performed at various unscheduled time points, if deemed necessary by the Investigator.

Single 12-lead ECGs will be interpreted and signed and dated by the Investigator. The ECGs will be classified as normal, having a non-clinically significant abnormality (NCS), or having a clinically significant abnormality (CS). In addition, ECG parameters of ventricular rate, PQ or PR interval, QRS duration, and QT interval (corrected according to Bazett's formula [QTcB] and uncorrected) will be noted on the CRF.

14.1.6 Clinical Laboratory Tests

All tests listed below will be performed as outlined in the Study Events Flow Chart (Section 6). In addition, laboratory safety tests may be performed at various unscheduled time points, if deemed necessary by the Investigator. The clinical laboratory tests include the following:

14.1.6.1 Hematology

- Hemoglobin
- Hematocrit
- RBC count
- Platelet count
- Mean Corpuscular Hemoglobin (MCH)
- Mean Corpuscular Volume (MCV)
- Mean Corpuscular Hemoglobin Concentration (MCHC)
- RDW
- White blood cell (WBC) count with differential (including eosinophil, neutrophil, basophil, lymphocytes, leukocyte, reticulocyte)

14.1.6.2 Serum Chemistry

Serum chemistry tests will be performed after at least an 8-hour fast; however, in case of dropouts or rechecks, patients may not have fasted for 8 hours before the serum chemistry sample is taken.

- BUN
- Creatinine*
- Bilirubin (total and direct)
- Uric acid
- Albumin
- Alkaline phosphatase (ALP)
- Creatine kinase (CK)
- Lactate dehydrogenase (LDH)
- Estimated glomerular filtration rate
- Alpha-1 Antitrypsin**
- AST
- ALT
- Amylase
- Lipase
- Glucose (fasting)
- Carbon dioxide (CO_2)/Bicarbonate (HCO_3)
- Sodium
- Potassium
- Chloride

* Creatinine clearance will be calculated using Cockcroft-Gault formula at screening.

** To be performed at screening only.

14.1.6.3 Serology

- HIV
- HBsAg
- HCV

14.1.6.4 Human Chorionic Gonadotropin (Serum Pregnancy Test)

The test will be performed for females only.

14.1.6.5 Follicle-Stimulating Hormone

The test will be performed in postmenopausal females only.

14.1.6.6 Urinalysis

- pH
- Specific gravity
- Protein
- Glucose
- Ketones
- Bilirubin
- Blood
- Nitrite
- Urobilinogen
- Leukocyte Esterase

If urinalysis is positive for protein, blood, nitrite and/or leukocyte esterase, a microscopic examination will be performed.

14.1.6.7 Urine Drug/Alcohol Screen

- Cannabinoids
- Alcohol
- Cocaine
- Amphetamines
- Barbiturates
- Benzodiazepines
- Opiates

14.1.7 Chest X-Ray

A baseline chest x-ray will be performed at the screening visit. If the patient has had an x-ray within the last 3 months prior to the screening visit, and the CRU has access to the report and images, this can be used as the baseline chest x-ray and does not need to be repeated.

14.1.8 Adverse Events

14.1.8.1 Adverse Event Definition

An AE means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.[3]

14.1.8.2 Monitoring

The patients will be instructed to inform the Investigator or clinic staff of any AEs and intercurrent illnesses experienced during the trial. Additionally, a specific inquiry regarding AEs will be conducted prior to each dosing at the CRU, at the end-of treatment

(or upon early withdrawal), and at the follow-up visit. The inquiry will be made in a non-specific manner using open-ended questions so as not to bias the response (e.g., How have you been feeling since your last visit?).

All symptoms will be evaluated by the Investigator.

Any patient who has a clinically significant AE (whether serious or non-serious) or clinically significant abnormal laboratory test value will be evaluated by the Investigator, or other monitoring physician, and will be treated and/or followed up until the symptoms or values return to normal or acceptable levels, as judged by the Investigator.

Treatment of SAEs will be performed by a physician, either at the CRU or at a nearby hospital emergency room. Where appropriate, medical test(s) and/or examination(s) will be performed to document resolution of event(s). Outcome may be classified as resolved, improved, unchanged, worse, fatal or unknown (lost to follow-up).

14.1.8.3 Reporting

AEs will be coded using the most current MedDRA® available at Celerion (e.g., 17.0 or higher). The Sponsor will inform the Celerion Global Project Manager which version is to be used prior to initiation of the study.

The Investigator will review each event and assess its relationship to drug treatment (unrelated, unlikely, possible, probable, definite). The severity of each sign or symptom reported will be graded based on the NIH NCI CTCAE toxicity grading scale 5-point severity scale (Grade 1, 2, 3, 4 and 5) [4] and the date and time of onset, time relationship to drug dosing, duration, and outcome (resolved, improved, unchanged, worse, fatal, or unknown/lost to follow-up) of each event will be noted.

The relationship of each AE will be assessed using the following definitions:

Unrelated	▪ Event occurring before dosing. ▪ Event or intercurrent illness due wholly to factors other than drug treatment.
Unlikely	▪ Poor temporal relationship with drug treatment. ▪ Event easily explained by patient's clinical state or other factors.
Possible	▪ Reasonable temporal relationship with drug treatment. ▪ Event could be explained by patient's clinical state or other factors.
Probable	▪ Reasonable temporal relationship with drug treatment. ▪ Likely to be known reaction to agent or chemical group, or predicted by known pharmacology. ▪ Event cannot easily be explained by patient's clinical state or other factors.

Definite	▪ Distinct temporal relationship with drug treatment. ▪ Known reaction to agent or chemical group, or predicted by known pharmacology. ▪ Event cannot be explained by patient's clinical state or other factors.

The following definitions for rating severity will be used:

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**. Note**:** An experience may be severe but may not be serious, e.g., severe headache).
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

14.1.8.4 Serious Adverse Events

If any AEs are serious, as defined by the Food and Drug Administration (FDA) Code of Federal Regulations (CFR), Chapter 21, special procedures will be followed. All SAEs will be reported to the Sponsor via fax or e-mail within one working day of becoming aware of the event, whether or not the serious events are deemed drug-related. All serious event reporting will adhere to 21 CFR 312.32 for Investigational New Drugs (IND) and to the Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE, dated December 2012[3]. The institutional review board (IRB) will be notified of the Alert Reports as per FDA regulations.

If an SAE occurs to a patient on this study, the Sponsor's Medical Expert is to be contacted (see Section 3).

A SAE is any AE or suspected adverse reaction that in the view of either the Investigator or Sponsor, results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or

patient and may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Life-threatening is defined as an AE or suspected adverse reaction that in the view of the investigator or sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Unexpected is defined as an AE or suspected adverse reaction that is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

14.2 Symptom Assessments

14.2.1 Electronic Diary

On Day 1 of the Run-in Period, each patient will be issued and trained on the use of the e-diary. They will record their self-administered doses and whether the dose was administered with food, concomitant medications and daily respiratory symptoms throughout the Run-in and Treatment Periods. Patients will return the e-diary device on Day 56 to CRU staff.

Prior to each dose, patients will record in the e-diary their daily PEF, major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale), and activity (DASI).

14.2.2 Peak Expiratory Flow

PEF assessments will be made daily prior to each dose from Day 1 of the Run-in Period to Day 56 of the Treatment Period. Three measurements will be made at each time point using a hand held PEF meter. Readings not performed in the CRU will be recorded in the patient e-diary. All PEF assessments should be performed before administration of a bronchodilator where possible.

14.2.3 Symptoms of Chronic Obstructive Pulmonary Disease Exacerbation

Patient will be asked to record the major (e.g., sputum quality, color, consistency) and minor (e.g., cough, wheeze, sore throat, nasal congestion, discharge, and body temperature above 100°F) symptoms of COPD exacerbation via the e-diary before each dosing.

14.2.4 Dyspnea (Modified Borg Dyspnea Scale)

Severity level of patient's dyspnea will be assessed via the modified Borg dyspnea scale programmed within the e-diary. The modified Borg dyspnea scale is a self-administered categorical scale with a score from 0 to 10, where 0 (as a measure of dyspnea)

corresponds to the sensation of normal breathing (absence of dyspnea) and 10 corresponds to the patient's maximum possible sensation of dyspnea.

14.2.5 Activity (Duke Activity Status Index)

Patient's functional capacity and activity status will be assessed via the DASI programmed within the e-diary. DASI is a self-administered 12-item questionnaire that assesses daily activities such as personal care, ambulation, household tasks, sexual function and recreation with respective metabolic costs. Each item has a specific weight based on the metabolic cost. The final score ranges between 0 and 58.2 points. The higher the score, the better the functional capacity.

14.3 Pharmacodynamic Assessments

14.3.1 Pulmonary Function (Spirometry)

Spirometry measures will be taken at the time points delineated in the Study Events Flow Chart (Section 6) using a standard calibrated spirometer to determine the parameters detailed below.

- FEV_1;
- FVC (forced vital capacity);
- FEV_1/FVC;
- IC.

Short acting β2-agonist and anticholinergic bronchodilators (e.g., albuterol, ipratropium bromide) and long acting β2-agonist and anticholinergic bronchodilators (e.g., salmeterol, tiotropium) agents will be withheld approximately 4 and 12 hours, respectively, before each pre-bronchodilator spirometry.

Every effort will be made to perform all assessments for a given patient on the same instrument throughout the study and all sites should be using the same brand and model of spirometer for this study.

At screening, baseline pre-bronchodilator spirometry will be performed (prior to albuterol administration) for a minimum of 3 times and a maximum of 8 times in order to obtain 3 manoeuvers with FEV_1 values within 150 mL of each other, using the manoeuver with the highest value of FEV_1 and FVC as the basis for comparison.

Patients shall receive 4 inhalations of albuterol, (100 µg/inhalation), for a total dose of 400 µg via metered-dose inhaler using a spacer. Within approximately 20 to 30 minutes after albuterol administration, the baseline post-bronchodilator spirometry will be performed.

Assessment of FEV_1 stability will take place:

1. Prior to Day 1 dosing of the Treatment Period (Day -1 measurement): Predose FEV_1 is defined as the time-point prior to Day 1 dosing in the Treatment Period and will be performed pre- and post-bronchodilatator administration. Predose FEV_1 will be compared to the corresponding baseline measurement. If the best

FEV_1 measurement at predose on Day -1 of the Treatment Period has declined by greater than 20% from the best FEV_1 at screening, the visit may be rescheduled up to 3 times, at the discretion of the Investigator.

2. Following Day 1 dosing: At all other spirometry time point, measurements will be performed once. If the value shows a difference of greater than 150 mL decline than the best FEV_1 value collected predose on Day -1, up to 3 measures will be performed.

   Consideration should be given, if a patient experiences any change in post Day 1 dose FEV_1 from the Day 1 predose FEV_1 value (measured following dosing with albuterol) equal to or greater than 20 % and should alert the Investigator to consider whether individual patients should continue to dose. The pulmonary function manoeuver(s) used to make this assessment must be valid and meet acceptable quality spirometry standards.

The Investigator may also use his or her discretion as to the completion of dosing for any period in which an FEV_1 decline and/or respiratory symptoms occur(s).

14.3.2 Bronchoscopy and Bronchoalveolar Lavage (BAL) Biomarkers

Patients will be asked to refrain from smoking approximately 48 hours before the bronchoscopy procedures and will be fasted for 12 hours before. If required, blood pressure medications can be taken with small sip of water based on preapproval of local Investigator.

14.3.2.1 Bronchoscopy

The bronchoscopy with bronchial brushings will be performed at the time points delineated in the Study Events Flow Chart (Section 6) by a licensed physician experienced in conducting the procedure according to guidelines published on the use of bronchoscopy for research on airway diseases such as COPD.[5,6]

Albuterol will be administered 20 minutes prior to the beginning of the bronchoscopy. An intravenous line will also be established to administer conscious sedation, and to administer emergency medications if the need were to arise. During the procedure, oxygen saturation (S_PO_2), blood pressure, and heart rate and rhythm (continuous electrocardiogram) will be monitored. Oxygen 2-4 L via nasal canula will be administered during bronchoscopy and oxygen saturation will be maintained at ≥95%. Conscious sedation will be achieved with incremental doses of 1–4 mg midazolam and 50-100 µg fentanyl. Local upper and lower airway topical anesthesia will be achieved with 1% or 2% lidocaine. The dose of lidocaine administered during the procedure will not exceed a total of 450 mg. The bronchoscope will usually be inserted preferably through the nares into trachea. The bronchoscope will be wedged into 2 subsegments of the right middle or lower lobe, as deemed appropriate by the Investigator. Emergency treatments for cardiopulmonary arrest and pneumothorax will be immediately available in the bronchoscopy room. The patient will remain in the recovery suite for observation for a minimum of 2 hours after the procedure.

14.3.2.2 Bronchial Brushings

Prior to BAL, a cytology brush is inserted into the bronchoscope channel and brushings are collected twice from each of 4 quadrants of visible subsegments of the right middle or lower lobe, as deemed appropriate by the Investigator, under direct visualization. The cellular material is washed off in saline following each brushing. The brushing is performed a total of 8 times. The liquid is centrifuged and the cell pellet is stored at -70°C.

14.3.2.3 Bronchoalveolar Lavage (BAL)

BAL in the right middle or lower lobe, as deemed appropriate by the Investigator, will be performed at the time points delineated in the Study Events Flow Chart (Section 6) by a licensed physician experienced in conducting the procedure. A 180 mL BAL will be performed in each subsegment of the right middle or lower lobe, as deemed appropriate by the Investigator, using 6 x 30 mL aliquots of normal saline warmed to room temperature. BAL fluid will be aspirated following each 30 mL instillation. The lavage material, which averages 25% return in COPD patients, typically yields 1-10 x 10^6 macrophages. The centrifuged cell pellet is divided into 2 aliquots. One (1) aliquot will be stored at -70°C and the other will be cooled and stored in an ice bath until processing. The supernatant is divided into 4-5 aliquots and stored in cryotubes in ice bath until processing.

14.3.2.4 Biomarkers

BAL samples will be analyzed for:

- YPL-001 component levels in epithelial brushings;
- total cell count (cells/mL) of macrophages, lymphocytes, and eosinophils as a percentage of total cells
- total cell count (cells/mL) of neutrophils, macrophages, lymphocytes, and eosinophils as absolute inflammatory cell numbers
- concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9.

14.3.3 Blood Biomarkers

Blood samples will be collected via direct venipuncture at the time points delineated in the Study Events Flow Chart (Section 6) for PD assessments of biomarkers. Biomarker assessments include:

- inflammatory markers (total and differential cell counts as absolute and percentage for neutrophils, macrophages, eosinophils, and lymphocytes)
- concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9.

Blood will be drawn into 4.5 mL pre-chilled evacuated tubes containing K_2EDTA and stored in an ice bath until processing.

14.3.4 Quality of Life Questionnaires

14.3.4.1 Baseline Dyspnea Index/Transition Dyspnea Index (BDI/TDI)

Dyspnea at baseline (Day 1 of the Treatment Period) will be assessed with the BDI. This instrument has 3 domains (functional impairment, magnitude of task and magnitude of effort) with the values added for a combined focal score. Functional impairment determines the impact of breathlessness on the ability to carry out activities; magnitude of task determines the type of task that causes breathlessness, magnitude of effort establishes the level of effort that results in breathlessness. The BDI scores range from 0 (very severe impairment) to 4 (no impairment) for each domain with the baseline focal score consisting of the sum of each domain (0 to 12).

Dyspnea throughout the study will be performed at the time points delineated in the Study Events Flow Chart (Section 6). The change from baseline is measured by the TDI score which ranges from -3 (major deterioration) to +3 (major improvement) for each domain with the TDI focal score consisting in the sum of each domain (-9 to +9).

The same Investigator or designee will interview specifically the patients during the study.

A copy of the questionnaire to be used will be kept in the study binder.

14.3.4.2 COPD Assessment Test (CAT)

CAT is a short and simple questionnaire of 8 items completed by patients to be performed at the time points delineated in the Study Events Flow Chart (Section 6). Scores for each of the 8 items are summed to give a single, final score ranging from 0 (no impact on daily activities) to 40 (very high impact on daily activity). This is a measure of the overall impact of a patient's condition on their life. Scores for the individual items within the questionnaire will provide insight into the relative influence that the different components of COPD have on its overall impact on a patient's life.[7,8]

A copy of the questionnaire to be used will be kept in the study binder.

14.4 Pharmacokinetic Assessments

The sampling schedule and/or collection intervals delineated in the Study Events Flow Chart (Section 6) may be modified based on the results from previously dosed patients.

14.4.1 Blood Sampling and Processing

Samples must be protected from UV light during collection, processing, and storage.

Samples will be collected via direct venipuncture at the time points delineated in the Study Events Flow Chart (Section 6).

Blood will be drawn into 5 mL pre-chilled evacuated tubes containing K_2EDTA. A manual for blood sampling, collection, processing, and sample shipment will be provided in a separate document.

14.5 Blood Volume for Study Assessments

Table 5: Blood Volume during Study

Sample Type	Number of Time Points	Volume per Time Point*	Sample Volume Over Course of Study
Screening laboratory safety tests (including hematology, serum chemistry, serology), FSH (for postmenopausal female patients only) and serum pregnancy (for female patients only).	1	~ 17 mL	~ 17 mL
On-study serum chemistry and serum pregnancy (for female patients only) when scheduled at the same time	4	~ 8.5 mL	~ 34 mL
Additional on-study serum pregnancy (for female patients only)	2	~ 3.5 mL	~ 7 mL
On-study hematology	4	~ 4 mL	~ 16 mL
Blood samples for PD biomarkers	8	~ 4.5 mL	~ 36 mL
Blood samples for PK of verproside and picroside II	37	~ 5 mL	~ 185 mL
Total Blood Volume for males →			~ 288 mL
Total Blood Volume for females →			~ 295 mL

* Represents the largest collection tube that may be used for this (a smaller tube may be used).

15. DATA ANALYSIS

Data will be handled and processed according to Celerion Standard Operating Procedures, which are written based on the principles of GCPs.

15.1 Statistical Analysis

Detailed methodology for summary and statistical analyses of the data collected in this trial will be documented in a SAP. The SAP will be prepared by Celerion and agreed upon with the Sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the SAP.

15.1.1 Sample Size Calculation

According to the exploratory nature of this study no formal statistical hypotheses will be tested. However, a sample size of 60 evaluable patients is deemed to be sufficient to assess the safety and tolerability and to provide an indication of the potential effect of YPL-001 on COPD exacerbation symptoms, selected biomarkers and pulmonary function parameters. An additional 9 patients will be enrolled to account for a 15% drop-out rate.

15.1.2 Patients to Analyze

Safety population: the safety population data set will include all available data for patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo. Safety data for all discontinued patients will be included in this set for the time points for which their data are available.

Symptom monitoring population: the symptom monitoring population data set will include all available data for patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo. Symptom monitoring data for all discontinued patients will be included in this set for the time points for which their data are available.

PK population:

- The PK full data set will include all patients receiving at least one dose of YPL-001 and having at least one measurable plasma and/or urine concentration of verproside and picroside II.
- The PK per-protocol data set will include all patients receiving all scheduled doses of YPL-001 and having sufficient samples collected to determine PK parameters from plasma concentrations of verproside and picroside II on Days 1 and/or 56.

PD population:

- The PD full data set will include all patients who received at least one dose of the investigational product (i.e., YPL-001) or placebo and provide at least 1 post-baseline PD measurement.

- The PD per-protocol data set will include all patients receiving all scheduled doses of the investigational product (i.e., YPL-001) or placebo and having measurable PD data.

PK/PD population: All patients who receive at least one dose of YPL-001 and having any measurable concentration of verproside and picroside II and measurable PD data will be included in the PK/PD relationship assessment, as applicable.

15.1.3 Safety Analysis

The following analyses will be performed. Safety analyses will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative safety data and frequency counts will be compiled for classification of qualitative safety data, when appropriate.

Medical History:

Medical history will be listed by patient.

Adverse Events:

AEs will be coded using the most current MedDRA® available at Celerion (e.g., 17.0 or higher) and data will be summarized by SOC and preferred term. The number of TEAEs will be reported. In addition, the number and percent of patients reporting each TEAE will be summarized separately for each treatment.

A by-patient AE data listing, including verbatim term, preferred term, treatment, severity, outcome, and relationship to treatment, will be provided.

Physical Examination:

Changes in physical examinations will be described in the text of the final report and significant findings will be reported as AEs.

Clinical Laboratory Tests, Electrocardiograms, Vital Signs and Pulse Oximetry:

All clinical laboratory tests, 12-lead ECGs, vital signs, and pulse oximetry measurements and their change from baseline, if applicable, will be summarized by treatment and time point of collection.

A shift table describing out-of-normal range shifts will be provided for clinical laboratory results.

A normal-abnormal shift table will be presented for ECGs.

Peak Expiratory Flow:

PEF measurements and its change from baseline, will be summarized by treatment and time point of collection.

Concomitant Medications:

Concomitant medications will be listed by patient and coded using the most current WHO drug dictionary available at Celerion (e.g., 01-MAR-2014 or later).

15.1.4 Symptom Monitoring Analysis

Symptom free days and overall symptom burden will be evaluated and compared across treatment groups. Secondary outcome analysis will be based on treatment actually received by patients. Descriptive statistics will be calculated for quantitative data and frequency counts will be compiled for classification of qualitative data, when appropriate.

Peak Expiratory Flow and Symptoms of COPD Exacerbation:

PEF measurements and symptoms of COPD exacerbation and their change from baseline, will be summarized by treatment and time point of collection.

Dyspnea and Activity:

The Modified Borg Dyspnea Scale and DASI scores will be listed and presented descriptively.

Additional analysis may be performed if deemed appropriate.

15.1.5 Pharmacodynamic Analysis

15.1.5.1 Biomarkers

When applicable, the following PD biomarkers will be summarized by treatment group using descriptive statistics (arithmetic means, SD, CV, N, minimum, maximum, and median). Figures will be created to display mean and individual level or activity as a function of time, as appropriate:

- Pulmonary biomarker (i.e., Pulmonary Function measurements [Spirometry]): pre- and post-bronchodilator change in activity by time point will be calculated relative to the pre- and post-bronchodilator baseline activity;
- BAL biomarkers (i.e., total cell count [cells/mL] of macrophages, lymphocytes and eosinophils as a percentage of total cells; total cell count [cells/mL] of neutrophils, macrophages, lymphocytes and eosinophils as absolute inflammatory cell numbers; and concentrations of TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MPO, neutrophil elastase, MCP-1, and MMP-9): raw and % change from baseline levels; and
- Blood biomarkers (i.e., inflammatory markers [total and differential cell counts as absolute and percentage for neutrophils, macrophages, eosinophils and lymphocytes] and concentrations of CRP, fibrinogen, TNF-α, IL-1β, IL-4, IL-5, IL-6, IL-8, IL-13, MCP-1, and MMP-9): raw and % change from baseline levels.

PK/PD relationship may be explored graphically using scatter plots and an appropriate regression model.

15.1.5.2 Quality of Life

The quality of life parameters reported from the BDI/TDI and CAT questionnaires will be listed and presented descriptively. Additional analysis may be performed if deemed appropriate.

15.1.6 Pharmacokinetic Analysis

15.1.6.1 Pharmacokinetic Parameters

15.1.6.1.1 Plasma

PK parameters will be computed from the individual plasma verproside and picroside II concentrations using a noncompartmental approach. Appropriate validated PK software (e.g., WinNonlin Professional) will be used. PK parameters for other components of YPL-001 and its metabolites may also be computed, as appropriate.

The following PK parameters will be computed following Day 1 morning dose:

AUC_{0-12}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to 12 hours.
AUC_{0-t}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (Ct). This parameter will be reported only if plasma concentrations fall below the lower limit of quantitation before the last time point prior to the evening drug administration on Day 1 for at least one patient. Otherwise, only AUC_{0-12} will be reported.
AUC_{0-inf}	Area under the drug concentration-time curve from time zero to infinity, $AUC_{0-inf} = AUC_{0-t} + Ct/k_{el}$, where k_{el} is the terminal elimination rate constant. †
C_{max}	Maximum observed drug concentration.
t_{max}	Time of the maximum drug concentration (obtained without interpolation).
k_{el}	Apparent terminal elimination rate constant, calculated by linear regression of the terminal linear portion of the log concentration vs. time curve. †
$t_{1/2}$	Apparent elimination half-life, calculated as $\ln(2)/k_{el}$. †
CL/F	Oral clearance [$Dose/AUC_{0-inf}$]. †
V_Z/F	Apparent volume of distribution at the terminal phase, calculated as $Dose/(k_{el} * AUC_{0-inf})$.†

† All k_{el} and related PK parameters (AUC_{0-inf}, $t_{1/2}$, CL/F, and V_z/F) will be reported only if the half-life of verproside or picroside II can be appropriately estimated from a 12-hour sampling period following dosing.

The following PK parameters will be computed following Day 56 morning dose:

AUC_{τ}	The area under the plasma concentration versus time curve over the final dosing interval, as calculated by the log-linear trapezoidal method (e.g., 0-12 hours).
AUC_{0-t}	Area under the drug concentration-time curve, calculated using linear trapezoidal summation from time zero to time t, where t is the time of the last measurable concentration (C_t).
C_{max_ss}	Maximum observed drug concentration at steady-state.
$C_{min,ss}$:	Minimum observed/measured non-zero concentration at steady-state.
C_{trough}	Concentration at the end of a dosing interval.
C_{avg}	Ratio of AUC_{τ} to the dosing interval, τ.
%Fluc:	Percent fluctuation will be calculated as follows: $\frac{C_{\max\_ss} - C_{\min\_ss}}{C_{avg}} \; x \; 100$
Swing:	Percent swing will be calculated as follows: $\frac{C_{\max\_ss} - C_{\min\_ss}}{C_{\min\_ss}} \; x \; 100$
t_{max_ss}	Time to reach the maximum drug concentration (obtained without interpolation) at steady-state.
CL_{ss}/F	Total body clearance estimated at steady-state after oral administration, calculated as Dose/AUC_{τ}.
V_{z_ss}/F	Apparent volume of distribution at steady-state, calculated as $(CL_{ss}/F)/k_{el}$.*

* All k_{el} and related PK parameters ($t_{1/2}$ or V_{z_ss}/F) will not be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

If metabolite data are available, metabolite to parent ratios may be calculated for AUC_{0-t}, AUC_{τ}, and C_{max_ss}.

15.1.6.1.2 Bronchoalveolar Lavage

Levels of YPL-001 components in epithelial brushing will be listed.

15.1.6.2 Statistical Methods for Pharmacokinetic Analyses

PK parameters will be summarized by treatment group using descriptive statistics (arithmetic means, SD, CV, N, minimum, maximum, and median). In addition, geometric means will be calculated for AUC_{τ} and C_{max_ss}, as appropriate. Figures will be created to display mean and individual verproside and picroside II concentration-time curves. Additional PK analyses may be performed if deemed appropriate.

No value for k_{el}, $t_{1/2}$, and V_{z_ss}/F, as appropriate, will be reported for cases that do not exhibit a terminal log-linear phase in the concentration versus time profile.

An estimate of the relative systemic exposure of AUC_{τ} and C_{max_ss} will be performed by dose normalized ratio analysis expressing the geometric mean ratio and 90% CI of the geometric mean ratio.

Steady-state will be assessed by visual inspection of predose plasma C_{trough} values on Days 15, 29, 43, and 56 following multiple oral dose administration of YPL-001.

Additional analyses will be performed as deemed necessary upon review of the data.

15.1.7 Assessment of Efficacy

Efficacy will not be assessed in this study.

16. STUDY ADMINISTRATION

16.1 Ethics

16.1.1 Institutional Review Board

This protocol will be reviewed by an IRB and the study will not start until the Board has approved the protocol or a modification thereof. The Board is constituted and operates in accordance with the principles and requirements described in the US Code of Federal Regulations (21 CFR Part 56). The board is ICH compliant.

16.1.2 Ethical Conduct of the Study

This research will be carried out in accordance with the protocol, US Code of Federal Regulations, GCP, 21 CFR Parts 50, 56, and 312, the ethical princliples set forth in the Declaration of Helsinki, and the ICH harmonized tripartite guideline regarding GCP (E6 Consolidated Guidance, April 1996).

16.1.3 Patient Information and Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the patients in non-technical terms. Patients will be required to read, sign and date an informed consent form summarizing the discussion prior to screening, and will be assured that they may withdraw from the study at any time without jeopardizing their medical care.

Patients will be given a copy of their informed consent form.

16.2 Termination of the Study

The Sponsor reserves the right to discontinue this study and the Investigator reserves the right to terminate their participation at any time.

16.3 Data Quality Assurance

Standard operating procedures are available for all activities performed at Celerion relevant to the quality of this study. Designated personnel of Celerion will be responsible for maintaining quality assurance (QA) and quality control (QC) to ensure that the trial is conducted, and that data are generated, documented and reported in compliance with the study protocol, GCP and Good Laboratory Practice requirements as well as applicable regulatory requirements.

The Clinical Study Report will be audited by the QA department and the quality assurance audit certificate will be included in the study report.

All clinical data will undergo a 100% quality control check prior to clinical database lock. Edit checks are then performed for appropriate databases as a validation routine using SAS® to check for missing data, data inconsistencies, data ranges etc. Corrections are made prior to statistical database lock.

Patient compliance will be monitored throughout the study via procedures such as questioning at check-in to review inclusion and exclusion criteria, urine drug screen at

check-in, mouth check following dosing, and confinement for all conduct procedures with clinical research staff on site at all times.

16.4 Direct Access to Source Data/Documents

The Investigator must maintain, at all times, the primary records (i.e., source documents) of each patient's data. Examples of source documents are laboratory reports, drug inventory, study drug label records, and eCRFs that are used as the source.

Celerion will ensure that the sponsor, IRB and inspection by domestic and foreign regulatory authorities will have direct access to all trial-related sites, source data/documents, and reports for the purpose of monitoring and auditing (ICH[E6] 5.1.2 & 6.10). In the event that other trial-related monitoring should be done by other parties, they will be required to sign a confidentiality agreement prior to any monitoring and auditing.

16.5 Drug Supplies, Packaging and Labeling

The Sponsor will supply sufficient quantities of YPL-001 80 mg tablets, and matching placebo tablets to allow completion of this study. The lot numbers and expiration dates (where available) of the drugs supplied will be recorded in the final report.

Records will be made of the receipt and dispensing of the drugs supplied. At the conclusion of the study, any unused drugs (including placebo) will either be retained by the CRU, or returned to the Sponsor, depending on the specific requirements of the regulatory bodies to whom the study report will be submitted. If no supplies remain, this fact will be indicated in the Drug Accountability section of the final report.

16.6 Data Handling and Record Keeping

Celerion standard eCRFs will be used. Each eCRF is reviewed and signed off by the Investigator.

All raw data generated in connection with this study, together with the original copy of the final report, will be retained at each CRU in a designated storage facility, until at least 5 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 5 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator/Institution as to when these documents no longer need to be retained.

16.7 Protocol Amendments

Any amendments to the study protocol that seem to be appropriate as the study progresses will be discussed between Sponsor and the Investigator. All revisions and/or amendments to the protocol in writing must be approved by the Sponsor, the Investigator, and the IRB before implementation.

16.8 Finance and Insurance

Finance and insurance will be addressed in a separate document.

16.9 Publication Policy

All unpublished information given to Celerion by the Sponsor shall not be published or disclosed to a third party without the prior written consent of the Sponsor.

The data generated by this study are considered confidential information and the property of the Sponsor. This confidential information may be published only in collaboration with participating personnel from the Sponsor or upon Sponsor's written consent to publish the article.

17. REFERENCES

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[4] National Cancer Institute. Common Terminology Criteria for Adverse Events v4.0. NCI, NIH, DHHS. May 29, 2009. NIH publication # 09-7473. Available online at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm The quick reference guide is available online at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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[8] The COPD Assessment Test healthcare professional user guide: expert guidance on frequently asked questions (issue 3: February 2012). Jones PW, Jenkins C, Bauerle O (on behalf of the CAT Development Steering Group).

18. APPENDIXES

18.1 Appendix 1 - UGT Drug Interaction Table

The following list provides medications that are substrates or inhibitors of UGT. Adapted from Williams JA, et al. Drug-drug interactions for UDP-glucuronosyltransferase substrates: a pharmacokinetic explanation for typically observed low exposure (AUCi/AUC) ratios. Drug Metab Dispos. 2004;32(11):1201-8. Epub 2004 Aug 10.

Substrates	Inhibitors
17-beta-estradiol glucuronide Amitriptyline Carvedilol Clofibric acid Codeine Cyclobenzaprine Diclofenac DMXAA Fenofibrate Flavopiridol Furosemide Gemfibrozil Glipizide Irbesartan Lamotrigine Levothyroxine Metoclopramide Metronidazole Morphine Naloxone Naproxen Olanzapine Oxazepam Paracetamol Propofol Raloxifene Tramadol Valdecoxib Valproic acid Zidovudine	17-beta-estradiol glucuronide Flavonoids (citrus fruit) Silybin (herb supplement milk thistle)

18.2 Appendix 2 - SULT Drug Interaction Table

The following list provides medications that are substrates and inhibitors of sulfotransferase. Adapted from Zhang H, Cui D, Wang B, Han YH, et al. Pharmacokinetic drug interactions involving 17alpha-ethinylestradiol: a new look at an old drug. Clin Pharmacokinet. 2007;46(2):133-57; Coughtrie MW, Johnston LE. Interactions between dietary chemicals and human sulfotransferases-molecular mechanisms and clinical significance. Drug Metab Dispos. 2001;29(4 Pt 2):522-528; King RS, Ghosh AA, and Wu J Inhibition of human phenol and estrogen sulfotransferase by certain non-steroidal anti-inflammatory agents. Curr Drug Metab. 2006;7(7):745–753; Nagai M, et al. Inhibitory effects of herbal extracts on the activity of human sulfotransferase isoform sulfotransferase 1A3 (SULT1A3). Biol Pharm Bull. 2009;32(1):105-109; and Harris, R. M.; Waring, R. H. Sulfotransferase inhibition: potential impact of diet and environmental chemicals on steroid metabolism and drug. Current Drug Metabolism 2008;9(4):269-275.

Substrates	Inhibitors
17-beta-estradiol glucuronide Vitamin C Acetaminophen	17-beta-estradiol glucuronide Vitamin C Brown rice Beer Meclofenamate Nimesulide Salicylic acid Acetylsalicylic acid Naproxen Banaba extract Rafuma extract Grape seed extract Peanut seed coat extract Gingko extract Biloba leaf extract St. John’s wort Gymnema Milk thistle