Statistical Analysis Plan

Version: 1.0
Version Date: 3rd of April 2024

For the

CORVIS-Study: Community participants with COPD or bronchiectasis and at risk of Respiratory Viral Infections including SARS-CoV-2: An open-label, multicentre feasibility study of an inhaled nitric oxide generating solution (RESP301)

Protocol No.:	RESP301-005
Study Phase:	Phase 2
ClinicalTrials.gov ID:	NCT04858451
Regulatory Agency Identifier Number(s):	CTA 53004/0002/001-0006
EudraCT No:	2020-004951-34
Protocol Version No.:	5.0
Date of Protocol:	18 November 2021

Sponsor contact details

Thirty Respiratory Limited
[redacted]

SIGNATURE PAGE

Prepared by: [redacted]

Approved by: [redacted]

Approved by: [redacted]

Approved by: [redacted]

TABLE OF CONTENTS

GLOSSARY OF ABBREVIATION

AE	Adverse Event
ATC	Anatomical Therapeutically Chemical
BMI	Body Mass Index
CCQ	Clinical COPD Questionnaire
CFR	Code of Federal Regulations
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 2019
eCRF	electronic Case Report Form
CRO	Contract Research Organization
CT	Computerized Tomography
DMC	Data Monitoring Committee
DRE	Disease Related Event
ECG	Electrocardiogram
EDC	Electronic Data Capture
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Council for Harmonization
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intent To Treat
MedDRA	Medical Dictionary for Regulatory Activities
mHb	Methaemoglobin
NHS	National Health Service
NO	Nitric oxide
NO2	Nitrogen dioxide
NOx	Oxide of nitrogen
PEoT	Post End of Treatment
PR	Pulse Rate
PT	Preferred Term
PP	Per Protocol
QC	Quality Control
RTD	Recommended Therapeutic Dose
SAC	Safety Advisory Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis system
SD	Standard Deviation

SEM	Standard Error of the Mean
SoA	Schedule of activities
SOC	Standard of Care or System Organ Class
SP	Safety population
SpO_2	Oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
SOP	Standard Operative Procedure
TEAE	Treatment-emergent adverse event
TID	Three Times Daily
TMF	Trial Master file
VAS	Visual Analogue Scale
WHO-DD	World Health Organization Drug Dictionary

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a more technical and detailed description of the statistical methods mentioned in the protocol of study RESP301-005:

> CORVIS-Study: Community participants with COPD or bronchiectasis and at risk of Respiratory Viral Infections including SARS-CoV-2: An open-label, multicentre feasibility study of an inhaled nitric oxide generating solution (RESP301).

This analysis plan is developed based on ICH E3 and E9 guidelines and in reference to the following documents:

- the last version of the protocol (18th of November 2021, vers. 5.0)
- the annotated eCRF (13th of September 2021, vers. 1.0)
- the trial monitoring plan for Clinical Trials Sponsored by Thirty Respiratory Limited, Version 4.0, 17th of February 2022

Any significant changes from the methodology defined in the current protocol/eCRF or protocol amendments agreed after the approval of this SAP may require changes to this SAP, see section 5.13 for details.

2. STUDY OVERVIEW

2.1 Study Objectives and Hypotheses

This study is divided in two parts, a dose finding part (part 1) followed by an expansion phase (part 2):
In part 1, the maximum tolerable dose (MTD) and the recommended therapeutic dose (RTD) of a single agent RESP301 in patients with mild to moderate COPD or bronchiectasis will be determined. In an additional cohort, the safety and tolerability of administering RESP301 at the MTD with the co-administration of a short acting bronchodilator will be investigated.
In part 2, the effects on recruiting and retaining patients with COPD or bronchiectasis who have viral infection symptoms and treating these patients with RESP301 in a community setting will be investigated.

The secondary objectives of this study are:

- To assess the safety and tolerability of single doses of RESP301 in patients with COPD or bronchiectasis, who are at high risk of SARS-CoV-2 and other acute respiratory pathogens.
- To assess the safety and tolerability of single doses of RESP301 in combination with a short acting bronchodilator.
- To collect preliminary data on the efficacy of RESP301.

2.2 Study Design

This is a phase II, single-group, non-randomized, two-center, open-label study conducted in two parts.
In part 1 (Dose Finding Phase), eligible patients will be administered a single dose of RESP301 under clinical supervision. The first eight patients (group 1) will receive a dose of 1 ml, the next eight patients (group 2) 2 ml, the next eight patients (group 3) 3 ml, etc. until a maximum dose of 6 ml. After the completion of each dose level (treatment group) the safety data will be reviewed by the PIs and Sponsor before proceeding to the next higher dose. After the completion of all groups a safety advisory committee (SAC) will review the data from all participants and determine a Maximum Tolerated Dose(MTD) and a Recommended Therapeutic Dose (RTD).
Thereafter eight eligible patients will be administered a single dose of RESP301 at the MTD in combination with a short acting bronchodilator also under clinical supervision.

In part 2 (Expansion Phase), a minimum of 150 patients will be enrolled into the Expansion Phase and treated at the Recommended Therapeutic Dose (RTD) determined in Part 1. The expansion phase is split into three periods, a baseline visit, a dormant period (max. 12 months) and a treatment period (7 days). The first 50 patients at baseline will receive a RTD test dose on site to further investigate the safety and tolerability of RESP301.
An Independent Data Monitoring Committee (IDMC) will review this data and decide whether further RTD test doses should be administered to further patients before enrolling them into the Dormant Period or whether patients could be enrolled into the dormant period without a RTD test dose at baseline.

Female of non-childbearing potential or male ≥35 years of age, at the time of signing the informed consent with spirometry-confirmed COPD or computerized tomography (CT) proven bronchiectasis are included in the study. Further details of the inclusion/exclusion criteria are defined in sections 6.2 and 6.3 of the protocol.
Eligible patients in part 1 may be enrolled in more than one of the seven treatment groups and patients from part 1 will also be eligible to enter Part 2 of the trial.
The overall study duration for each patient will be at approximately 60 weeks, including one or more visits at a study center in parts 1/2, monthly follow-up calls, and, for those who experience an exacerbation (part 2), one week of treatment and additional monitoring calls at the beginning, during and following the treatment period.

The eight treatment groups, the number of subjects per group and the corresponding treatment labels used for the statistical evaluation are summarized in table 1.

Table 1: Treatment Groups

Part	Treatment group*	Label	Short label**
1	1 (N=8)	RESP301 1 ml	1ml
	2 (N=8)	RESP301 2 ml	2ml
	3 (N=8)	RESP301 3 ml	3ml
	4 (N=8)	RESP301 4 ml	4ml
	5 (N=8)	RESP301 5 ml	5ml
	6 (N=8)	RESP301 6 ml	6ml
	7 (N=8)	RESP+Vent 6 ml	R+V
2	8 (N=150)	RESP301 RTD	RTD

* During a meeting on the 11th of January 2022 it was decided that the RTD dose is 4 ml and the MTD dose 6 ml.

** Short labels may be used due to paper space requirements.

RESP301 is prepared by mixing two sterile solutions (one of NaNO2/mannitol and one of citric acid buffered to pH [redacted]) in the nebulizer. The solution is to be nebulized within 5 minutes post mixing as per the instructions given in the SoA. The inhalation of the medication should start within 5 minutes of mixing the solutions and the inhalation process should be complete within 20 minutes of starting inhalation.

An overview of the study procedures is provided in table 2 below for part 1 of the study and in table 3 for part 2, see protocol page 51, table 8-1:

Table 2: Schedule of Study Assessments (Part 1)

Procedure	Screen 1	Screen 2/Dosing Visit (Day 1)[3]	Follow-up Phone call (Day 2)
Informed Consent	X		
Inclusion and Exclusion Criteria	X	X	
Demographics	X		
Medical History	X		
Medication history and concomitant medications	X	X	X
Height, Weight and BMI	X		
Physical Examination[1]	X	X	
Pulmonary function test	X	X	
Vital signs	X	X	
Methaemoglobin level	X	X	
Short acting bronchodilator[2]		X[1]	
RESP301 administration		X	
Follow-up			X
AE/SAE review	X	X	X

1) Only done if deemed necessary by the investigator
2) Only done in the combination group, i.e., RESP301 + short acting bronchodilator (group 7)
3) Screen 1 and Screen 2 may be combined if the patient has historic evidence of a FEV1/FVC ratio<0.7.

Table 3: Schedule of Study Assessments (Part 2)

Procedure	Screen 1	Screen 2/ Baseline Visit[1]	Dormant Period (monthly calls)	Pre-Treatment call (within 24-72 hrs of exacerbation onset)	Treatment Period (daily monitoring calls for 8 days)	Post Treatment Follow-up call (Day 14±3 PEoT)	Post Treatment Follow-up call (Day 28±3 PEoT)	Early withdrawal (Days 0, 14 or 28 ± 3)
Informed Consent	X	X						
Inclusion and Exclusion Criteria	X	X						
Demographics	X							
Medical History	X			X	X	X	X	X
Medication history and concomitant medications	X	X		X	X	X	X	X
Height, Weight and BMI	X							
Physical Examination[2]	X	X						
Pulmonary function test[3]	X	X						
Vital signs	X	X						
Methemoglobin level	X	X						
RESP301 administration[4]		X			X			
CCQ		X	X		X[5]	X		
Instructions of nebulizer		X		X	X			
Follow-up[6]			X					
Review of symptoms				X	X	X		
AE/SAE review	X	X			X	X	X	X
VAS[7]					X	X		

Body temperature[7]				X	X	X		
Treatment compliance					X			

[1]) Patients who received a RTD test dose only and did not proceed to the dormant period, will receive a follow-up call on day 7±3 to discuss and record AEs.
[2]) Only done if deemed necessary by the investigator
[3]) Only done in patients who received a RTD test dose at the Baseline visit
[4]) At baseline a single RTD dose for patients who were assigned to test dose and at the treatment period TID for 1- 7 days in patient with an exacerbation
[5]) Done at Day 1 and Day 7
[6]) Patients reminded to contact the study team if they experience exacerbation symptoms
[7]) Daily during the treatment period, and if not recovered by end of treatment, continued until recovery or Day 14 post end of treatment

2.3 Data and Analysis Quality Control

The trial monitoring plan for Clinical Trials Sponsored by Thirty Respiratory Limited for this study will detail the quality assurance and quality control systems to be implemented to assure the quality of the data. Similarly, the quality control of the statistical analysis will follow the SOPs of institution performing the statistical analysis.

3. EFFICACY AND SAFETY VARIABLES

3.1 Efficacy

The primary objective in part 1 (Dose Finding Phase) is to determine the maximum tolerable dose (MTD) and the recommended therapeutic dose (RTD) of the single agent RESP301. For these decisions individual and cohort stopping criteria were defined, see section 7.7.2 and 7.7.3 of the protocol. In a Safety Advisory Committee (SAC) meeting prior to part 2 of this study these doses will be determined. Hence no single primary and/or secondary endpoint for part 1 was defined.

In part 2 (Expansion Phase), the primary endpoints are:

- Percentage of patients entering the dormant period who, having experienced and correctly reported an exacerbation, commence self-administration of the treatment at home on the day the treatment is delivered.
- Percentage of patients who, having experienced and correctly reported an exacerbation, receive the treatment within 48 hours of reporting their exacerbation.
- Compliance with RESP301 administration schedule over the treatment period: for those participants commencing treatment, the percentage of total doses taken.

The secondary endpoints, which will be analyzed by treatment dose and separately in the sub-group of patients who had a positive test result for SARS-CoV-2 are defined as:

- % of participants able to tolerate the test dose in Part 1(a), Part 1(b) and Part 2, i.e. able to complete the test dose without any of the following:
    - Troublesome cough, chest pain or tightness, bronchospasm or dyspnea that is deemed unacceptable by the patient.
    - methemoglobin >5% during or >3% post dose (30 or 60 mins)
    - any treatment-related AE that led to participant not being able to complete the test dose, and/or be suitable to be enrolled into the dormant period in the Investigator's opinion
    - for the first 50 patients who will undergo pre and post-test dose spirometry, >20% reduction in FEV1 from pre-test dose to post

test at 60 min dose with symptoms listed above (patients with >20% reduction in FEV1 without symptoms would be offered the option to continue in the study).

3.2 Safety variables

The safety end-points for this study are:

- Adverse Events (AEs)
- Serious Adverse Events (SAEs)
- Suspected Unexpected Serious Adverse Reactions (SUSARs)
- Severe AEs
- Treatment-related AEs/SAEs Adverse events (AEs) and serious adverse events (SAEs)

4. SAMPLE SIZE JUSTIFICATION

The primary objective of this study is to determine the MTD and RTD of RESP301 and to assess feasibility. No formal sample size calculation was performed. In Part 1, we aim to recruit up to 56 participants (8 per dose group) to receive one dose of RESP301 (alone or in combination).
In Part 2, we aim to recruit around 150 patients from secondary care and primary care sites in the UK into the dormant period. The first 50 consented participants will receive an initial test dose of RESP301 before progressing to the dormant period. If, based on the first 50 participants, the DMC determines that it is safe to do so, the remaining consenting participants will not be required to receive a test dose before progressing to the dormant period. It is estimated that over 12 months, 30 of the 150 enrolled participants will exacerbate. These participants will commence self-administered RESP301 treatment. Non-exacerbating participants will receive no further study interventions.

5. METHODS OF ANALYSIS AND PRESENTATION

5.1 General Principles

The statistical analysis will be performed using the validated software package SAS version 9.4 or higher (SAS Institute Inc., Cary, NC 27513, USA).
All recorded and derived variables will be presented by treatment group and visits (if appropriate) using descriptive summary tables (continuous data: sample size, mean, standard deviation (SD), minimum, median, maximum; categorical data: sample size, absolute and relative frequency).
The mean and median will be presented to one more decimal place than the raw data. The SD will be presented to two more decimal places than the raw data. The percentages will be presented to 1 decimal place. In all the summaries, the treatment groups will be displayed in the following order: part 1 (RESP301 1 ml, 2 ml, …6 ml, RESP+Vent 6 ml) and then part 2.

For all parameters, baseline is defined as the last available pre-treatment value (i.e. the last non-missing value available before study drug administration. In general, missing data will be treated as missing and no attempts will be made to impute values for missing data.

No formal interim efficacy analyses are planned in this study; however, several safety interim analyses by the Safety Advisory Committee (SAC) will be performed as detailed in the protocol, see section 7.7 for part 1 and an Independent Data Monitoring Committee (IDMC) will review the safety data on an ongoing basis as described in the DMC charter, see section 10.6 of the protocol.

Subjects who did not receive any study medication (screening failures) will be listed separately and not presented in any table or figure, except in the patient's disposition table.

The versions of the following international dictionaries (MedDRA version 26.1 and WHO DD, version 2024) will be used for medical coding:
Adverse events: Medical Dictionary for Regulatory Activities (MedDRA).
Medical Histories: Medical Dictionary for Regulatory Activities (MedDRA).
Medications: World Health Organization (WHO) Drug Dictionary including Anatomical Therapeutic and Chemical (ATC) classification.
If a medication in the drug dictionary (DD) table is associated with more than one ATC code, the first ATC code will be assigned to that medication.

5.2 Definition of Analysis Populations

The following analysis sets will be identified prior to database lock, see section 10.3 of the protocol. Please note, that the FAS definition is slightly different from the ITT population in the protocol.

Screening	All patients who were screened (i.e. given informed consent)
Safety Set (SS)	All patients who inhaled at least one dose of (complete or partial) study medication. Subjects will be analyzed as treated.
Full Analysis Set (FAS)	All patients in the safety set (SS) who have at least one post treatment assessment.
Per-Protocol Set (PPS)	All patients in the FAS without a major protocol deviation that may significantly impact data integrity or patient safety.

The FAS set will be the primary analysis set for all efficacy analyses and the PPS set will be used to demonstrate robustness of results for the efficacy

endpoints. Alll other analyses will be based on the patients from the safety set.
All protocol violations/deviations will be reviewed and classified as either 'minor' (unlikely to appreciably affect trial outcomes) or 'major' (likely to affect outcomes) and this classification will be utilised to define the study populations for analysis purposes.
The assessment of major violations will be performed before the study database is locked and will be documented in the corresponding meeting/TC minutes. At a minimum the investigator, a sponsor representative and the CRA/monitor will participate in this review and will sign the meeting minutes.

5.3 Disposition of Subjects

A summary of the subject disposition will be created including number of patients screened, number of screen failures, if any, number of patients treated, number of patients who completed the study in each treatment group. In addition, a summary of the number and percentage of patients in the safety set who were available at each visit will be presented by treatment group and overall.

5.4 Demographic and Baseline Characteristics

Demographic characteristics (age, gender and ethnicity) and body measurements (height, weight and BMI) and vital signs (body temperature, systolic blood pressure, diastolic blood pressure, heart rate and respiratory rate) collected at baseline will be summarized by treatment group and overall, for the safety set.
Body mass index (BMI in kg/m**2) will be calculated as weight (in kg) divided by height (in m) **2.
Any additional baseline characteristics, like smoking status, COPD and bronchiectasis history will also be presented descriptively be treatment group and overall.

5.5 Medical History

Medical history and concurrent diseases will be coded using MedDRA. The number and percentage of patients with past medical conditions grouped by MedDRA SOC will be displayed on the preferred term level (PT) by treatment group for the safety set. A similar summary will be produced for concurrent medical conditions at baseline (before start of first administration of study medication).

5.6 Physical Examination

The number and percentage of patients with abnormal physical examination at baseline will be displayed for each body system as indicated in the eCRF in the safety set.
All the details collected in the eCRF of the physical examination at baseline will be presented in a separate listing for all subjects in the safety set.

5.7 Protocol Deviations

Any protocol deviations (minor and major) will be identified by the clinical team prior to locking the database. The number and percentage of patients with each deviation and each treatment group will be summarized for the safety set.

5.8 Prior and Concomitant Medications

Prior and concomitant medications will be coded using WHO-DD and will be assigned to the first corresponding ATC code. All the medications will be listed for the safety set.
The number and percentage of subjects with concomitant medications ongoing at baseline (i.e. ongoing the day before administration of first dose of study medication) classified by ATC levels 2 and 3 will be displayed by treatment group in the safety set. A similar summary will be produced for concomitant medication started after baseline (i.e. those medications started on or after the day of first dose and on or before the date of last dose). Any medications starting after last dose will be listed only.

5.9 Extent of Exposure

Overall compliance regarding the administration of the study medication during the study part 2 will be calculated for the dormant phase based on the number of dispensed medications minus the number of medications returned as a percentage of the number of medications that should have been administrated. A summary with descriptive statistics will be produced by treatment group in the safety set. For part 1 and the test dose phase in part 2 the number and percentage of correct administrations will be presented.
The exposure to study medication will be calculated in days as:
Last dose date of study medication – First dose date + 1.

5.10 Analysis of Efficacy Variables

All primary and secondary efficacy parameters, see section 3, will be summarized descriptively and no formal statistical analyses will be performed. The analyses will be performed by treatment group and overall, for both the FAS and PPS set using appropriate descriptive statistics.
The results of the spirometry will also be presented over time, i.e. baseline, 30-, 60- and 90-minutes post baseline.

Explorative /Sub-group analysis

Summary statistics of the primary and secondary endpoints may also be presented for specific sub-groups, if the number of patients in these sub-groups are high enough to allow a meaningful interpretation of the results.

5.11 Analysis of Safety Variables

These analyses will be conducted for the safety set (SS) only and no formal statistical testing will be performed in the safety endpoints.

Adverse Events
For the safety analysis only adverse events with an onset after the first administration of the study medication (TEAEs) will be displayed in summary tables. AEs starting before the first administration will be listed only.
Adverse event summaries will be presented by treatment group and overall.
An overall summary of AEs will be produced including the number of TEAEs; the number and % of subjects reporting at least 1 TEAE, serious TEAE (where SAE is reported as 'Yes'), TEAE leading to withdrawal from the study and the number and % of subjects reporting TEAEs by severity and relationship to study drug. A subject with multiple occurrences of the same AE is counted only once at the maximum level of severity or the highest association to study drug.
Adverse events will be coded using MedDRA and will be presented on the MedDRA preferred term (PT) level.
The tables will list for each adverse event, the number of events and the number and percentage of patients in each treatment group in whom the event occurred. Adverse events will be grouped by system organ class.
All serious adverse events (SAEs) will be listed separately.

VAS Scores
For each parameter will be summarized by treatment group using descriptive statistics at each time point.

5.12 Interim Analysis and Data Monitoring

There are no planned interim efficacy analyses. However, an Independent Data Monitoring Committee (IDMC) will review the safety data on an ongoing basis.

5.13 Revised/Additional Versions

Not applicable, this is the first version.

6. REFERENCES

1) Study protocol: CORVIS-Study: Community participants with COPD or bronchiectasis and at risk of Respiratory Viral Infections including SARS-CoV-2: An open-label, multicentre feasibility study of an inhaled nitric oxide generating solution (RESP301), Version: 5.0, 18th of November 2021.

2) Annotated eCRF for the CORVIS-Study, Part 1 13th of September 2021, Part 2 9th of March 2022.

3) TRIAL MONITORING PLAN for Clinical Trials Sponsored by Thirty Respiratory Limited, Version 4.0, 17th of February 2022.

4) ICH Guideline E3, Structure and content of clinical study reports,

November 1995.

5) ICH Guideline E9, Statistical Principles for Clinical Trials, February 1998.

6) SAS Institute Inc., Cary, NC, USA. Software Release Version 9

7) CORVIS Dose Finding Phase, Summary of safety data (after Part 1), 11th of January 2022.

End-of-Text Tables and Figures

The default tables, figures and listings (TFL) layout will be as follows:

Orientation	A4 Landscape
Margins	Top: 2.0 cm Bottom: 2.0 cm Left: 2.0 cm Right: 2.0 cm
Font	Courier New 8pt
Headers (Centre)	Sponsor Protocol Number, TLF Number, Title, Population
Footers (Left)	Source listing, date/time TFL produced and additional clarification

The font size may be reduced as necessary to allow additional columns to be presented, but not at the expense of clarity. Also, the orientation of the table may be changed to portrait if appropriate. At the time of programming footnotes will be added to the listing, table, or figure as needed. All footnotes will be used for the purpose of clarifying the presentation.
The table, listing and figure numbering may be changed depending on the available paper space and variables presented.

Section 15 End-of-Text Tables and Figures

15.1 Demographic and Baseline Characteristics

Table 1.1	Subject disposition – All patients screened
Table 1.2	Study withdrawal – Safety set
Table 1.3	Protocol violations – Safety set
Table 2.1	Gender, age, ethnicity – Safety set
Table 2.2	Height, weight and BMI – Safety set
Table 2.3	Smoking status – Safety set
Table 2.4	COPD and bronchiectasis history – Safety set

Table 3.1	Medical history (MedDRA system organ classes) – Safety set
Table 3.2	Concurrent diseases (MedDRA system organ classes) – Safety set
Table 3.3	Concomitant medications ongoing at baseline – Safety set
Table 3.4	Concomitant medications started after baseline – Safety set
Table 4.1	Summary of physical examination – Safety set
Table 5.1	Compliance with study medication – Safety set

15.2 Efficacy Results

Table 1.1	Summary of primary endpoints, part 2 – FAS/PPS set
Table 1.2	Summary of secondary endpoints – FAS/PPS set
Table 1.3	Summary statistics of spirometry over time – FAS/PPS set
Table 1.4	Summary of VAS scales – FAS/PPS set
Table 1.5	Summary statistics of explorative/sub-group analyses, if any – FAS/PPS set

15.3 Safety Results

Table 1.1	Overview of all adverse events – Safety set
Table 1.2	Patients with adverse events at MedDRA system organ class level – Safety set
Table 1.3	Patients with adverse events, preferred term grouped by MedDRA system organ class – Safety set

Appendix 16.2 Subject Data Listings

Appendix 16.2.1 Subject Disposition

Listing 1	End of study assessment – Safety set
Listing 2	Screening failures – All screened subjects
Listing 3	Subjects treated – Safety set
Listing 4	Protocol deviations - Safety set

Appendix 16.2.2 Informed Consent, Protocol Deviations, and Inclusion and Exclusion Criteria

Listing 1	Informed consent – Safety set
Listing 2	Inclusion criteria – Safety set
Listing 3	Exclusion criteria – Safety set

Appendix 16.2.3 Subjects Excluded from Analyses

Listing 1	Reasons for non-eligibility for the Full Analysis Set – Safety set
Listing 2	Reasons for non-eligibility for the Per Protocol Set – Full analysis set

Appendix 16.2.4 Demographics, Medical History, and Prior/Concomitant Medications

Listing 1	Demographics – Safety set
Listing 2	Medical history – Safety set
Listing 3	Concurrent conditions – Safety set

Listing 4	Prior and concomitant medication – Safety set

Appendix 16.2.5 Study Drug Administration

Listing 1	Treatment received – Safety set
Listing 2.1	Compliance – Safety set

Appendix 16.2.6 Efficacy Data

Listing 1	Primary endpoint, part 2 – Safety set
Listing 2	Secondary endpoints – Safety set
Listing 3	Spirometry – Safety set
Listing 4	VAS scales – Safety set

Appendix 16.2.7 Adverse Events

Listing 1	Adverse events – Safety set
Listing 2	Serious adverse events – Safety set

Appendix 16.2.9 Vital Signs, ECGs, and Physical Examination

Listing 1	Vital signs – Safety set
Listing 2	Physical examination findings – Safety set
Listing 3	Pregnancy test – Safety set
Listing 4	Additional notes (Safety set)