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A Randomized, Double-blind, Placebo-controlled, 12-week Treatment Study to Evaluate the Effect of ACT-774312 in Subjects With Bilateral Nasal Polyposis

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A Study to Evaluate the Effect of ACT-774312 in Subjects With Bilateral Nasal Polyposis

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ACT-774312

Nasal Polyposis

Protocol ID-084A201

A randomized, double-blind, placebo-controlled, 12-week treatment study to evaluate the effect of ACT-774312 in subjects with bilateral nasal polyposis

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ACT-774312

Indication

Nasal polyposis

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ID-084A201, A randomized, double-blind, placebo-controlled, 12-week treatment study to evaluate the effect of ACT-774312 in subjects with bilateral nasal polyposis

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INVESTIGATOR SIGNATURE PAGE

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I agree to the terms and conditions relating to this study as defined in this protocol, the Case Report Form, and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the sponsor would constitute a violation of the protocol, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the well-being of the subjects).

I agree to conduct this study in accordance with the Declaration of Helsinki principles, International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, and applicable regulations and laws. In particular, I will obtain approval by an Independent Ethics Committee or Institutional Review Board (IEC/IRB) prior to study start and signed informed consent from all subjects included in this study. If an amendment to the protocol is necessary, I will obtain approval by an IEC/IRB and ensure approval by regulatory authorities (if applicable) has been obtained before the implementation of changes described in the amendment. In addition, I will allow direct access to source documents and study facilities to sponsor representative(s), particularly monitor(s) and auditor(s), and agree to inspection by regulatory authorities or IEC/IRB representative(s). I will ensure that the study treatment(s) supplied by the sponsor are being used only as described in this protocol. Furthermore, I confirm herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to health authorities worldwide.

Investigator	Site number	Date	Signature
[redacted]			

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LIST OF ABBREVIATIONS AND ACRONYMS

ACQ	Asthma Control Questionnaire
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AQLQ	Asthma Quality of Life Questionnaire with Standardised Activities
AST	Aspartate aminotransferase
ATS	All-treated set
AUC	Area under the plasma concentration-time curve
AUC_{τ}	Area under the plasma concentration-time curve during a dose interval
AUC_{0-4}	Area under the plasma concentration-time curve from zero to 4 h
AUC_{0-t}	Area under the plasma concentration-time curve from zero to time t of the last measured concentration above the limit of quantification
b.i.d.	Twice daily
[redacted]	[redacted]
BLQ	Below the limit of quantification
BMI	Body mass index
BP	Blood pressure
CDISC	Clinical Data Interchange Standards Consortium
CFR	Code of Federal Regulations (US)
CI	Confidence interval
C_{max}	Maximum plasma concentration
CNS	Central nervous system
CRO	Contract Research Organization
CRS	Chronic rhinosinusitis
CRSsNP	Chronic rhinosinusitis phenotype without nasal polyps
CRSwNP	Chronic rhinosinusitis phenotype with nasal polyps
CRTH2	Chemoattractant receptor-homologous molecule expressed on Th-2 cells

CT	Computed tomography
CV	Coefficient of variation
CYP	Cytochrome P450
DBP	Diastolic blood pressure
DK-PGD2	13,14-dihydro-15-keto-prostaglandin D2
ECG	Electrocardiogram/graphy
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ENT	Ears, nose, and throat
EOS	End-of-Study
EOT	End-of-Treatment
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
hCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HR	Heart rate
i.v.	Intravenous
IB	Investigator's Brochure
IC_{50}	Half maximum inhibitory concentration
ICF	Informed consent form
ICH	International Council for Harmonisation
ICS	Inhaled corticosteroids
IEC	Independent Ethics Committee
IgE	Immunoglobulin E
IL	Interleukin
ILC2	Group 2 innate lymphoid cells
IMP	Investigational medicinal product
INCS	Intranasal corticosteroids
IRB	Institutional Review Board

ISF	Investigator Site File
K3-EDTA	Tri-potassium ethylene diamine tetra-acetic acid
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LOQ	Limit of quantification
MAD	Multiple-ascending dose
MAP	Mean arterial pressure
MDRP	Multidrug-resistant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MFNS	Mometasone furoate nasal spray
MMRM	Mixed model for repeated measurements
NOAEL	No-observed-adverse-effect level
NP	Nasal polyposis
NPS	Nasal polyp score
NSAID	Nonsteroidal anti-inflammatory drug
o.d.	Once daily
[redacted]	[redacted]
[redacted]	[redacted]
OCS	Oral corticosteroids
OMC	Ostiomeatal complex
p.o.	Orally
PD	Pharmacodynamic(s)
PGA	Physician Global Assessment
PGAC-DS	Physician Global Assessment of Change in Disease Severity
PGA-DS	Physician Global Assessment of Disease Severity
PGD2	Prostaglandin D2
PGIC-DS	Patient Global Impression of Change in Disease Severity
[redacted]	[redacted]
PK	Pharmacokinetic(s)
PPS	Per-protocol set
PT	Preferred term
QoL	Quality of life

QTcB	QT interval corrected with Bazett's formula
QTcF	QT interval corrected with Fridericia's formula
RSI	Reference safety information
SAD	Single-ascending dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SDTM	Study Data Tabulation Model
SE	Standard error
SNOT-22	Sino-Nasal Outcome Test
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
Th-2	T helper 2 cell
t_{max}	Time to reach maximum plasma/blood concentration
TMF	Trial Master File
ULN	Upper limit of normal
UPSIT	University of Pennsylvania Smell Identification Test
URL	Upper Airways Research Laboratory
US	United States
VAS	Visual analog scale(s)
WHO	World Health Organization

PROTOCOL SYNOPSIS ID-084A201

TITLE	A randomized, double-blind, placebo-controlled, 12-week treatment study to evaluate the effect of ACT-774312 in subjects with bilateral nasal polyposis.
OBJECTIVES	**Primary objective** To evaluate the effect of ACT-774312 on bilateral nasal polyposis (NP). **Secondary objectives** • To evaluate the safety and tolerability of ACT-774312 during 12 weeks of treatment. • To evaluate the pharmacokinetics (PK) of ACT-774312 in subjects with NP. • To evaluate the pharmacodynamic (PD) responses to ACT-774312 based on T helper 2 cell (Th-2) biomarkers.
DESIGN / PHASE	Randomized, double-blind, 12-week, placebo-controlled, exploratory proof-of-concept Phase 2 study.
STUDY PLANNED DURATION	**First subject First visit** 3Q18 **Last subject First visit** 3Q20 **Last subject Last visit** 4Q20
CENTERS / COUNTRIES	The study will be conducted in up to 4 sites in 4 countries
SUBJECTS / GROUPS	24 subjects with bilateral NP: • 16 subjects on ACT-774312 • 8 subjects on placebo.
INCLUSION CRITERIA	• Signed informed consent in the local language prior to any study-mandated procedure. • A minimum bilateral nasal polyp score (NPS) of 5 out of a maximum of 8 for both nostrils (with at least a score of 2 for each nostril) despite completion of a prior intranasal corticosteroids (INCS) treatment for at least 8 weeks before screening, with at least the 6 last weeks on INCS spray.

	• Presence of at least 2 of the following symptoms at screening: – nasal blockade/obstruction – nasal discharge (anterior/posterior nasal drip) – reduction or loss of smell • Male and female subjects aged between 18 and 70 years (inclusive) at screening. • Subjects with a body mass index ≥ 18 kg/m^2. • Systolic blood pressure 90−160 mmHg, diastolic blood pressure 50−100 mmHg, and pulse rate 45−100 bpm (inclusive), measured on the dominant arm, after 5 min in the supine position at screening. • Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test pre-dose on Day 1. Women of childbearing potential must consistently and correctly use (from at least first dosing, during the entire study, and for at least 30 days after last study treatment intake) 1 highly effective method of contraception with a failure rate of < 1% per year, be sexually abstinent, or have a vasectomized partner. Hormonal contraceptives must have been initiated at least 1 month before first study treatment administration. Women not of childbearing potential are defined as post-menopausal (i.e., amenorrhea for at least 1 year without an alternative medical cause confirmed by follicle-stimulating hormone > 40 mIU/mL at screening), or surgically or naturally sterile. • Ability to communicate well with the investigator in the local language, and to understand and comply with the requirements of the study.
EXCLUSION CRITERIA	• CYP2C9 poor metabolizer subject. • Subject with severe renal function impairment (≤ 29 mL/min/1.73 m^2) which is defined by estimated glomerular filtration rate estimated at screening using the Modification of Diet in Renal Disease formula. • Subject with Sino-Nasal Outcome Test (SNOT-22) < 20.

	• Subject who has taken other investigational drugs or prohibited therapy for this study within 3 months before screening or 5 half-lives, whichever is longer, or participation in more than 3 investigational drug studies within 1 year prior to screening. • Pregnant or lactating women. Women who intend to become pregnant during the study. • Known allergic reactions or hypersensitivity to the study treatment or drugs of the same class, or any of the excipients. • Subject with prohibited medication at screening without full wash-out period. • Subject who has required oral corticosteroids (OCS) within 2 months before screening or is scheduled to receive OCS during the study period for another condition. • Subject who has required INCS drops within 6 weeks before screening. • Subject who was injected with long-lasting activity corticosteroids within 3 months before screening or is scheduled to receive these during the study period for another condition. • Subject diagnosed with a parasitic infection. • Subject ever diagnosed with cancer. • Positive results from the HIV or hepatitis B or C serology at screening (except for vaccinated subject or subject with past and resolved hepatitis). • Subject who has received specific allergen immunotherapy within the previous 3 months. • Any circumstances or conditions, which, in the opinion of the investigator, may affect full participation in the study or compliance with the protocol. • Subject considered as vulnerable (e.g., sponsor or site employee, investigator subordinate, subject incapable of giving consent, subject committed to an institution by way of official or judicial order).

	• Legal incapacity or limited legal capacity at screening. • Veins unsuitable for intravenous puncture on either arm (e.g., veins that are difficult to locate, access or puncture, veins with a tendency to rupture during or after puncture). • Subject who has undergone any nasal surgery within 6 months before screening. • Subject with unstable NPS during the run-in period, i.e., altered score at Day 1 when compared to the screening NPS (assessed by the investigator). • Subjects with conditions / concomitant diseases making them non-evaluable for the primary efficacy endpoint such as: – Antrochoanal polyps. – Nasal septal deviation that occludes at least one nostril. – Acute sinusitis, nasal infection or upper respiratory infection at screening or in the 2 weeks before screening. – Ongoing rhinitis medicamentosa. – Churg-Strauss syndrome, Young's syndrome, Kartagener's syndrome or dyskinetic ciliary syndromes, cystic fibrosis. – Signs or a CT scan suggestive of allergic fungal rhinosinusitis. • Subjects with co-morbid asthma are excluded if: – Forced expiratory volume in one second ≤ 60% of predicted normal. OR – An exacerbation requiring systemic (oral and/or parenteral) steroid treatment or hospitalization (> 24 h) for treatment of asthma has occurred within 3 months prior to screening. OR – They are on a dose higher than 1000 µg fluticasone or the equivalent of inhaled corticosteroids (ICS).

	• Subject with short life expectancy (less than 6 months). • Concomitant severe diseases (e.g., active and inactive pulmonary tuberculosis, diabetes mellitus, etc.). • Subject with active autoimmune disease (e.g., Hashimoto's thyroiditis, Graves' disease, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, psoriasis vulgaris, rheumatoid arthritis). • Subject with liver injury related criteria: – Underlying hepatobiliary disease OR – Alanine aminotransferase > 3 × upper limit of normal (ULN) OR – Bilirubin > 2 × ULN • Subject with evidence of acute or chronic infection: Visit 1 or Visit 2 oral temperature > 38 °C, a chronic persistent or recurring infection requiring active treatment with antibiotics, antivirals or antifungals within 4 weeks prior to the screening visit, or other frequent recurrent infections as per investigator judgment. • Subject with any contraindications or warning/precaution of use related to mometasone furoate nasal spray (MFNS) as described in the Summary of Product Characteristics.
CONCOMITANT MEDICATIONS	**Mandatory from screening up to End-of-Study (EOS)** • MFNS from screening to EOS as standard background therapy. • Mandatory therapy includes any treatments required for contraception purposes in women of childbearing potential. **Prohibited from screening up to EOS** • Use of intranasal medication that would interfere with the symptoms of diseases (antihistamines, atropine, ipratropium bromide, cromolyn), except normal saline solution.

	• INCS drops. • Systemic corticosteroids. • Decongestants (topical or systemic) are not allowed, except before endoscopy. • Long-term use of systemic antibiotics (for 2 weeks or more). • [redacted] • [redacted] • [redacted] • [redacted] • CYP2C9 inhibitors[#] (e.g., fluconazole) and inducers (e.g., rifampin). • Lipoxygenase inhibitors and leukotriene antagonists/ modifiers, unless subject is on continuous leukotriene antagonist/modifier treatment for at least 30 days prior to screening. • Any immunosuppressive treatment including but not limited to methotrexate, cyclosporine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine, cyclophosphamide. • Anti-immunoglobulin E therapy. • Monoclonal antibody therapy. • Acetylsalicylic acid or nonsteroidal anti-inflammatory drugs (NSAIDs) in subjects with hypersensitivity to acetylsalicylic acid or NSAIDs. [#] prohibited from Day 1 to EOS. **Permitted** • Nasal normal saline. • Topical decongestants, e.g., oxymetazoline (to reduce the swelling and widen the path for the endoscope) and topical

	anesthetics, e.g., lidocaine, are only allowed before endoscopy. • Short-term use of antibiotics (< 2 weeks). • For subjects with asthma: – Short- and long-acting beta-agonists. – Methylxanthines (e.g., theophylline and aminophyllines). – ICS on a stable daily dose ≤ 1000 µg fluticasone (or the equivalent dose of another ICS) only for subjects that were on a stable dose for ≥ 30 days prior to screening). • Leukotriene antagonists/modifiers if subject is on continuous treatment for at least 30 days prior to screening. • Initiation of allergen immunotherapy (allergen immunotherapy in place for ≥ 3 months prior to Visit 1 is permitted). • Medications needed for the treatment of adverse events (AEs) and which are not prohibited. • Hormonal contraceptives.
STUDY PERIODS	The clinical trial will be divided into 3 periods: **Screening and run-in period:** (4 weeks ± 2 days) This period will start with the screening visit (Visit 1) and will end on Day 1 (Visit 2) just before the first ACT-774312 administration. At screening, subjects must have been on a stable regimen of INCS for at least 8 weeks. If a subject is using an INCS product different from MFNS prior to the screening visit, the investigator must switch the patient to MFNS at screening. At Visit 1, all subjects will enter a run-in period of 4 weeks on MFNS of 2 actuations (50 µg/actuation) in each nostril twice daily (b.i.d.), total daily dose of 400 µg, unless they are

	intolerant to b.i.d. INCS in which case they may use a lower dose regimen, i.e., once daily (o.d.). **Treatment period:** (ACT-774312/placebo for 12 weeks) This period will start on Day 1 after the first administration of ACT-774312 and will consist of 4 visits: Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 8), and Visit 6 (Week 12). Provided that the NPS does not change during the run-in period, subjects will be randomized to one of the following treatments: • ACT-774312 400 mg b.i.d. for 12 weeks. • Placebo b.i.d. for 12 weeks. During the double-blind randomized treatment: All subjects will continue MFNS (200 µg) either b.i.d. or o.d. over the treatment period with the investigational medicinal product (IMP). **Post-treatment period** This period will start after Visit 6 (Week 12) and will end at Visit 7 (Week 16). After completing 12 weeks of study treatment, subjects will be instructed to: • Continue on MFNS stable dose. • Contact the investigator if the symptoms worsen and require medical attention. • Report any AEs / serious AEs (SAEs). The end of the post-treatment period constitutes the EOS. Subjects who discontinue prematurely from study treatment will be recommended to continue with the study assessments up to EOS or at least perform EOS visit 38 days (+2 days) after study treatment discontinuation.

STUDY TREATMENT	**ACT-774312** ACT-774312 will be administered orally as 400 mg b.i.d. for 12 weeks. Subjects will receive 2 × 200 mg capsules in the morning and evening, with or without food. **Placebo** Matching ACT-774312 placebo capsules. **Non-IMP (standard background therapy)** MFNS ([redacted] 50 µg/actuation nasal spray, suspension. Dosing regimen: 2 actuations (50 µg/actuation) in each nostril b.i.d. (or o.d. if b.i.d. is not tolerated).
EFFICACY ENDPOINTS	Baseline: Defined as the last value measured prior to first intake of study treatment. **Primary endpoint** • Change from baseline to Week 12 in NPS as measured by nasal endoscopy assessed centrally. **Secondary endpoints** • Change from baseline to Week 12 in sinus opacifications as assessed by CT scan using the Zinreich-modified Lund-Mackay score assessed centrally. • Change from baseline to Week 12 in 3D volumetric computerized values. • Change from baseline to Weeks 2, 4, 8, 12, and EOS in University of Pennsylvania Smell Identification Test. • Change from baseline to Weeks 2, 4, 8, 12, and EOS in the sum of visual analog scale symptom scores for nasal obstruction, nasal discharge, mucus in the throat, loss of smell, and facial pain. • Change from baseline to Weeks 2, 4, 8, 12, and EOS in Physician Global Assessment score. • Change from baseline to Weeks 2, 4, 8, 12, and EOS in SNOT-22. • Patient global impression of change in disease severity at Weeks 2, 4, 8, 12, and EOS.

TOLERABILITY / SAFETY ENDPOINTS	Baseline: Defined as the last value measured prior to first intake of study treatment. • Change from baseline to Weeks 2, 4, 8, 12, and EOS in vital sign (supine) measurements. • Change from baseline to EOS in body weight measurement. • Change from baseline to End-of-Treatment (EOT) in ECG variable measurements: heart rate, and the intervals: PQ/PR, QRS, QT, RR, QT interval corrected with Bazett's formula, and QT interval corrected with Fridericia's formula. • Treatment-emergent[#] ECG abnormalities at EOT. • Change from baseline to Weeks 2, 4, 8, 12, and EOS in clinical laboratory tests. • Treatment-emergent AEs up to EOS. • Treatment-emergent SAEs up to EOS. • AEs leading to premature discontinuation of study treatment up to EOT. • Treatment discontinuation due to systemic corticosteroids administration for NP and/or surgery for nasal polyps before Week 12. [#] Treatment-emergent is defined from first study treatment administration up to EOS.
PHARMACOKINETIC/ PHARMACODYNAMIC ENDPOINTS	**Pharmacokinetics** The plasma PK parameters of ACT-774312 at Week 2 will be derived by non-compartmental analysis of the plasma concentration-time profile. Maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) values are assumed to be log-normally distributed. **Pharmacokinetic endpoints** • Trough ACT-774312 concentration at Weeks 2, 4, 8, and 12.

	• AUC from zero to 4 h (AUC_{0-4}; during a dosing interval at steady state) at Week 2. • AUC during a dosing interval (AUC_{τ}; during a dosing interval at steady state) at Week 2 by extrapolation of the 12 h trough concentration based on the pre-dose trough concentration. • C_{max} at Week 2. • The time to reach C_{max} (t_{max}) at Week 2. **Pharmacodynamic endpoints** Baseline: Defined as the value measured prior to first intake of study treatment. [redacted]
STATISTICAL METHODOLOGY	**Sample size** No formal sample size calculation was performed. Twenty-four subjects (16 in the ACT-774312 group and 8 in the placebo group) provide a certain precision to estimate the treatment difference in the mean change from baseline in NPS. Assuming a within-group standard deviation of 2 points [Bachert 2016b], the standard error of the estimated treatment difference (expected to be around 1.5 points) will be approximately 0.9 points. **Randomization** Subjects will be randomized using a 2:1 randomization ratio to ACT-774312 400 mg b.i.d. for 12 weeks or placebo b.i.d. for 12 weeks. The 2:1 randomization ratio was chosen in order to obtain more information on ACT-774312. **Analysis sets** Four different analysis sets are defined.

	All-treated set (ATS): This analysis set includes all randomized subjects who received at least one dose study treatment. Per-protocol set (PPS): This analysis set includes all randomized subjects who completed the treatment up to Week 12 without protocol deviations that may affect the evaluation the primary endpoints (to be defined the statistical analysis plan [SAP]). The target number of subjects in the PPS is 21. If this number is unlikely to be reached, the number of subjects to be randomized may be increased over 24. Pharmacokinetic set: This analysis set comprises all subjects from the ATS who completed treatment with ACT-774312 at least up to Week 2 without protocol deviations that may affect the evaluation of the PK endpoints. Pharmacodynamic set: This analysis set comprises all subjects from the ATS who completed treatment with ACT-774312 or placebo at least up to Week 2 without protocol deviations that may affect the evaluation of the PD endpoints. **Analysis of the primary endpoint** The primary analysis will be conducted on the PPS. All NPS values observed between baseline and Week 12 will be included in this analysis. Changes from baseline to post-baseline visits in NPS will be analyzed using a mixed model for repeated measurements (MMRM) with factors for treatment group, study site, visit, treatment by visit interaction and covariates for baseline NPS, and the interaction between baseline NPS and visit. An unstructured covariance matrix will be used to account for the correlation between repeated measurements from the same subject.

	Estimation of the treatment difference for the primary endpoint, change from baseline to Week 12 in NPS, will be based on the mixed model. *Missing data handling in the primary analysis* All subjects in the PPS are expected to have a Week 12 NPS. Any intermediate missing data will be handled by the mixed model. Missing values will not be imputed. *Sensitivity analyses* A sensitivity analysis will be conducted on the ATS using the same mixed model as for the primary analysis. In this approach missing values will not be imputed, but will be handled by the model assuming that the data are missing at random. Additionally, an analysis of covariance (ANCOVA) will be performed for the change from baseline to Week 12 in NPS with missing data imputed using last observation carried forward. **Analysis of secondary endpoints** Change from baseline to Week 12 in Zinreich-modified Lund-Mackay score will be analyzed using an ANCOVA model with a factor for treatment group and a covariate for the baseline score. Other continuous endpoints will be summarized by time point and treatment group using descriptive statistics. Some secondary endpoints (to be defined in the SAP) will also be analyzed using the same MMRM as for the primary endpoint. **Tolerability and safety analyses** Safety analyses will be conducted on the ATS. The treatment-emergent period for the safety assessments is defined as the time from the first administration of study treatment to Visit 7 (Week 16). Tolerability and safety data will be summarized by treatment group using descriptive statistics. **Analysis of PK and PD endpoints** The PK set and PD set will be used for analysis of the PK and PD endpoints, respectively.

	PK parameters will be derived using non-compartmental methods. PK and PD endpoints will be analyzed descriptively.

Table 1 Visit and assessment schedule

	Screening/Run-in	Treatment				EOT	Post-Treatment EOS
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Week (Days)	**–4 (Day –30 to Day –26)**	**0 (Day 1)**	**2 (Day 12 to Day 16)**	**4 (Day 26 to Day 30)**	**8 (Day 54 to Day 58)**	**12 (Day 81 to Day 84)**	**16 (Day 111 to Day 116)**
Informed consent	X						
Medical/Surgical history	X						
Previous/Concomitant medications	X[1]	X[4]	X	X	X	X	X
Physical examination	X	X[4]				X	X
cyp2c9 genotyping	X						
ACQ[8] and AQLQ[8]	X						
IgE titer	X						
Serum pregnancy test[2]	X	X[4, 7]	X[7]	X[7]	X[7]	X[7]	X[7]
Body weight and height[3]	X						X
Virus serology	X						
Spirometry[8]	X						
Vital signs (BP and pulse rate)	X	X[4]	X	X	X	X	X
12-lead ECG		X[4]				X	
Hematology	X	X[4]	X	X	X	X	X
Clinical chemistry	X	X[4]	X	X	X	X	X
Urinalysis (dipstick)	X	X[4]	X	X	X	X	X
MFNS[5]	←	—	—	—	—	—	→
Study treatment[5]		←	—	—	—	→	
Nasal endoscopy	X	X[4]		X	X	X	X
CT scan		X[4]				X	
VAS score		X[4]	X	X	X	X	X
UPSIT		X[4]	X	X	X	X	X
SNOT-22	X	X[4]	X	X	X	X	X

Patient global impression of change in disease severity			X	X	X	X	X
PGA of disease severity and change in disease severity		X[9]	X	X	X	X	X
Blood PK trough sampling			X[4, 6]	X[4]	X[4]	X[4]	
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	←	←	←	←	←	←	→
Serious adverse events	←	←	←	←	←	←	→

AEs and SAEs will be followed up until EOS. After EOS, SAEs are only reported if this is felt to be appropriate by the investigator. AEs and SAEs will be considered treatment-emergent up to EOS. In the event of premature discontinuation, EOS will take place 30 days (+2 days) after last dosing

AE = adverse event; ACQ = Asthma Control Questionnaire; AQLQ = Asthma Quality of Life Questionnaire with Standardised Activities; b.i.d. = twice daily; BP = blood pressure; CT = computed tomography; ECG = electrocardiogram; EOT = End-of-Treatment; EOS = End-of-Study; IgE = immunoglobulin E; MFNS = mometasone furoate nasal spray; o.d. = once daily; PD = pharmacodynamic; PGA = Physician Global Assessment; PK = pharmacokinetic; SAE = serious adverse event; SNOT-22 = Sino-Nasal Outcome Test; UPSIT = University of Pennsylvania Smell Identification Test; VAS = visual analog scale.

[1] Previous medications. [2] Women of childbearing potential only at screening. [3] Only at screening. [4] Prior to study treatment administration. [5] b.i.d. administration or o.d. administration if b.i.d. is not tolerated. [6] PK profile sample collection. [7] Urine pregnancy test. [8] Only for asthmatic subjects based on medical history. [9] Only PGA of disease severity.

1 BACKGROUND AND RATIONALE

1.1 Indication

Chronic rhinosinusitis (CRS) is defined as an inflammation of the nose and paranasal sinuses, characterized by two or more symptoms, one of which should be nasal blockage or nasal discharge and/or facial pain or pressure and/or reduction or loss of smell [Fokkens 2012]. The presence (CRSwNP) or absence (CRSsNP) of nasal polyps based on results from endoscopy and computed tomography (CT) is a critical item to phenotype CRS. Additional subtypes can, however, be identified based on underlying conditions, such as allergic fungal rhinosinusitis, CRS associated with acetylsalicylic acid-exacerbated respiratory disease, CRS in patients with cystic fibrosis, primary ciliary dyskinesia, systemic diseases, or immune deficiency (all present in CRSwNP or CRSsNP) [Bachert 2015]. Additionally, subjects might have comorbidities, such as inhalant allergies and asthma (30% of patients with CRSwNP).

Nasal polyposis (NP) is a clinical condition characterized by the presence of multiple polyps in the upper nasal cavity, originating from the ostiomeatal complex (OMC). Up to 4% of the general population is estimated to be affected by nasal polyps [Lange 2013]. Symptoms experienced by patients with NP include nasal blockage, loss of smell, rhinorrhea, and symptoms derived from lower airway involvement [Alobid 2005]. Nasal polyps often have a deleterious effect on many aspects of quality of life (QoL), including physical health, general health, social functioning, sleep, and mental health [Erskine 2016, Hoehle 2016, Rudmik 2011].

Recent efforts to better characterize the pathophysiology of CRS has led to a refined classification by endotype [Bachert 2016a, Avdeeva 2018]. The latter can be differentiated on cells involved, such as by the abundance of eosinophils or neutrophils, on T helper cell populations or levels of immunoglobulin E (IgE) or cytokines, including interleukin (IL)-4, IL-5, or IL-13.

As an example, mucosal eosinophilia exhibits significant geographic and ethnic differences. In Europe and in the US, the most prevalent endotype in CRSwNP presents a type 2 inflammatory response [Mygind 2000] and is characterized by high prevalence of eosinophils, mast cells, with elevated type 2 cytokines (IL-4, IL-5, IL-9, IL-13, IL-25, and IL-33), and Th2 cells. In contrast, in East Asia, this eosinophilic endotype constitutes less than half of the CRSwNP cases [Cao 2009].

Current treatment options for patients with NP are not based on endotypes, and are limited to intranasal and oral corticosteroids, long-term antibiotics and surgery [Sharma 2014, Van Zele 2010, Fokkens 2012]. Intranasal corticosteroids (INCS) are usually the initial treatment for nasal polyps, with good outcomes for patients with mild NP [Kalish 2012]. The use of systemic corticosteroids is reserved for more severe cases but due to the side

effects, long-term high-dose treatment is discouraged [Fokkens 2012]. Surgery should only be considered for patients without improvement after maximal medical treatment, and does not prevent recurrence [Dalziel 2006].

This medical need led to investigation of new therapeutic options. Several proof-of-concept studies have been performed with monoclonal antibodies such as omalizumab (anti-IgE) [Gevaert 2013], reslizumab and mepolizumab (anti-IL-5) [Gevaert 2011, Bachert 2017], and dupilumab (anti-IL-4 receptor α) [Bachert 2016b]. These studies have all shown improvement of the symptoms combined with significant reduction of polyp and CT scores.

An alternative to these monoclonal antibodies that are to be administered parenterally could be the development of small molecules targeting the same pathways. An antagonist of the human chemoattractant receptor-homologous molecule expressed on T helper 2 cell (Th-2) cells (CRTH2) could be one of the possible options. CRTH2 is expressed on the surface of blood-borne eosinophils, basophils, mast cells, group 2 innate lymphoid cells (ILC2), and Th-2 cells. CRTH2 binds prostaglandin D2 (PGD2) to induce eosinophilic Th-2 inflammation, including ILC2 chemotaxis [Chang 2014, Townley 2012, Xue 2014]. The activation of CRTH2 by PGD2 induces the production of type 2 cytokines, IL-4, IL-5, and IL-13 in ILC2. Moreover, mast cells are the most important source of PGD2 in NP.

1.2 ACT-774312

ACT-774312 is a potent, selective, orally (p.o.) available, [redacted] antagonist of CRTH2. In previous proof-of-concept studies, antagonism of CRTH2 has shown some beneficial effects in asthma and allergic rhinitis [Diamant 2014, Gonem 2016, Erpenbeck 2016, Ratner 2017]. As the disease pathology of NP is also driven by type-2 inflammation, it may be amenable to treatment with CRTH2 antagonists.

1.2.1 Nonclinical data

1.2.1.1 Pharmacology

[redacted] This demonstrates that the inhibition of CRTH2 receptor by ACT-774312 interferes with key signaling events of cells involved in the allergic cascade.

The core battery of Good Laboratory Practice (GLP)-compliant studies assessing the cardiovascular, respiratory, and central nervous systems (CNS) was completed according to the ICH S7 guideline.

In the *in vitro* human ether-à-go-go-related gene (hERG) assay, no changes in the K^+ current were measured up to the highest concentration of ACT-774312 tested [redacted]

[redacted]

[redacted]

No effect on the cardiovascular system was observed in the Phase 1 single- and multiple-ascending dose (SAD and MAD, respectively) study.

BP and HR will be routinely monitored in this clinical study.

1.2.1.2 Pharmacokinetics and metabolism

The pharmacokinetic (PK) profile of ACT-774312 was investigated in rats and dogs after single and multiple oral dosing and after single intravenous (i.v.) dosing. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.2.1.3 Toxicology

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

For human safety margin calculation, the mean exposures of male and female animals at the NOAELs were used.

1.2.2 Effects in humans

The human clinical experience with ACT-774312 consists of a three-part study in healthy subjects. The tolerability, safety, PK (including food interaction), and pharmacodynamics (PD) of ACT-774312 were evaluated in the SAD and MAD study parts, respectively. The PK of a single dose of ACT-774312 were also evaluated in a healthy CYP2C9 poor metabolizer. A total of 89 subjects were included in the study, 67 of whom were treated with ACT-774312.

The SAD part was a double-blind, randomized study in which subjects received 7 dose levels of ACT-774312 (1, 3, 10, 30, 100, 300, or 1000 mg) or placebo in the fasted condition. Each dose level was studied in a different group of 8 healthy subjects (6 on active drug and 2 on placebo). The effect of food on the PK of the compound was evaluated in the 100 mg group.

The MAD part was a double-blind, randomized study in which subjects received 4 dose levels of ACT-774312 (30 mg o.d., 50 mg twice daily [b.i.d.], 150 mg b.i.d., and 500 mg b.i.d. for 4 days). Each dose level was investigated in a different group of 8 subjects (6 on active drug and 2 on placebo).

The results showed that ACT-774312 was quickly absorbed (median time to reach maximum plasma concentration [t_{max}] 1–2 h following single doses in the SAD and following multiple doses in the MAD part of the study). The terminal elimination half-life was between 10.7 h and 14.0 h in the SAD and between 14.8 h and 17.0 h in the MAD part of the study. ACT-774312 exposure (area under the plasma concentration-time curve [AUC] and maximum observed plasma concentration [C_{max}]) increased in a dose-proportional manner up to 1000 mg and 500 mg b.i.d. in the SAD and MAD parts of the study, respectively.

After 100 mg single-dose administration and 500 mg b.i.d. administration for 4 days, the mean fraction of ACT-774312 recovered unchanged in urine was 27 and 19%, respectively.

The rate and extent of ACT-774312 absorption were decreased (exposure based on AUC from time zero to time t [AUC_{0-t}] decreased by around 18%) without affecting the trough

concentration (12 h post-dose) when ACT-774312 was given concomitantly with a high-fat, high-calorie breakfast. As the goal is to maintain CRTH2 blockade over the full dosing interval, ACT-774312 trough concentration is a critical parameter. ACT-774312 can therefore be administered with or without food.

ACT-774312 fully blocked CRTH2 at the surface of eosinophils for at least 9 h post-dose at 50 mg b.i.d. The E_{max} model indicated that ACT-774312 was able to maintain 90% of CRTH2 blockade over the full dosing interval in 80% of healthy subjects at a dose of 110 mg b.i.d.

Neither severe nor serious adverse events (SAEs) were reported. The most frequent adverse events (AEs) observed following multiple-dose intake of ACT-774312 were headache and dizziness. No clinically relevant effects on vital signs, laboratory variables, or 12-lead ECG were observed.

More detailed information can be found in the Investigator's Brochure (IB) [ACT-774312 IB].

1.3 Study rationale

NP is a Th-2-driven inflammatory process in which eosinophils are the predominant inflammatory cells found in the sinuses and nasal polyps. ACT-774312 is an antagonist of CRTH2 which is expressed on the surface of blood-borne cells that play a central role in allergy and type-2 inflammation: eosinophils, basophils, mast cells, ILC2, and Th-2 cells. Therefore, ACT-774312 might reduce the inflammatory process involved in NP.

1.3.1 Medical and regulatory background

This study is a proof-of-concept Phase 2 study designed to assess the effects of ACT-774312 on bilateral NP. In addition, tolerability, safety, PK, and PD of ACT-774312 in this population will be investigated.

Risk-benefit assessment

In Europe and in the US, the most prevalent endotype in CRSwNP presents a type 2 inflammatory response [Mygind 2000] and is characterized by high prevalence of eosinophils, mast cells, and Th-2 cells, with elevated type 2 cytokines (IL-4, IL-5, IL-9, IL-13, IL-25, and IL-33), in NP. Recent clinical studies with monoclonal antibodies against IL-5 (reslizumab and mepolizumab [Gevaert 2011, Bachert 2017]) or against IL-4 receptor α (dupilumab [Bachert 2016b]) have shown improvement of CRSwNP symptoms combined with significant reduction of polyp and computed tomography scores. Therefore, it is expected that ACT-774312, by targeting the type 2 inflammatory pathway like the monoclonal antibodies, has the potential to be effective in the treatment of patients suffering from diseases with a Th-2-associated allergic etiology, including NP.

ACT-774312 might reduce the inflammatory process involved in NP, and the proposed study aims to evaluate its efficacy in subjects with bilateral NP.

[redacted]

[redacted]

[redacted]

ACT-774312 is metabolized by CYP2C9. Due to the PK variability associated with CYP2C9 enzymes, CYP2C9 poor metabolizers will be excluded from the study and medications inhibiting or inducing CYP2C9 will be forbidden.

[redacted]

The human clinical experience with ACT-774312 consists of a three-part study (AC-084-101) conducted in healthy subjects. In this study, neither severe nor serious AEs were reported. The most frequent AEs observed following multiple-dose intake of ACT-774312 were headache and dizziness. No clinically relevant effects on vital signs,

laboratory variables, or 12-lead ECG were observed up to 1000 mg and 500 mg b.i.d. for 4 days in the SAD and MAD parts, respectively. Therefore, based on the limited information available from healthy subjects receiving ACT-774312 in this study, no safety concerns have been identified. Steady-state conditions are reached on the second day of b.i.d. treatment, therefore no additional safety concerns are expected with a 12-week treatment period compared to the 4-day treatment of the MAD. In addition, there are no specific safety concerns due to potential class effects based on the experience with other CRTH2 antagonists currently in late-stage development (mainly for the treatment of asthma and allergic rhinitis) [Norman 2014, Ratner 2017].

Due to the absence of data in patients with renal function impairment and hepatic function impairment, these will be excluded from the study. NP is not considered a life-threatening disease with irreversible morbidity if not treated immediately. It is hence considered acceptable and ethical to include a placebo-treated arm in a clinical study of subjects with NP [ICH 2000]. Subjects will be aware of the probability of being assigned to the placebo arm and of the therapeutic alternatives.

No particular safety concern related to the concomitant administration of ACT-774312 and mometasone furoate nasal spray (MFNS) is expected. Subjects with any contraindications or warning/precaution of use related to MFNS, as described in the Summary of Product Characteristics, will be excluded from the study [see [redacted]].

In conclusion, based on available data on ACT-774312, the expected risk-benefit assessment supports the conduct of the proposed ID-084A201 study in subjects with bilateral NP. Exclusion criteria, safety monitoring activities, and strict medical management will further ensure the safety of the subjects included in the trial.

1.3.2 Subject population

The study population of ID-084A201 will consist of subjects with a physician endoscopic diagnosis of bilateral NP (nasal polyp score [NPS] of ≥ 5, with a minimum of 2 in each nostril) despite having completed a prior INCS treatment for at least 8 weeks before screening, with at least the 6 last weeks on INCS spray. A bilateral score of 5 is the standard grade at which INCS is not able to reduce the NPS further.

In this study, ACT-774312 will be administered on top of MFNS, see the Summary of Product Characteristics [redacted].

Taking the high co-morbidity of NP with asthma, chronic sinusitis, and previous surgeries into account, these subjects will be allowed to enter the study unless they meet any of the exclusion criteria described in Section 3.2.3.

1.3.3 Study design

The study is a randomized, double-blind, 12-week treatment, placebo-controlled, exploratory proof-of-concept study evaluating the effect of 400 mg ACT-774312 administered b.i.d. for 12 weeks.

The clinical study consists of three periods:

- Run-in period on MFNS for 4 weeks.
- Treatment period (12 weeks).
- Post-treatment period (30 days).

The study is double-blind to avoid the bias incurred by an unblinded design on safety and efficacy assessments. Both the subject and investigator are blinded to the assigned study treatments. The study is placebo-controlled to provide a control group to which efficacy and safety can be compared.

A 2:1 randomization ratio was chosen to obtain more information on ACT-774312. This unequal randomization ratio is only 6% less precise than a 1:1 ratio (as measured by the standard error [SE] of the mean difference).

1.3.4 Dose selection

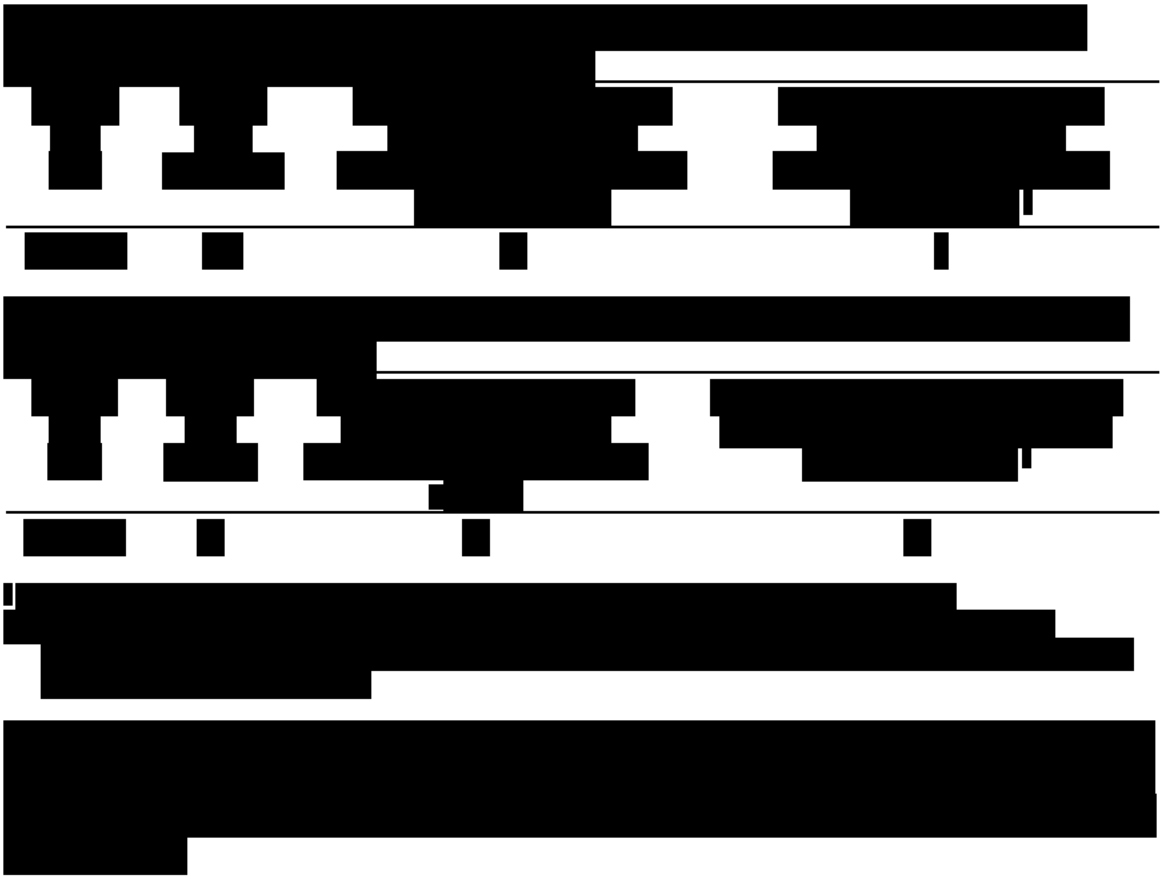
The selection of the dose is based on the tolerability, safety, and PK/PD data from the completed entry-into-man study. In that study, doses of ACT-774312 up to 1000 mg and 500 mg b.i.d. were administered in the SAD and MAD part, respectively.

The dose in this Phase 2 study will be an intermediate dose of those investigated in the MAD study, namely, a 400 mg b.i.d. dose of ACT-774312. This dose is anticipated to maintain a 90% blockade of CRTH2 over the full dosing interval. In the AC-084-101 study, PK/PD modeling predicted that 110 mg b.i.d. ACT-774312 would be able to fully block *ex vivo* the agonist effect of 300 nM of DK-PDG2 in whole blood.

1.3.5 Safety margin calculations, dose selection, and stopping criteria

The safety margins calculated by comparing the plasma exposure in animals at the NOAEL with the human exposure after multiple-dose administration of 500 mg are shown in Table 2. The dose of 500 mg b.i.d. of ACT-774312 is the closest dose for which actual PK data are available.

Table 2 Safety margins of ACT-774312



Laboratory variable and vital sign will be measured regularly in order to monitor the signals observed in animals.

Furthermore, a subject will be immediately and permanently discontinued from study treatment if either of the following occurs:

- severe thrombopenia (platelets count < 50,000/µL) while on investigational treatment.
- systolic blood pressure (SBP) < 80 mmHg and diastolic blood pressure (DBP) < 60 mmHg (confirmed by repeated BP measurement within 10 min) and associated with significant clinical symptoms while on investigational treatment.

If 2 or more subjects on investigational treatment experience a severe thrombopenia, which is considered to be related to study treatment, the study will be halted. If, following an internal safety review, it is deemed acceptable to restart the trial a substantial amendment with relevant data will be submitted to the competent authorities.

1.3.6 Comparator(s) and/or placebo

In this study, ACT-774312 will be compared to placebo. Both study treatments will be administered on top of standard background therapy: MFNS.

1.3.7 Treatment duration

The study treatment duration will be 12 weeks. This period has been proven sufficient to observe significant change in NPS [Gevaert 2011].

1.3.8 Primary endpoint

The primary endpoint is the change from baseline at Week 12 in bilateral NPS.

Bilateral NPS is an objective endpoint commonly used to evaluate the effect of medications or surgery in NP at the early stage of clinical development.

The secondary efficacy endpoints, including symptom evaluations required as co-primary endpoint in later stages of development, are measured to more comprehensively evaluate the efficacy of ACT-774312. This study will also explore the improvement of NP and associated sinus inflammation on a CT scan, and improvement in condition with specific and general medical questionnaires to obtain a better understanding of the impact of NP on the subjects' QoL.

These endpoints, together with the biomarkers analysis, will provide information on the therapeutic value of ACT-774312 to reduce the NPS and to improve symptoms in NP.

1.3.9 Statistical hypotheses and sample size

Statistical hypotheses will not formally be tested in the estimation study. Thus, no formal sample size calculation was performed. Twenty-four subjects (16 in the ACT-774312 group and 8 in the placebo group) provide a certain precision to estimate the treatment difference in the mean change from baseline in NPS [see Section 5.5].

2 STUDY OBJECTIVES

2.1 Primary objective

To evaluate the effect of ACT-774312 on bilateral NP.

This primary objective will be assessed by several endpoints including the change from baseline to Week 12 in NPS assessed by endoscopy (the primary endpoint) as well as secondary endpoints assessed by CT, University of Pennsylvania Smell Identification Test (UPSIT), Sino-Nasal Outcome Test (SNOT-22), Physician Global Assessment (PGA), visual analog scales (VAS), and patient global impression of change in disease severity.

2.2 Secondary objectives

- To evaluate the safety and tolerability of ACT-774312 during 12 weeks of treatment.

- To evaluate the PK of ACT-774312 in subjects with NP.
- To evaluate the PD responses to ACT-774312 based on Th-2 biomarkers.

3 INVESTIGATIONAL PLAN

3.1 Overall study design and plan

This is a randomized, double-blind, 12-week treatment, placebo-controlled, exploratory proof-of-concept study to evaluate the effect of ACT-774312 400 mg b.i.d. for 12 weeks in subjects with bilateral NP.

The study will be conducted at up to 4 sites in 4 countries.

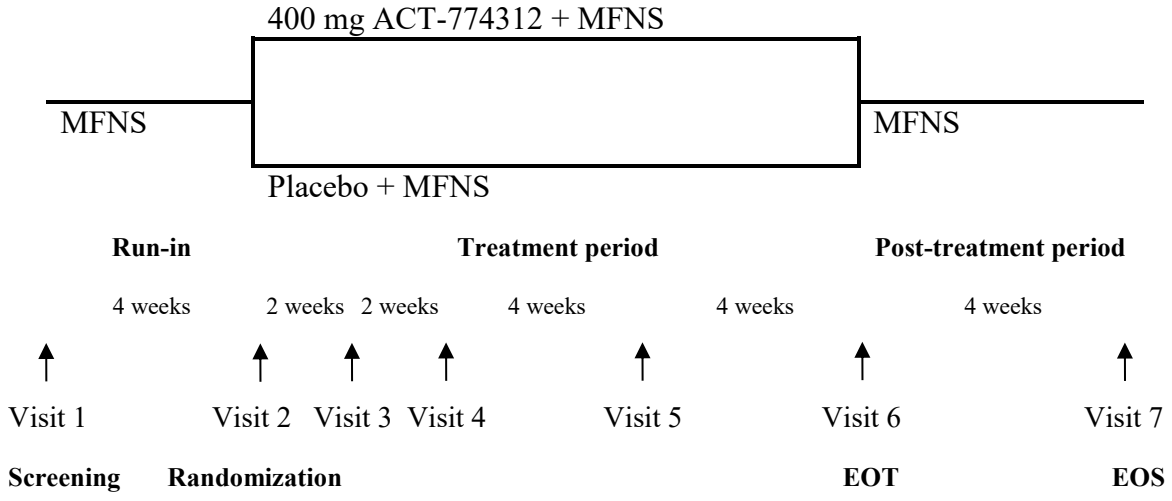
Approximately 24 adult subjects will be randomized in a 2:1 ratio to either ACT-774312 (approximately 16 subjects) or placebo (approximately 8 subjects).

The clinical study will consist of 3 periods:

- Run-in period: from screening to the end of run-in period (4 weeks).
- Treatment period: from randomization to Visit 6 (12 weeks).
- Post-treatment period: after Visit 6 to Visit 7 (30 days).

The total duration of the study participation for each patient is up to 20 weeks.

Figure 1 Study design



EOS = End-of-Study; EOT = End-of-Treatment; MFNS = mometasone furoate nasal spray.

3.1.1 Screening and run-in period

This period will start with the screening visit (Visit 1) and will end on Day 1 (Visit 2) just before the first ACT-774312/placebo administration.

At screening, subjects must have been on a stable regimen of INCS for at least 8 weeks.

If the subject is using an INCS product different from MFNS prior to the screening visit, the investigator must switch the subject to MFNS at screening.

At Visit 1, all subjects will enter a run-in period of 4 weeks on MFNS of 2 actuations (50 µg/actuation) in each nostril b.i.d., total daily dose of 400 µg, unless they are intolerant to b.i.d. INCS in which case they may use a lower dose regimen, i.e., o.d.

It is permitted to re-screen subjects once if the reason for non-eligibility was transient (e.g., insufficient washout period of a forbidden medication, etc.).

3.1.2 Treatment period

This period will start on Day 1 after the first administration of ACT-774312/placebo and will consist of 4 visits: Visit 3 (Week 2), Visit 4 (Week 4), Visit 5 (Week 8), and Visit 6 (Week 12).

Provided that the NPS does not change during the run-in period, subjects will be randomized to one of the following study treatments:

- ACT-774312 400 mg b.i.d. for 12 weeks.
- Placebo b.i.d. for 12 weeks.

During the double-blind randomized treatment period, all subjects will continue MFNS (200 µg) either b.i.d. or o.d. in addition to the investigational medicinal product (IMP).

The End-of-Treatment (EOT) will take place at Visit 6 (or earlier in the event of premature discontinuation) between Day 81 and Day 84 to ensure subjects will still be receiving the study treatment.

3.1.3 Post-treatment period

The post-treatment period will start after Visit 6 (Week 12) and will end at Visit 7 (Week 16).

After completing the 12 weeks of study treatment or after premature discontinuation, subjects will be instructed to:

- Continue their MFNS stable dose.
- Contact the investigator if the symptoms worsen and require medical attention.
- Report any AE/SAE.

The end of the post-treatment period constitutes the End-of-Study (EOS).

3.1.4 End-of-Study

The EOS examination will take place at Visit 7 (30 days +2 days after EOT (last study drug intake). At this visit, the subjects will undergo efficacy, tolerability, and safety assessments.

Subjects who discontinue prematurely from the study treatment will be recommended to continue with the study assessments up to EOS or at least perform the EOS visit 30 days (+2 days) after study treatment discontinuation.

3.1.5 End of trial

The end of the complete trial is defined as the last subject last visit.

3.2 Study population

3.2.1 Subject population

The subjects will have to present bilateral NP (NPS of at least 5 out of 8) assessed by a physician endoscopic diagnosis despite having completed a prior INCS treatment for at least 8 weeks, with at least the 6 last weeks on INCS spray.

Subjects with an NPS of at least 5 will be approached to participate in the study. However, randomization to the study treatment will require that the NPS does not change during the run-in period as per local endoscopic assessment.

3.2.2 Inclusion criteria

Eligible subjects must meet all of the following inclusion criteria:

- Signed informed consent in the local language prior to any study-mandated procedure.
- A minimum bilateral NPS of 5 out of a maximum of 8 for both nostrils (with at least a score of 2 for each nostril) despite completion of a prior INCS treatment for at least 8 weeks before screening, with at least the 6 last weeks on INCS spray.
- Presence of at least 2 of the following symptoms at screening:
  - nasal blockade/obstruction.
  - nasal discharge (anterior/posterior nasal drip).
  - reduction or loss of smell.
- Male and female subjects aged between 18 and 70 years (inclusive) at screening.
- Subjects with a body mass index (BMI) ≥ 18 kg/m^2.
- SBP 90−160 mmHg, DBP 50−100 mmHg, and pulse rate 45−100 bpm (inclusive), measured on the dominant arm, after 5 min in the supine position at screening.

- Women of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test pre-dose on Day 1. Women of childbearing potential must consistently and correctly use (from at least first dosing, during the entire study, and for at least 30 days after last study treatment intake) 1 highly effective method of contraception with a failure rate of < 1% per year, be sexually abstinent, or have a vasectomized partner. Hormonal contraceptives must have been initiated at least 1 month before first study treatment administration. Women not of childbearing potential are defined as post-menopausal (i.e., amenorrhea for at least 1 year without an alternative medical cause confirmed by FSH > 40 mIU/mL at screening), or surgically or naturally sterile.
- Ability to communicate well with the investigator in the local language, and to understand and comply with the requirements of the study.

3.2.3 Exclusion criteria

Subjects must not fulfill any of the following exclusion criteria:

- CYP2C9 poor metabolizer subject.
- Subject with severe renal function impairment ($\leq$ 29 mL/min/1.73 m^2) which is defined by estimated glomerular filtration rate estimated at screening using the Modification of Diet in Renal Disease formula.
- Subject with SNOT-22 < 20.
- Subject who has taken other investigational drugs or prohibited therapy for this study within 3 months before screening or 5 half-lives, whichever is longer, or participation in more than 3 investigational drug studies within 1 year prior to screening.
- Pregnant or lactating women. Women who intend to become pregnant during the study.
- Known allergic reactions or hypersensitivity to the study treatment or drugs of the same class, or any of the excipients.
- Subject with prohibited medication at screening without full wash-out period.
- Subject who has required oral corticosteroids (OCS) within 2 months before screening or is scheduled to receive OCS during the study period for another condition.
- Subject who has required INCS drops within 6 weeks before screening.
- Subject who was injected with long-lasting activity corticosteroids within 3 months before screening or is scheduled to receive these during the study period for another condition.
- Subject diagnosed with a parasitic infection.

- Subject ever diagnosed with cancer.
- Positive results from the HIV or hepatitis B or C serology at screening (except for vaccinated subject or subject with past and resolved hepatitis).
- Subject who has received specific allergen immunotherapy within the previous 3 months.
- Any circumstances or conditions, which, in the opinion of the investigator, may affect full participation in the study or compliance with the protocol.
- Subject considered as vulnerable (e.g., sponsor or site employee, investigator subordinate, subject incapable of giving consent, subject committed to an institution by way of official or judicial order).
- Legal incapacity or limited legal capacity at screening.
- Veins unsuitable for i.v. puncture on either arm (e.g., veins that are difficult to locate, access or puncture, veins with a tendency to rupture during or after puncture).
- Subject who has undergone any nasal surgery within 6 months before screening.
- Subject with unstable NPS during the run-in period, i.e., altered score at Day 1 when compared to the screening NPS (assessed locally by the investigator).
- Subjects with conditions / concomitant diseases making them non-evaluable for the primary efficacy endpoint such as:
  - Antrochoanal polyps.
  - Nasal septal deviation that occludes at least one nostril.
  - Acute sinusitis, nasal infection or upper respiratory infection at screening or in the 2 weeks before screening.
  - Ongoing rhinitis medicamentosa.
  - Churg-Strauss syndrome, Young's syndrome, Kartagener's syndrome or dyskinetic ciliary syndromes, cystic fibrosis.
  - Signs or a CT scan suggestive of allergic fungal rhinosinusitis.
- Subjects with co-morbid asthma are excluded if:
  - Forced expiratory volume in one second (FEV_1) ≤ 60% of predicted normal.

    OR
  - An exacerbation requiring systemic (oral and/or parenteral) steroid treatment or hospitalization (> 24 h) for treatment of asthma has occurred within 3 months prior to screening.

OR

– They are on a dose higher than 1000 µg fluticasone or the equivalent of inhaled corticosteroids (ICS) [see Appendix 1].

- Subject with short life expectancy (less than 6 months).
- Concomitant severe diseases (e.g., active and inactive pulmonary tuberculosis, diabetes mellitus, etc.).
- Subject with active autoimmune disease (e.g., Hashimoto's thyroiditis, Graves' disease, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, psoriasis vulgaris, rheumatoid arthritis).
- Subject with liver injury related criteria at Visit 1:
  – Underlying hepatobiliary disease
    OR
  – Alanine aminotransferase (ALT) > 3 × upper limit of normal (ULN)
    OR
  – Bilirubin > 2 × ULN
- Subject with evidence of acute or chronic infection: Visit 1 or Visit 2 oral temperature > 38 °C, a chronic persistent or recurring infection requiring active treatment with antibiotics, antivirals or antifungals within 4 weeks prior to the screening visit, or other frequent recurrent infections as per investigator judgment.
- Subject with any contraindications or warning/precaution of use related to MFNS as described in the Summary of Product Characteristics.

3.2.4 Concomitant medications

Use of concomitant medications must be recorded on the relevant forms of the electronic Case Report Form (eCRF).

3.2.4.1 Mandatory medications

- MFNS from screening to EOS as standard background therapy.
- Mandatory therapy includes any treatments required for contraception purposes in women of childbearing potential.

3.2.4.2 Allowed medications

- Nasal normal saline.
- Topical decongestants, e.g., oxymetazoline (to reduce the swelling and widen the path for the endoscope), and topical anesthetics, e.g., lidocaine, are only allowed before endoscopy.

- Short-term use of antibiotics (< 2 weeks).
- For subjects with asthma:
  - Short- and long-acting beta-agonists.
  - Methylxanthines (e.g., theophylline and aminophyllines).
  - ICS on a stable daily dose ≤ 1000 µg fluticasone (or the equivalent dose of another ICS) only for subjects that were on a stable dose for ≥ 30 days prior to screening).

  Fixed dose combinations of ICS / long-acting beta-agonists are also allowed provided that the above-mentioned restrictions for ICS are followed.

  Appendix 1 provides equipotent daily doses of ICS.
- Leukotriene antagonists/modifiers if subject is on continuous treatment for at least 30 days prior to screening.
- Initiation of allergen immunotherapy (allergen immunotherapy in place for ≥ 3 months prior to Visit 1 is permitted).
- Medications needed for the treatment of AEs (which are not prohibited).
- Hormonal contraceptives.

3.2.4.3 Forbidden medications

- Use of intranasal medication that would interfere with the symptoms of diseases (antihistamines, atropine, ipratropium bromide, cromolyn), except normal saline solution.
- INCS drops.
- Systemic corticosteroids.
- Decongestants (topical or systemic) are not allowed, except before endoscopy.
- Long-term use of systemic antibiotics (for 2 weeks or more).
- [redacted]
- CYP2C9 inhibitors[#] (e.g., fluconazole) and inducers (e.g., rifampin). The full list is provided [redacted].

- Lipoxygenase inhibitors and leukotriene antagonists/modifiers unless subject is on continuous leukotriene antagonist / modifier treatment for at least 30 days prior to screening.
- Any immunosupressive treatment including but not limited to methotrexate, cyclosporine, mycophenolate, tacrolimus, gold, penicillamine, sulfasalazine, hydroxychloroquine, azathioprine, cyclophosphamide.
- Anti-IgE therapy.
- Monoclonal antibody therapy.
- Acetylsalicylic acid or nonsteroidal anti-inflammatory drugs (NSAIDs) in subjects with hypersensitivity to acetylsalicylic acid or NSAIDs.

[#] prohibited from Day 1 to EOS.

3.2.5 Dietary aspects, alcohol, smoking, physical activities

There are no restrictions in terms of dietary aspects, alcohol, smoking, or physical activities.

ACT-774312 can be administered with or without food. For Visit 3, Visit 4, Visit 5, and Visit 6, subjects should arrive fasted at site in the morning without having taken the study treatment to collect trough PK samples.

3.3 Study treatments

Subjects will take either ACT-774312 or matching placebo.

Subjects will be instructed to start taking the study treatment on the evening of the randomization visit (Visit 2). Thereafter, the subject should take each study treatment dose in the morning and evening irrespective of food intake with approximately 12 hours between dosings. It is preferable that the study treatment is taken each day (morning and evening) at approximately the same time and at the same time as the standard background therapy (non-IMP: MFNS [redacted] 50 µg/actuation nasal spray, suspension; dosing regimen: 2 actuations [50 µg/actuation] in each nostril b.i.d. or o.d. if b.i.d. is not tolerated).

Subjects will be instructed not to take study treatment in the morning of study visit days. On the day of the study visits, study treatment must be administered only after completion of the pre-dose assessments as indicated in Table 1.

If a dose is missed, it should be taken as soon as possible. However, the missed dose should be skipped if it is almost time for the next dose. To ensure compliance, the study personnel must remind subjects at each visit of the study treatment intake requirements. The reminders must be documented in the hospital chart.

Study treatment must be discontinued if one of the study-treatment stopping criteria is met [see Section 3.6.3].

3.3.1 Investigational treatment

ACT-774312 will be available for clinical study use as hard gelatin capsules containing 200 mg of ACT-774312 and inactive excipients [redacted]

ACT-774312 will be administered p.o. as 400 mg b.i.d. for 12 weeks. Subjects will receive 2 × 200 mg capsules in the morning and evening with or without food.

The batch number of the study treatment and the retest date will be given on the certificates of analysis.

3.3.2 Placebo

Matching placebo capsules will contain the same inactive excipients [redacted] but without ACT-774312.

The batch number of the study treatment and the retest date will be given on the certificate of analysis.

3.4 Packaging, labeling, and preparation

Idorsia Pharmaceuticals Ltd, Allschwil, Switzerland will supply ACT-774312 and matching placebo. The study treatments will be packed and dispatched in bottles.

Study treatments will be provided as capsules (36 capsules per bottle) and supplied with double-blind packaging. [redacted].

3.4.1 Labeling

The labeling complies with the applicable laws and regulations of the country in which the study is conducted.

3.4.2 Preparation

No study treatment preparation is needed as it is supplied as ready-to-use capsules.

3.5 Randomization, treatment assignment, replacement, blinding, study treatment administration, storage, and dosing

3.5.1 Randomization code

The randomization code (including code-break envelopes) will be provided by an independent Contract Research Organization (CRO), [redacted].

The randomization code will be generated using SAS® software Version 9.4 or newer. No stratification factors will be employed in the randomization.

The randomization list (including code-break envelopes) must be provided to Idorsia Pharmaceutical Development Department and the study site prior to the IMP shipment release (for more details on blinding/unblinding, see Sections 3.5.4 and 3.5.5).

The randomization code must be kept strictly confidential and must be accessible only to authorized persons who are not involved in the conduct and analysis of the study, until the time of unblinding. A sealed randomization code is to be kept by Idorsia Pharmaceutical Development Department in a safe cabinet.

If a suspected unexpected serious adverse reaction (SUSAR) occurs for a subject participating in the study, Idorsia Global Drug Safety will request the unblinding of the study treatment assignment. Unblinded SUSAR information will be provided to Idorsia Global Drug Safety, respective health authorities, and Independent Ethics Committee / Institutional Review Board (IEC/IRB) only. SUSARs will be reported to investigators in an unblinded fashion by Idorsia (for more details on blinding/unblinding, see Sections 3.5.4 and 3.5.5).

The randomization code will be released to the bioanalytical laboratory (Idorsia Pharmaceuticals Ltd, Preclinical Pharmacokinetics and Metabolism, Allschwil, Switzerland) in accordance with internal procedures. Provisions will be in place to maintain the blinding of sponsor personnel.

At least 24 subjects will be randomized in a 2:1 ratio as follows:

- 16 subjects will receive ACT-774312 400 mg b.i.d.
- 8 subjects will receive the matching placebo.

3.5.2 Treatment assignment

At the randomization visit (Visit 2), and after having verified that the subject meets all inclusion criteria and none of the exclusion criteria, the investigator/delegate will assign a three-digit number to the subjects in the order of their inclusion in the study before the following baseline assessments are performed:

- CT scan
- VAS score
- UPSIT
- SNOT-22
- Patient global impression of disease severity

- PGA of disease severity (PGA-DS)
- [redacted]

The assignment of number and code for subject identification is based on the obligation for anonymity.

Table 3 Subject and replacement numbers

Dose (mg)	Subject numbers	Replacement numbers
400 (2 capsules of 200 mg)	101 – 130	201 – 230

The unblinded pharmacist will receive the material list to distinguish the active bottles from placebo and will dispense the IMP bottles according to the randomization list.

3.5.3 Replacement policy

Subjects who replace discontinuing subjects who have taken at least the study treatment on Day 1 are to receive the number of this subject +100, e.g., Subject 206 will replace Subject 106, etc. The substitute subject will receive the treatment assigned to the withdrawn subject.

In the event of discontinuation before study treatment intake on Day 1, the substitute subject is to receive the same number as was foreseen for the subject he/she replaces.

Additional subjects may be randomized if it is unlikely that a Per-protocol set (PPS) of at least 21 subjects will be reached.

Subjects may withdraw from the study at any time. The reason(s) for premature discontinuation must be recorded in study source documents and the sponsor must be informed. If the reason for discontinuation is an abnormal result on a laboratory test, vital sign, ECG recording, or physical examination, this information will be recorded as an AE in the eCRF.

3.5.4 Blinding

This study is to be conducted in a double-blind fashion. The investigator and study staff, the subjects, the monitors, and the sponsor will remain blinded to study treatment until study closure (except the responsible pharmacist, his/her designee, the analytical laboratory and a second unblinded monitor exclusively performing the study treatment accountability visits). The investigational treatment and its matching placebo are indistinguishable.

The randomization code will be kept strictly confidential. It will only be accessible to authorized people who are not involved in the conduct and analysis of the study, until the

time of unblinding. Sealed randomization codes will be kept by the Idorsia Pharmaceutical Development Department in a safe cabinet.

The randomization code will be released to the bioanalytical laboratory (Idorsia Pharmaceuticals Ltd, Preclinical Pharmacokinetics and Metabolism, Allschwil, Switzerland) prior to database closure and unblinding, in accordance with internal procedures. Provisions will be in place to maintain the blinding of sponsor personnel.

3.5.5 Emergency procedure for unblinding

The investigator, study staff, and sponsor staff must remain blinded to the subject's study treatment assignment. The identity of the study treatment may be revealed only if the subject experiences a medical event, the management of which would require knowledge of the blinded treatment assignment. In this case, the investigator can receive the unblinded randomization code for study treatment allocation from the emergency code-break envelope. In these situations, the decision to unblind resides solely with the investigator. Whenever it is possible and if it does not interfere with (or does not delay) any decision in the best interest of the subject, the investigator is invited to discuss the intended code break with Idorsia.

The occurrence of any code break during the study must be clearly justified and explained by the investigator. In all cases, Idorsia must be informed as soon as possible before or after the code break. The circumstances leading to unblinding must be documented in the hospital charts and the Investigator Site File (ISF).

At each monitoring visit, the monitor must check the code-break envelopes. At the end of the study, the monitor must collect all code-break envelopes and code-break reports and return them to the sponsor for filing.

3.5.6 Study treatment administration

The subjects will receive sufficient study treatment to cover the following periods:

- From Day 1 (Visit 2) to Visit 4.
- Visit 4 to Visit 5.
- Visit 5 to Visit 6 (EOT).

Subjects will be instructed to store the study treatment at room temperature, protected from light and moisture. They will be asked to return all used, partially used, and unused study treatment bottles at each visit. Should the treatment bottle dispensed at a scheduled visit be lost or damaged, a replacement bottle can be requested.

The protocol-mandated study treatment dispensing procedures may not be altered without prior written approval from the sponsor. In exceptional circumstances (e.g., if the subject

lost the study treatment between two visits, or if the subject is unable to return to the site due to a medical emergency / hospitalization at another hospital), unscheduled dispensing and delivery of study treatment may occur outside of a scheduled visit. An accurate study treatment record of the date and amount of study treatment dispensed to each subject must be available at the site for inspection at any time.

The inventory of study treatment dispensed to and returned by the subject (i.e., study treatment accountability) must be performed by site personnel on the day of the visit and before dispensing further study treatment. The Study Treatment Dispensing and Administration Log(s) for ACT-774312 and placebo must be kept current by the investigator or his/her designee, and must contain as a minimum the following information:

- Subject number to whom the study treatment was dispensed.
- Initials and date of the person who dispensed the study treatment.
- Dispensed bottle ID number.
- Date dispensed / number of capsules dispensed (recorded in eCRF).
- Date returned / number of capsules returned (recorded in the eCRF).

All study treatment supplies, including partially used or empty bottles must be retained at the site until they are verified by the unblinded monitor.

If the subject omits to bring the remaining study treatment to a study visit, he/she must be instructed not to take any capsules from the remaining study treatment bottle and to return it at the next visit. At Visit 4 and Visit 5, study treatment will be taken from the newly dispensed bottles.

The Study Treatment Dispensing and Administration Log(s) will be collected upon completion of the study for archiving in the Trial Master File (TMF).

3.5.7 Storage and return of study treatment

The pharmacist is responsible for safe and proper handling and storage of the study treatment at the study site in an appropriate lockable room at room temperature (below 25 °C but not refrigerated). The study treatment should be protected from light. Only the pharmacist or his/her designee, who are otherwise not involved in the study, may handle the study treatment.

Upon receipt of the study treatment, the responsible pharmacist or his/her designee must inspect and count all study treatment for completeness. Subsequently, he/she must immediately return the enclosed acknowledgement of receipt form, duly completed and signed (the date of receipt must be noted).

The supplies and inventory must be available for inspection by the monitor. The Treatment Accountability Log(s) will be collected upon completion of the study for archiving in the TMF.

All unused investigational material (medication and packaging) must be returned to the sponsor on termination of the study after a study treatment accountability check by the monitor, listing the following:

- All administered capsules.
- All unused capsules.
- All capsules returned at the end of the study, and the date of return.

The pharmacist will be responsible for the inventory and accountability of all clinical supplies, exercising accepted pharmaceutical practices. An accurate, timely record of the clinical study supply must be maintained. Only after completion of the study (to avoid breaking the blind), will the supplies and the inventory be available for inspection by the designated representative(s) of Idorsia Pharmaceuticals Ltd, Allschwil, Switzerland, upon request. These records will, however, be made available to the unblinded monitor if needed.

Once the clinical study report has been finalized, the study treatment will be destroyed by the site if possible. If not, the IMP has to be sent back to Idorsia Pharmaceuticals Ltd, Allschwil, Switzerland, for destruction.

3.5.8 Study treatment dosing scheme

Table 4 Dosing scheme

Study period	Duration	Study treatments	Dose regimen	Standard background therapy (dose regimen)
Run-in	Day –30 to Day 1 4 weeks	–	–	MFNS (100 µg in each nostril b.i.d. or o.d.)
Treatment	Day 1 to EOT 12 weeks	Placebo or ACT-774312	400 mg b.i.d.	MFNS (100 µg in each nostril b.i.d. or o.d.)
Post treatment	EOT to EOS 30 days	–	–	MFNS (100 µg in each nostril b.i.d. or o.d.)

b.i.d. = twice daily; EOS = End-of-Study; EOT = End-of-Treatment; MFNS = mometasone furoate nasal spray; o.d. = once daily.

3.5.9 Study treatment up- and down-titration

Not applicable.

3.6 Study treatment discontinuation and study discontinuation

3.6.1 Study treatment dose adjustment

Study treatment dose adjustment is prohibited.

3.6.2 Study treatment interruption or discontinuation

The investigator must temporarily interrupt or permanently discontinue the study treatment if he or she believes continued administration of the study treatment to be contrary to the best interests of the subject. Interruptions of study treatment must be kept as short as possible.

The interruption or premature discontinuation of study treatment might be triggered by an AE, a diagnostic or therapeutic procedure, an abnormal assessment (e.g., laboratory abnormalities), or for administrative reasons – in particular, withdrawal of the subject's consent.

A subject has the right to prematurely discontinue study treatment at any time, without any justification, by withdrawing from study treatment only or by withdrawing from any further participation in the study (i.e., premature withdrawal from the study). Although a subject is not obliged to give his/her reason for prematurely withdrawing from the treatment or the study, it is recommended that the investigator makes a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

A subject who prematurely discontinues study treatment is not considered as withdrawn from the study and will be followed in the post-treatment period, provided that the subject's consent for this participation in the study has not been withdrawn.

A subject who prematurely discontinues study treatment and withdraws consent to participate in any further study assessments is considered as withdrawn from the study.

Subjects who die or are lost to follow-up are also considered as withdrawn from the study. Withdrawal from the study and follow-up medical care of subjects withdrawn from the study are described in Sections 3.6.5 and 3.6.6, respectively.

The date and the reason for study treatment interruption or premature discontinuation must be documented in the eCRF and the sponsor must be informed. If the reason for study treatment interruption or premature discontinuation from study treatment is an abnormal result on laboratory test, vital sign, ECG recording, or physical examination, this information must be recorded as an AE in the eCRF. The EOS assessments must be performed as planned 30 (+2 days) after the last study treatment administration. Study treatment may be temporarily interrupted in response to an AE (maximum 2 weeks of interruption), or other reasons (e.g., diagnostic or therapeutic procedure, study treatment forgotten).

If study treatment is interrupted by the subject for any reason, he/she must immediately inform the investigator.

All study treatment interruptions must be recorded in the eCRF.

If the number of subjects who prematurely discontinue study treatment is higher than expected, additional subjects may be randomized, see Section 3.5.3.

3.6.3 Study-specific criteria for interruption / premature discontinuation of study treatment

Pregnancy

If a subject becomes pregnant while on study treatment, study treatment must be permanently discontinued. The investigator/delegate must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

Vital signs

If a subject experiences SBP < 80 mmHg and DBP < 60 mmHg (confirmed by repeated BP measurement within 10 min) and associated with significant clinical symptoms while on investigational treatment, study treatment must be permanently discontinued.

Severe thrombopenia

If a subject experiences a severe thrombopenia (platelets count < 50,000/µL) while on investigational treatment, study treatment must be permanently discontinued.

3.6.4 Subject's follow-up after study treatment discontinuation

A subject who prematurely discontinues study treatment will be followed in the post-treatment period.

3.6.5 Study discontinuation

Subjects may voluntarily withdraw from the study without justification for any reason at any time. Subjects are considered withdrawn if they state an intention to withdraw further participation in all components of the study (i.e., withdrawal of consent), die, or are lost to follow-up. If a subject withdraws consent, no further data will be collected in the eCRF from the date of withdrawal onward. The investigator may withdraw a subject from the study (without regard to the subject's consent) if, on balance, he/she believes that continued participation in the study would be contrary to the best interests of the subject.

Withdrawal from the study may also result from a decision by the sponsor for any reason, including premature termination or suspension of the study.

Subjects are considered as lost to follow-up if all reasonable attempts by the investigator to communicate with the individual fail. The site must take preventive measures to avoid a

subject being lost to follow-up (e.g., document different ways of contact such as telephone number, home address, e-mail address, person to be contacted if the subject cannot be reached). If the subject cannot be reached, the site must make a reasonable effort to contact the subject and document all attempts and follow-up information on source. The following methods must be used: at least three telephone calls must be placed to the last available telephone number and one registered letter must be sent by post to the last available home address. Additional methods may be acceptable if they are compliant with local rules/regulations (e.g., site staff visit to the subject's home), respecting the subject's right to privacy. If the subject is still unreachable after all contact attempts listed above, he/she will be considered to be lost to follow-up.

The date and the reasons for premature discontinuation of the study must be documented in the eCRF, and the sponsor must be informed.

3.6.6 Subject follow-up after study discontinuation

If for whatever reason (except death or loss-to-follow-up) a subject is withdrawn from the study, the investigator should make best efforts to schedule a last appointment / telephone call to assess the safety and well-being of the subject, collect unused study treatment, and discuss follow-up medical care. Data obtained during this last appointment / telephone call will be recorded in the subjects' medical records but it will not be collected in the eCRF.

The investigator must provide follow-up medical care for all subjects who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

Subjects who discontinue the study may request that all biological samples drawn in the course of the study be destroyed.

3.6.7 Medical care of subjects after study completion / withdrawal from study

After the subject's study completion or premature withdrawal from the study, whichever applies, the investigator/delegate will explain to subjects what treatment(s) / medical care is necessary and available according to local regulations.

Female subjects of childbearing potential will be reminded of the contraception requirements as described in Section 3.2.2.

3.7 Study treatment exposure and compliance

Records of study treatment used, dosages administered, and intervals between visits are to be kept during the study. Study treatment accountability is to be performed on an ongoing basis by the study staff, and checked by the monitor during site visits and at completion of the study.

Study treatment compliance will be assessed based on the difference between the number of capsules provided to the subject and the number of capsules brought back at each

dispensing visit. In the event of loss of study treatment, the Subject Diary will be used to calculate compliance.

Study treatment compliance with the prescribed study treatment dose regimen will be confirmed by the sponsor based on Subject Diary data. On each day, subjects will be asked to enter in the Subject Diary the number of capsules taken in the morning and evening as well as the dosing time.

For each time interval between two visits, study treatment compliance will be calculated by the sponsor using the following formula:

Study treatment compliance = Number of capsules taken during the period / Total number of times the study treatment should have been taken during the period × 100

The prescribed dose corresponds to 400 mg ACT-774312 / placebo. The period is defined as the number of days between visit n (or date of first study treatment intake if randomization visit) and visit n+1 (or date of last study treatment intake if EOT visit).

The number of times the study treatment should have been taken at the prescribed dose regimen in each period is calculated as follows:

- (Number of days in the period – 1) × 2 + 1 for the first period and the last period as only 1 administration will take place on Day 1 and on EOT
- Number of days in the period × 2 for the period Visit 4 to Visit 5

Study treatment interruption(s) will be ignored when calculating study treatment compliance.

Between visits, study treatment compliance is expected to be at least 80%. The sponsor will inform the site staff and monitor about any compliance values below 80%. Compliance values below 80% without medical justification (e.g., AE) and not related to a Subject Diary completion issue will be considered as a protocol deviation, which will be reported as such to the sponsor by the monitor. In such cases, the investigator must discuss and clarify the reasons for non-compliance with the subject and take appropriate actions to avoid re-occurrence.

The measurement of plasma levels of ACT-774312 in the analytical phase will serve as a further check of compliance.

3.8 Study endpoints

3.8.1 Efficacy endpoints

Baseline: Defined as the last value measured prior to first intake of study treatment.

3.8.1.1 Primary efficacy endpoint

- Change from baseline to Week 12 in NPS as measured by nasal endoscopy assessed centrally.

3.8.1.2 Secondary efficacy endpoints

- Change from baseline to Week 12 in sinus opacifications as assessed by CT scan using the Zinreich-modified Lund Mackay score assessed centrally.
- Change from baseline to Week 12 in 3D volumetric computerized values.
- Change from baseline to Weeks 2, 4, 8, 12, and EOS in UPSIT.
- Change from baseline to Weeks 2, 4, 8, 12, and EOS in the sum of VAS symptom scores for nasal obstruction, nasal discharge, mucus in the throat, loss of smell, and facial pain.
- Change from baseline to Weeks 2, 4, 8, 12, and EOS in PGA score.
- Change from baseline to Weeks 2, 4, 8, 12, and EOS in SNOT-22.
- Patient global impression of change in disease severity at Weeks 2, 4, 8, 12, and EOS.

3.8.1.3 Exploratory efficacy endpoints

[redacted]

3.8.2 Safety and tolerability endpoints

Baseline: Defined as the last value measured prior to first intake of study treatment.

- Change from baseline to Weeks 2, 4, 8, 12, and EOS in vital sign (supine) measurements.
- Change from baseline to EOS in body weight measurement.
- Change from baseline to EOT in ECG variable measurements: HR, and the intervals: PQ/PR, QRS, QT, RR, QT interval corrected with Bazett's formula (QTcB), and QT interval corrected with Fridericia's formula (QTcF).

- Treatment-emergent[#] ECG abnormalities at EOT.
- Change from baseline to Weeks 2, 4, 8, 12, and EOS in clinical laboratory tests.
- Treatment-emergent AEs up to EOS.
- Treatment-emergent SAEs up to EOS.
- AEs leading to premature discontinuation of study treatment up to EOT.
- Treatment discontinuation due to systemic corticosteroid administration for NP and/or surgery for nasal polyps before Week 12.

[#] Treatment-emergent is defined from first study treatment administration up to EOS.

3.8.2.1 Safety and tolerability endpoints – derived variables

QTcF will be derived using the ECG variables QT and HR (for calculation of RR) recorded in the eCRF.

- QTcF (ms) = QT (ms)/RR (s) $^{0.33}$ where RR is 60/HR (bpm)

3.8.3 Pharmacokinetic and pharmacodynamic endpoints

The plasma PK parameters of ACT-774312 at Week 2 will be derived by noncompartmental analysis of the plasma concentration-time profile.

3.8.3.1 Pharmacokinetic endpoints

- Trough ACT-774312 concentration at Weeks 2, 4, 8, and 12.
- AUC from zero to 4 h ($AUC_{0–4}$) at Week 2.
- AUC over a dosing interval (AUC_{τ}) at Week 2 by extrapolation of the 12 h trough concentration based on the pre-dose trough concentration.
- C_{max} at Week 2.
- t_{max} at Week 2.

3.8.3.2 Calculation of pharmacokinetic endpoints and assumptions

The measured individual plasma concentrations of ACT-774312 will be used to directly obtain C_{max} and t_{max}.

$AUC_{0–4}$ will be calculated according to the linear trapezoidal rule using the measured concentration-time values above the limit of quantification (LOQ). AUC_{τ} will be extrapolated from $AUC_{0–4}$ by using the pre-dose concentration as well as the trough concentration at 12 h.

The PK parameters will be calculated on the basis of the actual blood sampling time points.

For ACT-774312 mean value calculations, all values below the limit of quantification (BLQ) will be set to zero. If > 50% of the values at a given time point are BLQ, no mean value will be calculated. Mean concentration-time profiles will be generated using these criteria.

The following assumptions have been made:

- C_{max} and AUC values are log-normally distributed [Julious 2000].

3.8.3.3 Pharmacodynamic endpoints

[redacted]

3.9 Study assessments

3.9.1 Efficacy assessments

3.9.1.1 Nasal endoscopy

Nasal endoscopy should be performed at the end of the scheduled visits [redacted] and may be preceded by local administration of an anesthetic drug in combination with a decongestant. Before introducing the endoscope, the nose should be cleaned of nasal secretions by suctioning.

Local assessment will be performed for all endoscopies. To confirm eligibility at Visit 2, only local assessment will be used.

Standard video sequences will be downloaded and videos from Visits 2–7 will be sent to a centralized reader [redacted]. Centralized imaging data assessments and scoring by independent physician reviewers for the imaging data will be performed for all endoscopies starting from Visit 2. The subject-identifying information from the video header (subject and visit identifiers) will be removed by [redacted] prior to sending the videos to the readers. The final results of central reading will be made available after EOS.

The local and central assessment of the NPS will be performed as described in Table 5. NPS will be the sum of the right and left nostril scores.

Table 5 Endoscopic nasal polyp score

Polyp score	Polyp size
0	No polyps
1	Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate
2	Polyps reaching below the lower border of the middle turbinate
3	Large polyps reaching the lower border of the inferior turbinate or additional large polyps medial to the middle turbinate
4	Large polyps causing near-complete obstruction of the inferior nasal cavity, i.e., touch the floor of the nose

The results of both the local and central assessments of the NPS will be reported in the eCRF.

Further details on nasal endoscopy will be available in a separate operational manual provided to the site.

3.9.1.2 CT scan

CT of the sinuses should be performed at Visit 2 and at EOT (Visit 6).

For Lund-Mackay score, Zinreich-modified Lund-Mackay score, and 3D volumetric measurement of the maxillary sinus, the same acquisitions (sequences) will be used for centralized imaging data assessments and scoring by independent physician reviewers for the imaging data. The subject-identifying information (subject and visit identifiers) will be removed by ERT prior to sending the data to the reader. The final results of central reading will be made available after EOS.

Local assessment of the Lund-Mackay score will also be performed.

Details on CT will be available in a separate operational manual provided to the site.

The Lund-Mackay and the Zinreich-modified Lund-Mackay systems are based on localization, with points given for degree of opacification.

Lund-Mackay score

The right or left sinuses are divided into six portions, i.e., maxillary sinus, anterior ethmoid sinuses, posterior ethmoid sinuses, sphenoid sinus, frontal sinus, and OMC. The score assignments are 0 if the sinus is totally patent, 1 if the sinus is partially opacified, and 2 if

the sinus is completely opacified. The maximum score for each side is thus 12, with a total score determined out of 24. The OMC is scored either 0 if not occluded or 2 if occluded.

Modification of the Lund-Mackay score

Each sinus is assigned a score based on the percentage of opacification from mucosal thickening as follows: 0 = 0%, 1 = 1% to 24%, 2 = 25% to 74%, 3 = 75% to 99%, 4 = 100% or completely occluded. Similar to the Lund-Mackay system, each side is graded and their sum is the total score out of a maximum of 48. The OMC is given a score of 0 (no obstruction) or 1 (obstruction) for the frontal recess, middle meatus, infundibulum, and the sphenoethmoidal recess channels.

For subjects in whom the OMC is missing (because of a previous surgery) the reader should consider the location of the former OMC and provide a scoring (as if the OMC was there).

3D volumetric measurement of the maxillary sinus (left and right)

This method is used to calculate:

- the volume of air (mL)
- the volume of mucosa (mL)
- % occupied by disease
- thickness of lateral wall

The subject-identifying information from the imaging data header will be removed by ERT prior to sending the imaging data to the physician for reading.

Both the Lund-Mackay score and the 3D volumetric measurements of the maxillary sinus will be reported in the eCRF.

3.9.1.3 UPSIT

UPSIT should be performed at all visits except Visit 1.

The UPSIT test is a rapid and easy-to-administer method to quantitatively assess human olfactory function [Doty 1984]. The UPSIT shows a high test-retest reliability (r: 0.981) and scores on this test are strongly correlated with the detection threshold for phenylethylalcohol in the same individuals. When the UPSIT is administered in the standardized manner, clinical subjects show a high degree of uniformity in UPSIT performance when tested in different laboratories.

The test consists of four booklets, each containing 10 odorants with one odorant per page. The test-time is about 15 min. The stimuli are embedded in 10–50 (μm) diameter plastic microcapsules on brown strips at the bottom of each page. Above each odorant strip is a multiple-choice question with four alternative words to describe the odor. The subject will

be asked to release the odorant by rubbing the brown-strip with the tip of a pencil and to indicate which of four words best describes the odor. Each subject will receive a score out of 40 possible correct answers. The final score will be recorded in the eCRF.

3.9.1.4 Visual analog scales for symptoms

The patient will be asked to indicate on a VAS the answer to the question: *"How troublesome are your symptoms?"* for the 5 following symptoms:

- nasal obstruction
- nasal discharge
- mucus in the throat
- loss of smell
- facial pain

Each symptom will be assessed individually based on total severity of the VAS score (0 to 10 cm). The VAS ranks from 0 (Not at all troublesome) to 10 (Extremely troublesome) The scores for the 5 symptoms will be added together and the total score will be categorized as MILD, MODERATE, or SEVERE, where:

MILD = VAS 0–15

MODERATE = VAS > 15–35

SEVERE = VAS > 35–50

The total score will be recorded in the eCRF.

A sample of the VAS for each symptom is provided [redacted].

3.9.1.5 Physician Global Assessment

- PGA-DS

  The questionnaire will be completed by the physician at Visit 2 and at each subsequent site visit until EOS. The questionnaire will be administered in a paper format.

  The physician will rate the overall severity of the disease symptoms on a 4-point scale (1–4) scored as: "none", "mild", "moderate", or "severe".

  A sample of the PGA-DS questionnaire is provided [redacted].

- PGA of Change in Disease Severity (PGAC-DS)

The questionnaire will be completed by the physician at Week 2 (Visit 3), and at each subsequent site visit until EOS. The questionnaire will be administered in a paper format.

The PGAC-DS questionnaire is a self-administered 1-item questionnaire designed to assess the physician's impression of change in disease severity since study treatment start. The physician will rate the change since the subject started study treatment in the overall severity of the disease symptoms on 7-point scales (1 to 7) scored as: "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse".

A sample of the PGAC-DS is provided [redacted].

The answers to the 2 questionnaires will be recorded in the eCRF.

3.9.1.6 Patient questionnaires

- SNOT-22

  The SNOT-22 is a validated questionnaire to assess the impact of CRS on QoL.

  The score ranges from 0 to 110. Higher total scores on the SNOT-22 imply greater impact on QoL. The SNOT-22 was validated and recommended for routine clinical practice. A minimal clinically important difference in score has been established to be 8.9 points [Hopkins 2009].

  The score will be reported in the eCRF.

  The sponsor has obtained approval from the developer of the SNOT-22 for its use in this study. Validated translation for Flemish has been obtained

  A sample of the SNOT-22 questionnaire is provided for each symptom [redacted].

- Patient Global Impression of Change in Disease Severity (PGIC-DS)

  A PGIC-DS questionnaire will be completed by the subject at Week 2 (Visit 3) and at each subsequent site visit until EOS. The questionnaire will be administered in a paper format.

  The PGIC-DS questionnaire is a self-administered 1-item questionnaire designed to assess subject's impression of change in disease severity since study treatment start. Subjects will rate their change since they started study treatment in the overall severity of the disease symptoms on 7-point scales (1 to 7) scored as: "very much improved," "much improved," "minimally improved," "no change," "minimally worse," "much worse," or "very much worse".

The answer to the questionnaire will be recorded in the eCRF.

A sample of the PGIC-DS questionnaire is provided [redacted].

3.9.2 Safety and tolerability assessments

The definitions, reporting, and follow-up of AEs, SAEs, and potential pregnancies are described in Section 4.

See Table 1 for the time points of assessments.

3.9.2.1 Specific safety and tolerability assessments

3.9.2.1.1 Weight and height

Height will be measured in cm at screening only. Body weight will be measured in kg at screening and the EOS visit. The results should be provided to one decimal place and the values, as well as the BMI, will be recorded in the eCRF.

The subjects' body weight will be measured using the same weighing scale for all subjects and throughout the study. The weighing scale should have a precision of at least 0.5 kg.

3.9.2.1.2 Physical examination

Physical examination (i.e., inspection, percussion, palpation, and auscultation) will be performed at Visits 1, 2, 6, and 7. Clinically relevant findings found after informed consent form (ICF) signature and meeting the definition of an AE (new AE, or worsening of previously existing condition) must be recorded on an AE form of the eCRF.

Date and time of physical examination and its results will be recorded on source documents only.

3.9.2.1.3 Vital signs

SBP, DBP and pulse rate will be measured at all visits using an automatic oscillometric device, always on the dominant (i.e., dominant arm right = writing with right hand).

In this study the normal range for vital signs is defined as follows:

SBP:	100–160 mmHg
DBP:	50–100 mmHg
Pulse rate:	45–100 bpm

Measurements should be recorded from the subject in the supine position after having rested for a 5-minute period. The date and time of the vital sign measurements and the corresponding results will be recorded in the eCRF.

Significant findings made after study treatment initiation which meet the definition of an AE must be recorded on an AE form of the eCRF.

If felt necessary by the investigator, additional vital signs may be recorded to substantiate abnormal findings on the vital signs, which will be also recorded in the eCRF.

3.9.2.1.4 Electrocardiography

A standard 12-lead ECG is to be recorded at rest with the subject in the supine position for a 5-minute period. Printouts for each ECG (at least three complexes for each standard lead) will include date and time of recording, subject's identification, physician's evaluation, and physician's initials. The date and time of the ECG recordings as well as the overall ECG evaluation and potential abnormal findings of the ECG recordings will be transcribed into the subject's eCRF.

The following variables are to be collected on the eCRF: PR (ms), QRS (ms), QT (ms), QTcB (ms), HR (bpm), and RR.

If felt necessary by the investigator, additional ECGs may be recorded to substantiate abnormal findings on the ECG, which will be also recorded in the eCRF.

Significant findings made after study treatment initiation, which meet the definition of an AE, must be recorded on an AE form of the eCRF.

3.9.2.2 Laboratory assessments

3.9.2.2.1 Type of laboratory

For each laboratory, the investigator must provide the sponsor with the name and professional degree, a copy of the laboratory's certification, and the normal range (by sex, if appropriate) for each variable being evaluated in the study. These laboratory references must be forwarded to the sponsor before study start, and be updated whenever necessary. However, the investigator must request that the clinical laboratory does not change any normal range during the course of the study.

If a sample is lost or cannot be analyzed by the laboratory the sample will not be re-collected.

For each assessment of routine laboratory variables, a total of 18 mL of blood will be taken from each subject (9 mL for hematology and 9 mL for clinical chemistry). Urinalysis will be performed by dipstick.

Virus serology and IgE titer will be measured at screening only; a total of 18 mL of blood will be taken from each subject.

A serum pregnancy test will be performed at screening (4 mL of blood) in women of childbearing potential, and a urine pregnancy test will be performed at Visit 2 prior to randomization. A negative result must be obtained at Visits 1 and 2 prior to randomization. Additional urine pregnancy tests will be performed at each visit until EOS visit.

For cyp2c9 genotyping, a total of 4 mL of blood will be taken from each subject at screening.

The blood samples will be taken under fasted conditions. As a rule, the blood samples will be taken from the subject in the sitting position by puncture of a vein in the cubital or the antebrachial region. The samples will be sent to the local certified laboratory immediately after blood sampling. The date and time of the blood sampling will be recorded in the eCRF.

If subjects present with abnormal laboratory test results during the study, additional re-checks and monitoring will be performed as applicable.

All abnormal laboratory values must be assessed by the investigator and marked as clinically significant (CS) or not clinically significant (NCS) on the laboratory printout and in the eCRF. Clinically significant laboratory abnormalities observed after study treatment administration, which meet the definition of an AE, must be reported by the investigator as an AE or SAE as appropriate [see Section 4].

The results from virus serology, urinalysis, and pregnancy test will be documented on a separate source document and entered in the eCRF.

3.9.2.2.2 Laboratory variables

Hematology

- Hemoglobin, hematocrit
- Red blood cell count
- White blood cell count
- Differential blood count (including: basophils, eosinophils, neutrophils, lymphocytes, monocytes)
- Platelet count

Clinical chemistry

- Urea
- Creatinine
- Total bilirubin
- Direct bilirubin
- Alkaline phosphatase
- Aminotransferases (AST/ALT)

- Creatine phosphokinase
- Gamma glutamyl transferase
- Lactate dehydrogenase
- Uric acid
- Glucose
- Cholesterol, triglycerides
- Sodium, potassium, chloride, calcium
- Protein, albumin

Pregnancy test

At screening, a human chorionic gonadotropin (hCG) serum pregnancy test will be performed by automated immunoassay using the clinical chemistry blood sample. At all other time points, pregnancy testing will be performed in urine using a qualitative chromatographic immunoassay hCG kit.

Urinalysis

- Glucose
- Bilirubin
- Ketone
- Specific gravity
- Blood
- pH
- Protein
- Urobilinogen
- Nitrite
- Leukocytes
- Microscopic urine analysis if dipstick positive (in the event of out of range data)

Virus serology

- HIV1 and HIV2 antibodies
- Hepatitis B antigen and hepatitis C antibodies

Virus serology will be measured at the screening visit.

FSH (females of non-childbearing potential only)

At screening, FSH will be measured to confirm the post-menopausal status of women of non-childbearing potential if necessary.

3.9.3 Pharmacokinetic and pharmacodynamic assessments

ACT-774312 concentration will be measured in plasma from all subjects. ACT-774312 will be measured using liquid chromatography with tandem mass spectrometry (LC-MS/MS).

[redacted].

3.9.3.1 Pharmacokinetic assessments

3.9.3.1.1 Timing for sampling

[redacted]

The date and exact actual clock time of collection of each blood sample will be entered in the eCRF.

3.9.3.1.3 Labeling

The tubes and labels will be provided and prepared by the site. The tubes for PK assessments will be pre-labeled and will carry the following information:

- ID-084A201: ACT-774312 Plasma PK
- Visit number
- Scheduled time point
- Subject number

3.9.3.1.4 Bioanalysis

[redacted]

No genetic analysis will be conducted with the PK or PD samples.

3.9.3.1.5 Shipping procedures

The site staff will be responsible for shipment of samples. Samples must be sent to Idorsia Pharmaceuticals Ltd, Preclinical Pharmacokinetics and Metabolism, Allschwil, Switzerland (see contact details, page 4) at time intervals agreed with the sponsor using the sponsor's preferred courier and account number. Samples must be packed securely together with completed shipment forms in polystyrene-insulated shipping containers, together with enough dry ice to last for 48 hours.

3.9.3.2 Pharmacodynamic assessments

[redacted]

[redacted]

The date and exact actual clock time of collection of each blood sample will be entered in the eCRF.

The labels will be provided and prepared by the site. The tubes for [redacted] assessments will be pre-labeled and will carry the following information:

[redacted]

The PD samples will be sent to Idorsia for analysis together with the PK samples.

After the analysis, the remaining volume of the PD samples [redacted] will be stored at −80 °C ± 20 °C for up to 15 years at Idorsia Research Biosample Repository, Allschwil, Switzerland. The samples might be used for measuring non-genetic markers of PD effect, if deemed appropriate. After 15 years, the samples will be destroyed by Idorsia Pharmaceuticals Ltd.

3.9.4 Baseline variables, previous and concomitant medications

3.9.4.1 Baseline demographics

The baseline demographic variables age, race, and sex will be recorded in the eCRF.

3.9.4.2 Medical history

All relevant medical history will be documented at the screening examination and recorded in the eCRF.

3.9.4.3 Body mass index

BMI will be calculated at screening by the site from the weight and height recorded in the eCRF, using the formula: BMI (kg/m^2) = weight (kg) / height $(m)^2$. Precision of one decimal place is required for weight and height values.

3.9.4.4 Previous and concomitant medications

A previous medication is any treatment for which the end date is prior to the first study drug administration.

All medication that is study-concomitant (i.e., ongoing or initiated after first study drug administration) must be captured in the eCRF.

Previous/concomitant medications (including contraceptives and traditional and alternative medicines, i.e., plant-, animal-, or mineral-based medicines) from 3 months prior to screening, or started during the course of the study, until EOS must be recorded in the eCRF. The generic name, start/end dates of administration (as well as whether it was ongoing at start of treatment), route, dose, and indication will be recorded in the eCRF.

3.9.4.5 Immunoglobulin E titer

Total IgE will be measured at Visit 1 and will be recorded in the eCRF.

3.9.4.6 Spirometry

Spirometry test will be performed at Visit 1 for subjects with asthma as based on their medical history. The following must be avoided for the duration shown prior to spirometry testing: caffeine-containing drinks (1 hour), alcoholic beverages (4 hours), strenuous exercise (30 minutes), and large meals (2 hours). Cold air should also be avoided immediately prior to testing.

Testing should be started after the patient has rested for at least 5 minutes. Testing will be conducted with the patient seated and wearing nose-clips. Subjects should be given clear instructions before and during the testing, and should be actively coached and encouraged during the test. When performing the test, subjects should remain erect and not bend forward excessively.

The FEV_1 value will be recorded in the eCRF.

3.9.4.7 Asthma Control Questionnaire

The Asthma Control Questionnaire (ACQ) will be completed by subjects with asthma (based on medical history) only. The ACQ is a self-administered tool that measures the adequacy of asthma control and the change in asthma control which occurs either spontaneously or because of a treatment [Juniper 1999]. The ACQ has seven questions, the first five of which score the asthma symptoms, and the last two of which score the daily reliever bronchodilator use during the previous week and the FEV_1% predicted on the day of the assessment. In the ACQ, subjects are asked to recall how their asthma has been during the previous week, and to respond to the symptom and bronchodilator use questions on a 7-point scale (0 = no impairment, 6 = maximum impairment). Clinic staff score the FEV_1% predicted on a 7-point scale. The questions are equally weighted and the ACQ

score is the mean of the seven questions; ACQ scores may therefore vary between 0 and 6. The ACQ will be self-administered at Visit 1 only, and only by the subjects with asthma. The responses to the ACQ questions are collected in the eCRF.

A sample of the ACQ (in English) is provided [redacted].

The sponsor has obtained approval from the developer of the ACQ for its use in this study. Validated translations for Flemish have been obtained.

3.9.4.8 Asthma Quality of Life Questionnaire

The Asthma Quality of Life Questionnaire with Standardised Activities (AQLQ) will be completed by subjects with asthma (based on medical history) only. The AQLQ was developed and validated to measure the functional problems (physical, emotional, social, and occupational) that are most troublesome to adults (17–70 years) with asthma [Juniper 1992]. This instrument has 32 questions in four domains (symptoms, activities, emotions, and environment) and takes 3–4 minutes to complete. Subjects are asked to think about how they have been during the previous 2 weeks and to respond to each of the 32 questions on a 7-point scale (7 = not impaired at all to 1 = severely impaired). The overall AQLQ score is the mean of all 32 responses, and the individual domain scores are the means of the items in those domains. The responses to the AQLQ questions are collected in the eCRF. The AQLQ will be assessed at Visit 1 only, and only for the subjects with asthma.

A sample of the AQLQ (in English) is provided [redacted].

The sponsor has obtained approval from the developer of the AQLQ for its use in this study. A validated translation for Flemish has been obtained.

3.10 Visit and assessment schedule

Table 1 provides an overview of the assessments during the study.

3.10.1 Sequence of assessments

All assessments must be scheduled in such a way that the time point of PK sampling is strictly kept ± 5% (in relation to the last study treatment intake).

Nasal secretion samples should be collected before the endoscopy.

3.10.2 Total blood volume

The total volume of blood to be taken per subject during the entire course of the study will be as follows:

Table 6 Example of total blood volume taken at the coordinating site

Procedure	Sample	Blood volume per sample (mL)	Number of blood samples per subject	Total volume per subject (mL)
Laboratory tests	Hematology	9	7	63
	Biochemistry incl. glucose	9	7	63
	Serology and IgE titer	18	1	18
	Pregnancy serum test	4	1	4
	cyp2c9 genotyping	4	1	4
Bioanalysis	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
		Total volume of blood collected		212

IgE = immunoglobulin E; PD = pharmacodynamics; PK = pharmacokinetics.

Overall, including potential additional safety laboratory assessments, the total volume of blood will not exceed 250 mL over 5 months at any of the sites. This volume is lower than the volume of blood collected during a blood donation.

4 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

4.1 Adverse events

4.1.1 Definitions of adverse events

An AE is any adverse change from the subject's baseline condition, i.e., any unfavorable and unintended sign, including an abnormal laboratory finding, symptom or disease, that occurs during the study, whether or not considered related to the study treatment.

A treatment-emergent AE is any AE temporally associated with the use of a study treatment, whether or not considered related to the study treatment.

AEs include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.

- Disease or medical condition detected or diagnosed after signature of the ICF even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at baseline that worsen following the first study treatment administration.
- Abnormal assessments, e.g., ECG, vital signs, or physical examination findings, if they represent a clinically significant finding that was not present at baseline or worsened during the study.
- Laboratory test abnormalities if they represent a clinically significant finding, symptomatic or not, which was not present at baseline or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study treatment.

Overdose, misuse, and abuse of the study treatment should be reported as an AE and, in addition, study treatment errors must be documented in the study treatment log of the eCRF.

4.1.2 Intensity of adverse events

The intensity of clinical AEs is graded on a three-point scale – mild, moderate, severe – and is to be reported on specific AE forms of the eCRF.

If the intensity of an AE worsens during study treatment administration, only the worst intensity is to be reported on the AE page. If the AE lessens in intensity, no change in the severity is required.

If an AE occurs during a washout or placebo run-in phase and afterwards worsens during the treatment phase, a new AE form must be filled out with the intensity observed during study treatment administration.

The three categories of intensity are defined as follows:

- Mild

The event may be noticeable to the subject. It does not influence daily activities, and usually does not require intervention.

- Moderate

The event may make the subject uncomfortable. Performance of daily activities may be influenced, and intervention may be needed.

- Severe

The event may cause noticeable discomfort, and usually interferes with daily activities. The subject may not be able to continue in the study, and treatment or intervention is usually needed.

A mild, moderate, or severe AE may or may not be serious [see Section 4.3.1]. These terms are used to describe the intensity of a specific event. Medical judgment should be used on a case-by-case basis.

Seriousness, rather than severity assessment, determines the regulatory reporting obligations.

4.1.3 Relationship to study treatment

Each AE must be assessed by the investigator as to whether or not there is a reasonable possibility of causal relationship to the study treatment, and reported as either related or unrelated. The determination of the likelihood that the study treatment caused the AE will be provided by an investigator who is a qualified physician.

4.1.4 Adverse events related to study design or protocol-mandated procedures

An AE is defined as related to study design or protocol-mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated procedures. Examples include discontinuation of a subject's previous treatment during a washout period leading to exacerbation of underlying disease.

4.1.5 Reporting of adverse events

All AEs with an onset date after signing of the ICF and up to 30 days after study treatment discontinuation or up to EOS must be recorded on specific AE forms of the eCRF.

Information to be collected in an AE form in the eCRF includes date of onset, action taken with the study treatment, outcome of AE, date of resolution (if applicable) and investigator's assessment of intensity, and relationship to study treatment, study design or protocol-mandated procedures.

If the intensity of an AE worsens during study treatment administration, only the worst intensity should be reported on the AE form. If the AE lessens in intensity, no change in the severity is required to be reported.

For AEs ongoing at the start of study treatment, information on worsening of intensity after the start of study treatment will be collected on the AE form.

Follow-up information on ongoing AE obtained after the subject's EOS visit will not be collected in the eCRF.

4.1.6 Follow-up of adverse events

AEs still ongoing at EOS for a given subject must be followed up until they are no longer considered clinically relevant. The final outcome of AEs that were ongoing at the EOS examination will not be recorded in the eCRF (kept in source document only); these events will be marked as ongoing in the eCRF. The final outcome of these AEs will be provided in the clinical study report.

4.2 Suspected unexpected serious adverse reactions

The expectedness of an SAE is determined by the sponsor according to the reference safety information (RSI) section provided in the most recent version of the IB.

Any SAE that is assessed as related and unexpected against the RSI is known as a SUSAR.

4.3 Serious adverse events

4.3.1 Definitions

4.3.1.1 Serious adverse events

An SAE is defined by ICH guidelines as any AE fulfilling at least one of the following criteria:

- Fatal.
- Life-threatening: refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death had it been more severe.
- Requiring inpatient hospitalization, or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Medically significant: refers to important medical events that may not immediately result in death, be life-threatening, or require hospitalization but may be considered to be SAEs when, based upon appropriate medical judgment, they may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The following reasons for hospitalization are exempted from being reported:

- Hospitalization for cosmetic elective surgery, or social and/or convenience reasons.
- Hospitalization for pre-planned (i.e., planned prior to signing informed consent) surgery or standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.

However, complications that occur during hospitalization are AEs or SAEs (for example if a complication prolongs hospitalization).

4.3.1.2 Serious adverse events associated with the study design or protocol-mandated procedures

An SAE is defined as related to study design or protocol-mandated procedures if it appears to have a reasonable possibility of a causal relationship to either the study design or to protocol-mandated procedures. Examples include discontinuation of a subject's previous treatment during a washout period leading to exacerbation of underlying disease or a complication of an invasive procedure that is specifically required by the protocol.

4.3.2 Reporting of serious adverse events

All SAEs occurring after signing of the ICF up to 30 days after study treatment discontinuation or up to EOS must be recorded on an SAE form.

4.3.2.1 After the follow-up period

New SAEs occurring at any time after the 30-day follow-up period after study treatment discontinuation must be reported to the Idorsia Global Drug Safety department within 24 h of the investigator's knowledge of the event, if considered causally related to previous exposure to study medication by the investigator. These SAEs are only entered in the drug safety database, and hence will not affect study closure.

4.3.2.2 Reporting procedures

All SAEs must be reported by the investigator to the Idorsia Global Drug Safety department without delay and at the latest 24 h after the investigator's first knowledge of the event.

All SAEs must be recorded on SAE forms, irrespective of the study treatment received by the subject, and whether or not this event is considered by the investigator to be related to study treatment.

These SAE forms must be e-mailed to the Idorsia Global Drug Safety department (for contact details, see page 3). The investigator must complete the SAE form in English, and must assess the causal relationship of the event to study treatment.

Such preliminary reports must be followed by detailed descriptions that should include copies of hospital case reports, autopsy reports, hospital discharge summaries and other documents when requested and applicable. Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The Idorsia Global Drug Safety department may contact the investigator to obtain further information.

If the subject is hospitalized in a hospital other than the study site, it is the investigator's responsibility to contact this hospital to obtain all SAE relevant information and documentation.

SUSARs will be expedited by the sponsor to health authorities, IECs/IRBs, and investigators, as appropriate. Unblinding of SUSARs will be performed as appropriate.

The IB is the reference safety document to assess whether or not an SAE must be reported by the sponsor to health authorities, IECs/IRBs, and investigators in an expedited fashion [ACT-774312 IB].

4.3.3 Follow-up of serious adverse events

SAEs still ongoing at EOS for a given subject must be followed until resolution or stabilization, or until the event is otherwise explained. The final outcome of SAEs that were ongoing after the EOS examination will not be recorded in the eCRF; these events will be marked as ongoing in the eCRF. Such follow-up information will only be entered in the sponsor's drug safety database, and hence will not affect study closure.

4.4 Pregnancy

4.4.1 Teratogenicity

[redacted]

Women must not become pregnant during the study and for up to 30 days after last study treatment administration or study treatment discontinuation.

If a woman becomes pregnant while on study treatment, study treatment must be discontinued.

The investigator must counsel the subject and discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

4.4.2 Reporting of pregnancy

Irrespective of the treatment received by the subject, any pregnancy occurring during study treatment administration or during the 30 days following study treatment discontinuation, must be reported within 24 hours of the investigator's knowledge of the event.

Pregnancies must be reported on the Idorsia Pregnancy form, which is to be faxed or e-mailed to the Idorsia Global Drug Safety department (for contact details, see page 2), and on an AE form of the eCRF, as applicable.

4.4.3 Follow-up of pregnancy

Any pregnancy must be followed to its conclusion, and its outcome must be reported to the Idorsia Global Drug Safety department.

Such follow-up information will only be entered in the sponsor's drug safety database, and hence will not affect study closure.

5 STATISTICAL METHODOLOGY AND ANALYSES

5.1 Statistical analysis plan

A statistical analysis plan (SAP) will be written and finalized before study closure, i.e., database closure and unblinding of the randomization code. The SAP will provide full details of the analyses, data displays, and algorithms to be used for data derivations.

The SAP will include the definition of major and minor protocol deviations and the link between major protocol deviations and the analysis sets. Major and minor protocol deviations will be identified by trained staff before study closure.

5.2 Analysis sets

Four analysis sets are defined.

- **All-treated set (ATS)**

This analysis set includes all randomized subjects who received at least one dose of the study treatment.

The ATS will be employed in the analysis of the demographic, baseline, (primary) efficacy, and safety variables.

- **Per-protocol set (PPS)**

This analysis set includes all randomized subjects who completed the treatment up to Week 12 without protocol deviations that may affect the evaluation of the primary endpoints (to be defined in the SAP).

The PPS will be employed in the analysis of efficacy variables.

The target number of subjects in the PPS is 21. If this number is unlikely to be reached, the number of subjects to be randomized may be increased over 24.

- **Pharmacokinetic set (PK set)**

This analysis set comprises all subjects from the ATS who completed treatment with ACT-774312 at least up to Week 2, had evaluable plasma concentrations, and did not deviate from the protocol in a way that might affect the evaluation of the PK endpoints.

The PK set will be employed in the analysis of the PK parameters.

- **Pharmacodynamic set (PD set)**

This analysis set comprises all subjects from the ATS who completed treatment with ACT-774312 or placebo at least up to Week 2 without protocol deviations that may affect the evaluation of the PD endpoints.

The PD set will be employed in the analysis of the PD variables.

5.3 Primary endpoint

The primary endpoint is the change from baseline to Week 12 in NPS as measured by nasal endoscopy (centrally assessed).

5.3.1 Statistical model

The statistical model for the changes from baseline in NPS is a mixed model for repeated measurements (MMRM):

$Y_{ijt} = \mu + \alpha_i + \beta_t + (\alpha\beta)_{it} + \gamma X_{ij} + \delta_t X_{ij} + \varepsilon_{ijt}$ where

Y_{ijt} is the change from baseline to time t (Week 2, Week 4, Week 8 or Week 12) for subject j in treatment group i;
μ is the overall mean change from baseline;
α_i is the effect of treatment group i ($\sum\alpha_i = 0$);
β_t is the effect of time t ($\sum\beta_t = 0$);
$(\alpha\beta)_{it}$ is the interaction of treatment i and time t ($\sum(\alpha\beta)_{it} = 0$);
X_{ij} is the baseline NPS for subject j in treatment group i;
δ_t is the interaction of baseline NPS and time ($\sum\delta_t = 0$);
ε_{ijt} is an error term where the vector ε_{ij} follows a multivariate normal distribution with mean (vector) 0 and an unstructured covariance matrix $\sum$.

Inference for the linear mixed model is based on restricted maximum likelihood estimation [Verbeke 2000]. Study site is not shown above but will be added to the model.

5.3.2 Hypotheses and statistical inference

Statistical hypotheses will not formally be tested in this estimation study.

5.3.3 Primary endpoint analysis

5.3.3.1 Main analysis

The main analysis of the primary efficacy endpoint will be conducted on the PPS. All NPS values observed between baseline and Week 12 will be included in this analysis.

Changes from baseline to post-baseline visits in NPS will be analyzed using an MMRM with factors for treatment group, study site, visit, treatment by visit interaction and covariates for baseline NPS and the interaction between baseline NPS and visit. An

unstructured covariance matrix will be used to account for the correlation between repeated measurements from the same subject.

Estimation of the treatment difference for the primary endpoint, change from baseline to Week 12 in NPS, will be based on the mixed model.

Missing data handling in the primary analysis

All subjects in the PPS are expected to have a Week 12 NPS. Any intermediate missing data will be handled by the mixed model. Missing values will not be imputed.

5.3.3.2 Confirmatory analyses

A sensitivity analysis will be conducted on the ATS using the same mixed model as for the primary analysis. In this approach missing values will not be imputed, but will be handled by the model assuming that the data are missing at random. Additionally, an analysis of covariance (ANCOVA) will be performed for the change from baseline to Week 12 in NPS with missing data imputed using last observation carried forward.

5.3.4 Primary endpoint display

The primary endpoint will be summarized by visit and treatment group displaying number of observations, mean, median, standard deviation (SD), minimum, and maximum.

5.4 Secondary efficacy endpoints

All secondary endpoints are listed in Section 3.8.1.

5.4.1 Secondary efficacy endpoint analysis

Secondary efficacy endpoints will be analyzed in the PPS. Change from baseline to Week 12 in Zinreich-modified Lund-Mackay score will be analyzed using an ANCOVA model with a factor for treatment group and a covariate for the baseline score.

5.4.2 Secondary efficacy endpoint display

All secondary endpoints will be summarized by visit and treatment group using descriptive statistics (i.e., number of observations, mean, median, SD, minimum, and maximum for continuous endpoints; number and percentages for categorical endpoints).

5.4.3 Other efficacy endpoint display

The display of the other efficacy endpoints is similar to that of the secondary endpoints.

Additionally, the correlation between the primary and secondary efficacy endpoints (restricted to Week 12) versus the change in disease severity from baseline to Week 12 as assessed by the physician [redacted] as well as by the patient [redacted] will be explored.

5.5 Sample size

No formal sample size calculation was performed. Twenty-four subjects (16 in the ACT-774312 group and 8 in the placebo group) provide a certain precision to estimate the treatment difference in the mean change from baseline in NPS. Assuming a within-group SD of 2 points [Bachert 2016b], the SE of the estimated treatment difference (expected to be around 1.5 points) will be approximately 0.9 points.

5.6 Pharmacokinetic and pharmacodynamic endpoints

The PK and PD sets will be used for analysis of the PK and PD endpoints, respectively.

5.6.1 Pharmacokinetic endpoints

Plasma concentrations per time point will be summarized using arithmetic mean, minimum, median, maximum, SD, and two-sided 95% confidence interval (CI) of the mean.

For mean value calculations, all values BLQ will be set to zero. If > 50% of the values at a given time point are BLQ, no mean value will be calculated. Mean concentration-time profiles will be generated using these criteria.

PK endpoints will be analyzed descriptively:

- C_{max}, t_{max}, AUC_{0-4}, and AUC_{τ} will be listed by subject number.
- C_{max}, t_{max}*, AUC_{0-4}, and AUC_{τ} will be summarized with arithmetic mean, geometric mean, minimum, median, maximum, SD, SE, coefficient of variation (CV) in %, and 95% CI of the arithmetic and geometric means.

  * For t_{max} the geometric mean and its 95% CI will not be calculated.

5.6.2 Pharmacodynamic endpoints

[redacted]

5.7 Safety and tolerability endpoints

Safety analyses will be conducted on the ATS. The treatment-emergent period for the safety assessments is defined as the time from the first administration of study treatment to Visit 7 (EOS) except for ECG (up to Visit 6, EOT).

All AEs and SAEs will be coded using MedDRA (Version 20.0 or a more recent version, if available). ECG abnormalities will be coded using CDISC SDTM terminology.

All safety and tolerability data will be listed by treatment group and subject number.

5.7.1 Adverse events

Treatment-emergent AEs will be tabulated by primary system organ class (SOC), preferred term (PT), and treatment group. The number (%) of subjects who experienced AEs coded with the same PT will be displayed (in descending order according to the incidence). Treatment-emergent AEs will also be tabulated by severity and by relationship to study treatment by SOC and PT.

AEs leading to premature discontinuation of study treatment will be summarized in a similar manner to that used for AEs. Reasons for premature discontinuation of study treatment will be listed, in particular to assess whether treatment discontinuation was caused by corticosteroid administration for NP and/or surgery for NP.

Treatment-emergent SAEs and deaths will be summarized in a similar manner to that used for AEs. SAEs/deaths occurring before study treatment initiation or after EOS will be listed.

5.7.2 Vital signs

At each time point, absolute values and change from baseline of supine BP and pulse rate will be summarized with mean, median, SD, minimum, and maximum values. The number (%) of out-of-range values (based on available observations) will be presented. Values outside the reference range will be flagged in the listing.

5.7.3 ECG recordings

Treatment-emergent ECG abnormalities will be summarized and presented in a similar manner to that used for AEs.

At each time point, absolute values and change from baseline of ECG numeric variables will be summarized using descriptive statistics. The number of available observations will be presented.

5.7.4 Clinical laboratory tests

At each time point, absolute values and change from baseline of clinical laboratory variables will be summarized with mean, median, SD, minimum, and maximum values.

The number (%) of out-of-range values (based on available observations) will be presented. Values outside the investigator's normal range will be flagged in the listing.

Treatment-emergent marked laboratory abnormalities will be summarized for each laboratory variable. The sponsor's internal guidelines will be used for the standardization of numeric values obtained from different laboratories and/or using different normal ranges. Standard numeric laboratory variables will be transformed into standard units. Absolute values and changes in laboratory values converted to standardized units during the course of the study will be summarized by computing the usual location and scale statistics by period and treatment group.

5.8 Exposure to study treatment

Duration of randomized treatment (i.e., date of last intake minus date of first intake plus one day) will be summarized by treatment group in the ATS.

5.9 Baseline variables and concomitant medications

These analyses will be performed for the ATS.

Continuous demographic variables (e.g., age, weight, BMI) will be summarized by descriptive statistics. Categorical demographic characteristics (e.g., sex, race) will be summarized by counts and percentages. Other baseline subject characteristics will only be listed.

Previous and concomitant medications will be coded according to the WHO Drug code and the Anatomical Therapeutic Chemical class code (Version March 2018, or a more recent version, if available). Concomitant medications will be listed by treatment group and subject number.

All reported medical history conditions will be coded using MedDRA (Version 20.0 or a more recent version, if available). Concomitant medications will be listed by treatment group and subject number.

5.10 Exploratory analyses

Exploratory, data-driven analyses may be performed, with the caveat that any statistical inference will not have confirmatory value.

5.11 Interim analyses

No interim analysis is planned.

6 PROCEDURES AND GOOD CLINICAL PRACTICE

6.1 Procedures

6.1.1 Protocol amendments

Any change to a protocol must be an amendment if the documents have already been submitted to IECs/IRBs or health authorities. An amendment could therefore occur before or after the approval of these documents by IECs/IRBs or health authorities. Each amendment must be documented in writing and approved by the sponsor, and must be reviewed by the investigator.

Changes to the Core Subject Information and Informed Consent requested by IECs/IRBs are not considered to be formal amendments, as long as they do not significantly change the core document or affect the protocol.

6.1.1.1 Non-substantial amendment

Purely administrative or minor logistical changes require only a non-substantial amendment. Such changes include but are not limited to changes in study staff or contact details (e.g., the sponsor instead of CRO monitors), or minor changes in the packaging or labeling of study treatment.

The implementation of a non-substantial amendment may be undertaken with or without notification to the appropriate IECs/IRBs and health authorities (subject to national regulations). It does not require their approval.

6.1.1.2 Substantial amendment

A substantial amendment is required for significant changes. These include, but are not limited to, new data affecting the safety of subjects, and changes to the objectives or endpoints of the study, eligibility criteria, dose regimen, study assessments/procedures, or treatment or study duration, with or without the need to modify the Core Subject Information and Informed Consent.

Substantial amendments must be approved by the appropriate IECs/IRBs, and in some jurisdictions by the health authorities. The implementation of a substantial amendment may only occur after formal approval by the appropriate IECs/IRBs and/or health authorities, and must be signed by the investigators.

6.1.1.3 Urgent amendment

An urgent amendment might become necessary to preserve the safety of the subjects included in the study. The requirements for approval must not prevent any immediate action being taken by the investigator or the sponsor in the best interests of the subjects. If deemed necessary, an investigator may therefore implement an immediate change to the protocol for safety reasons, and in such exceptional cases the implementation of urgent

amendments will occur before submission to, and approval by, IECs/IRBs and health authorities.

In such cases, the investigator must notify the sponsor within 24 hours. IECs/IRBs and health authorities must be notified immediately in writing. A related substantial amendment will be prepared and submitted by the sponsor to the appropriate IECs/IRBs and health authorities within 10 working days of receiving the notification.

6.1.2 Monitoring

Monitoring of this study is the responsibility of the sponsor. The sponsor's monitor must contact and visit the investigator regularly, and must be allowed, on request, to have access to all study-related documents and facilities used in the study, as well as all source documents needed, to verify the entries on the eCRFs; provided that subject confidentiality is maintained in agreement with local regulations. It is the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them.

The sponsor's monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of the study treatment dispensing, AEs, and SAEs. The amount of verification of other relevant safety, tolerability, PK, and PD endpoints will be defined based on the study objectives; the extent of additional checks for the consistency of the source data with the eCRFs will be discussed before the monitoring visit by the monitor and the clinical pharmacologist, and documented in the corresponding monitoring guideline.

The investigator must ensure that subject anonymity will be maintained. On all documents submitted to the sponsor, subjects must not be identified by their names and date of birth, but by subject number only. The investigator must keep a subject identification log showing the subject number, the subject's name, date of birth, and address or any other locally accepted identifiers. Documents identifying the subjects (e.g., subjects' signed ICF must not be sent to the sponsor, and must be kept by the investigator in strict confidence.

The investigator and sub-investigators agree to cooperate with the monitor(s) to ensure that any issues detected in the course of these monitoring visits are resolved. If the subject is hospitalized or dies in a hospital other than the study center, the investigator is responsible for contacting that hospital in order to document the SAE.

The investigator must supply the sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription into eCRFs are suspected. In the event of special problems and/or

government/regulator queries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

An initiation visit will be performed before the site before the first subject is screened. Following the initiation visit, a copy of the completed initiation visit report and follow-up letter will be provided to the investigator and filed in the ISF.

The study treatment will be shipped to the site upon approval of the required essential documents.

Monitoring visits and contacts will occur at regular intervals thereafter, and a close-out visit will be performed after study database closure.

6.1.3 Data management

6.1.3.1 Data collection

A subject Screening and Enrollment Log must be completed for all subjects, both eligible and non-eligible, with the reasons for exclusion where applicable.

Electronic Data Capture (EDC) via eCRFs ([redacted] will be used for this study. eCRFs will be made available by Idorsia. For each subject who received at least one administration of study treatment, an eCRF must be completed and signed electronically by the investigator or sub-investigator. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the eCRF.

Study data will be collected either by the investigator or by clinical research staff on paper source data documents and entered by the site staff into the eCRFs in a timely manner or transferred electronically and loaded into the eCRFs by Idorsia Data Management at specified time points. The eCRFs must be kept up-to-date so that they reflect the latest observations on the enrolled subjects.

All source documents will be retained by the clinical site. Photocopies of completed source documents will be provided only if essential (i.e., for regulatory purposes) at the request of the sponsor. In accordance with ICH-GCP, the location of data identified as source data will be specified on the Source Document Identification List. The investigator/delegate must confirm by electronic signature that all data entries in the eCRFs are accurate and correct. All eCRF entries, corrections, and alterations must be made by the investigator or other, authorized, study site personnel and only by individuals who have received training on the EDC system. Site staff may be allowed access to the system only after training is completed. Training must be documented and a log of all EDC users and their rights within the system be maintained.

All source document forms must be completed using a black ballpoint pen, and must be legible. Errors must be crossed out but not obliterated, the correction inserted (if necessary the reason must be noted), and the change initialed and dated by the investigator, sub-investigator, or study nurse.

After database lock, a CD including printouts of filled eCRFs for all subjects will be provided to the site (for contact details, pages 2 and 3). The investigator will have read-only access to the eCRF data until receipt of this CD.

6.1.3.2 Data management and quality control

Data management is the responsibility of Idorsia.

The data entered into the EDC system will be systematically checked by Idorsia and site staff, using error messages from validation programs and database listings. All queries are raised and answered electronically within the EDC system. Once all queries are resolved, the authorized physician will review and electronically sign the eCRFs.

With the eCRF, the data checks made for consistency and plausibility will be done via the EDC system or performed manually by Data Management as defined in the Data Validation Specifications.

Sponsor monitoring is performed on-site, reviewing the data for correctness, plausibility, and completeness.

Safety laboratory samples will be processed by the local laboratory and the results will be sent by the sites to the external service provider, [redacted] who will electronically send the data to Idorsia to load into the clinical database.

A data review will be performed by trained staff of Idorsia before database closure.

SAEs occurring after ICF signature and up to EOS will be reconciled between the clinical database at Idorsia and the Idorsia Drug Safety database before database closure.

The PD data will be stored separately and will be merged with the clinical database. Therefore, the availability of these results will not affect study closure.

The PK samples will be processed by the bioanalytical laboratory at Idorsia (Preclinical Pharmacokinetics and Metabolism) and the results will be sent electronically to Idorsia. The PK data will be stored separately and will be merged with the clinical database. Therefore, the availability of these results will not affect study closure.

After the clinical database has been declared complete and accurate, the clinical database will be locked. Any changes to the clinical database after that time may only be requested

by the Idorsia clinical pharmacologist and approved by the Idorsia Head of Clinical Pharmacology.

6.1.4 Recording of data and retention of documents

The investigator/delegate must maintain adequate records necessary for the reconstruction and evaluation of the study. A number of attributes are considered of universal importance to source data and the records that hold those data. These include that the data and records are accurate, legible, contemporaneous, original (or certified copy), attributable, complete, consistent, enduring, and available when needed.

These records are to be classified into two different categories of documents: investigator's file, and subject clinical source documents.

These records must be kept by the investigator for as long as is necessary to comply with Idorsia's requirements (e.g., as specified in the clinical study agreement), and national and/or international regulations, whichever would be the longest period. If the investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements, respecting the data confidentiality, must be made between the investigator and Idorsia to store these documents outside the site, so that they can be retrieved in the event of a regulatory inspection. No study document should be destroyed without prior written approval from Idorsia. Should the investigator wish to assign the study records to another party, or move them to another location, Idorsia must be notified in advance.

If the site is using an electronic/computerized system to store subject medical records, it can be used for the purpose of the clinical study if it is validated (as per 21 CFR Part 11 or equivalent standard) and if the monitor has been provided with personal and restricted access to study subjects only, to verify consistency between electronic source data and the eCRF during monitoring visits.

If the site is using an electronic/computerized system to store subject medical records but it could not be confirmed that the system is validated or if the monitor could not be provided access to the system, the site is requested to print the complete set of source data needed for verification by the monitor. The printouts must be numbered, stapled together with a coversheet, signed and dated by the investigator/delegate to confirm that these certified copies are exact copies containing the same information as the original subject's data. The printouts will be considered as the official clinical study records.

In order to verify that the process the site uses to prepare certified copies is reliable, the monitor must be able to observe this process and confirm that the comparison of the source documents and the certified copy did not reveal inconsistencies. The monitor does not need to verify this process for all data of all subjects but at least for some of them (e.g., first

subject; regular check during the study of critical data like inclusion/exclusion criteria, endpoints for some subjects) as per Idorsia's instructions. If it were not possible for the monitor to observe this process, it would not be possible to rely on the site's certified copies and therefore the site cannot be selected for the clinical study. The printouts should be filed with the subject medical records.

The site master file will contain all the essential documents that are required to always be up-to-date and filed at site as per ICH-GCP section 8.

The site master file will include a table of contents listing the essential documents. All study related documentation must be maintained in the site master file.

In some cases, exceptions can be discussed with the monitor regarding the filing of the study documents outside the site master file. It should be clearly documented where each document is filed. This note to file should be present in the specific tab of the document in the site master file.

The site master file must be stored in a secure and restricted-access area during and after the study. It must be kept by the site for as long as needed to comply with any applicable rules and regulations, ICH-GCP as well as instructions from Idorsia. If the site needs to transfer the site master file to another location and/or if site facility can no longer store the site master file the investigator must inform Idorsia immediately.

If the investigator will change, or if the site will relocate, the monitor must be notified as soon as possible.

6.1.5 Audit

Idorsia's Quality Assurance, Systems & Compliance representatives may audit the investigator site (during the study or after its completion). The purpose of this visit will be to determine the investigator's adherence to ICH-GCP, the protocol, and applicable regulations; adherence to Idorsia's requirements (e.g., standard operating procedures) will also be verified. Prior to initiating this audit, the investigator will be contacted by Idorsia to arrange a time for the audit.

The investigator and staff must cooperate with the auditor(s) and allow access to all study documentation (e.g., subject records) and facilities.

6.1.6 Inspections

Health authorities and/or IEC/IRB may also wish to conduct an inspection of Idorsia's clinical study (during the study or after its completion).

Should an inspection be requested by a health authority and/or IEC/IRB, the investigator must inform Idorsia immediately, (usually via the monitor), that such a request has been made.

The investigator and staff must cooperate with inspector(s) and allow access to all study documentation (e.g., subject records) and study facilities.

6.1.7 Handling of study treatment(s)

The sponsor will supply all study treatment(s) to the site according to local regulations. Study treatment supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the study treatment labels. The site must maintain an accurate record of the shipment and dispensing of study treatment(s) on an accountability form, which must be given to the monitor at the end of the study. An accurate record of the date and amount of study treatment(s) dispensed to each subject must be available for inspection at any time.

All study treatment supplies are to be used only in accordance with this protocol and not for any other purpose. The responsible person must not destroy any study treatment labels or unused study treatment supply. On termination of the study, the monitor will check accountability of all used and unused study treatment.

Used and unused study treatment containers must be returned to the sponsor depot once study treatment accountability is final and has been checked by the sponsor or its deputy, and written permission for destruction has been obtained from the sponsor.

6.1.8 Publication and reporting of study results

Study results will be documented in a clinical study report that will be signed by Idorsia representatives and the investigator.

The investigator will have the opportunity to review the analysis of the data and to discuss the interpretation of the study results with Idorsia prior to publication.

The sponsor will post the key elements of this protocol and the summary of results within the required timelines on publically accessible databases (e.g., clinicaltrials.gov, EU database), as required by law and regulation.

In accordance with Good Publication Practices and ethical practice, the results of the study will be submitted for publication in a peer-reviewed journal. Study results can be submitted for presentation at a congress before publication in a peer-reviewed journal.

Authorship will be determined in accordance with the International Committee of Journal Editors criteria, and be based on:

- Substantial contributions to: the conception or design of the study, or the acquisition, analysis or interpretation of data; and
- Drafting of the publication or critical review for important intellectual content; and
- Providing final approval of the version to be published; and
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The list of authors of any publication of study results may include representatives of Idorsia, and will be determined by mutual agreement.

Any study-related publication written independently by investigators must be submitted to Idorsia for review at least 30 days prior to submission for publication or presentation. Upon review, Idorsia may provide comments, and may also request alterations and/or deletions for the sole purpose of protecting its confidential information and/or patent rights. Neither the institution nor the investigator should permit publication during such a review period.

6.1.9 Disclosure and confidentiality

By signing this protocol, the investigator agrees to keep all information provided by the sponsor in strict confidence, and to request similar confidentiality from his or her staff and the IEC/IRB. Study documents provided by the sponsor (including IBs, protocols, eCRFs, and other protocol-related documents) will be stored appropriately to ensure their confidentiality. The information provided by the sponsor to the investigator may not be disclosed to others without direct written authorization from the sponsor, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial.

6.1.10 Premature termination or suspension of the study

Both the sponsor and the investigator reserve the right to terminate the study at any time.

The study may be prematurely terminated if the sponsor decides to discontinue the development of ACT-774312 (continuation has become scientifically meaningless) or due to significant safety findings occurring in this study.

If a study is prematurely terminated or suspended, the sponsor must promptly inform the investigator, the IECs/IRBs and health authorities, as appropriate, and provide the reasons for the termination or suspension.

If the study is prematurely terminated or suspended for any reason, the investigator, in agreement with the sponsor, must promptly inform all enrolled subjects, and ensure their appropriate treatment and follow-up.

In addition, if the investigator terminates or suspends a study without prior agreement from the sponsor, the investigator must promptly inform the sponsor and the IEC/IRB, and must provide the sponsor and the IEC/IRB with a detailed written explanation of the termination or suspension.

If the IEC/IRB terminates or suspends its approval / favorable opinion of a study, the investigator must promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

6.2 Good Clinical Practice

6.2.1 Ethics and Good Clinical Practice

Idorsia and the investigators will ensure that the study is conducted in full compliance with ICH-GCP guidelines, the principles of the "Declaration of Helsinki" and with the laws and regulations of the country in which the research is conducted.

6.2.2 Ethics Committee / Institutional Review Board

The investigator must submit this protocol and any related document provided to the subject (such as subject information used to obtain informed consent) to an IEC or IRB. Approval from the committee must be obtained before starting the study, and must be documented in a dated letter to the investigator, clearly identifying the study, the documents reviewed, and the date of approval. A list of members participating in the meeting must be provided, including the functions of these members. If study staff were present, it must be clear that none of these persons voted.

Modifications made to the protocol after receipt of the IEC/IRB approval must also be submitted as amendments by the investigator to the IEC/IRB in accordance with local procedures and regulations [see Section 6.1.1].

6.2.3 Informed consent

It is the responsibility of the investigator/delegate to obtain informed consent according to ICH-GCP guidelines and local regulations from each individual participating in this study and/or legal representative. The investigator/delegate must explain to subjects that they are completely free to refuse to enter the study, or to withdraw from it at any time for any reason.

The ICF will be provided in the country local language(s).

Site staff authorized to participate to the consent process and/or to obtain consent from the subject and/or legal representative will be listed on Idorsia Delegation of Authority (DoA) form. A study physician must always be involved in the consent process.

The subject and/or legal representative must sign, personally date and time (if appropriate) the ICF before any study-related procedures (i.e., any procedures required by the protocol) begin. The ICF must also be signed, personally dated and timed (if appropriate) by the authorized site staff listed on the Idorsia DoA form.

A copy of the signed and dated ICF is given to the subject and/or legal representative; the original is filed in the site documentation.

The informed consent process must be fully documented in the subject's medical records, including study reference, subject number, date/time (if applicable) when the subject was first introduced to Idorsia clinical study, date/time (if applicable) of consent, who participated in the consent discussion, who consented the subject and any additional person present during the consent process (e.g., subject family member), copy of the signed ICF given to the subject / legal representative.

In the case that the site would like to recruit a subject who would be considered as vulnerable (e.g., subject cannot read or write, does not speak or understand the ICF language), additional measures must be implemented in order to ensure subject rights are respected and the consent obtained is legally valid. Idorsia, the regulatory authorities (if applicable) and the IEC/IRB must be informed prior to the recruitment. The consent process (e.g., involvement of an impartial witness) must be fully described, submitted to, and approved by the IEC/IRB, according to procedures and before subjects are recruited.

6.2.4 Compensation to subjects and investigators

The sponsor provides insurance in order to indemnify (with both legal and financial coverage) the investigator/center against claims arising from the study, except for claims that arise from malpractice and/or negligence.

The compensation of the subject in the event of study-related injuries will comply with applicable regulations.

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8 APPENDICES