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

	• 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.

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.

- 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.

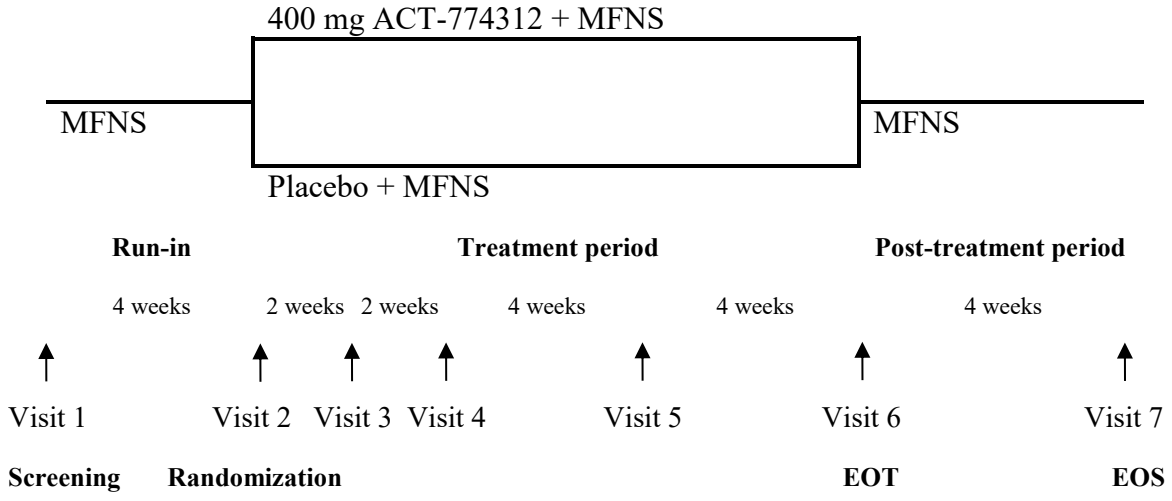
Approximately 24 adult subjects will be randomized in a 2:1 ratio to either ACT-774312 (approximately 16 subjects) or placebo (approximately 8 subjects).

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.

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).

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

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.

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.

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.

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

	• 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).

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

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.

- 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.

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

- 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.

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.

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