PROTOCOL

Treatment of rhinosinusitis with nasal polyposis with dupilumab and mepolizumab: A randomized, multi-centre, head-to-head comparison in real-world Danish patients

Trial ID: TORNADO

EU CT no.: 2022-502250-14-00

Abbreviations

ACQ: Asthma control questionnaire
CRS: Chronic Rhinosinusitis
CRSwNP: Chronic Rhinosinusitis with polyposis
CRSsNP: Chronic Rhinosinusitis without (sine) polyposis
CTIS: Clinical Trials Information System
DMC: Danish Medicines Council
EMA: European medicines agency
EOS: Eosinophils – white blood cells with high activity in type 2 inflammation
EPOS2020: European Position Paper on Rhinosinusitis and Nasal Polyps 2020
ESS and FESS: (functional) Endoscopic sinus surgery
FeNO: Fractional exhaled nitrous oxide
Hpf: High power field – the field of view under a microscope with x400 magnification
HRQoL: Health-related quality of life
ICS: inhaled corticosteroid – used for asthma treatment
Ig: Immunoglobulin
INCS: Intranasal corticosteroids – topical corticosteroids used in the nose for CRS
LoS: Loss of smell
LPLV: last patient, last visit
MCID: Minimal clinically important difference
NCS: Nasal congestion score – Subjective measure of nasal congestion (0-3).
N-ERD: NSAIDs Exacerbated Respiratory Disease – intolerance to NSAIDs
NPS: Nasal polyp score – objective measure of nasal polyp size (0–4 on either side, total 0–8)
NSAID: non-steroidal anti-inflammatory drugs
OCS: Oral corticosteroids
PROM: Patient reported outcome measure
QoL: Quality of life
SNOT-22: Sino-nasal outcome test – 22 (HRQoL)
SSIT-16: Sniff'n Sticks Identification Test 16 – Test of ability to identify house-hold smells (0–16)
STARR-15: Standard Tests of Asthma, Allergic rhinitis and Rhinosinusitis – 15 items (HRQoL)
VAS: visual analogue scale

1. Protocol synopsis/summary

Title of trial:

Treatment of rhinosinusitis with nasal polyposis with Dupilumab and Mepolizumab (TORNADO): A randomised, multi-center, head-to-head comparison in real-world Danish patients

Objectives:

- The primary objective is to compare the efficacy of mepolizumab versus dupilumab on objective and subjective symptoms of CRSwNP and related comorbidities in an attempt to determine non-inferiority between the two, or possibly; superiority of dupilumab over mepolizumab.
- The secondary objective is to explore any other relevant differences between mepolizumab and dupilumab in terms of frequency of AEs, need for rescue treatments, diversity in outcome based on endotype or comorbidity or other factors, that can lead to a patient-centred approach, when choosing treatment for CRSwNP.

Trial design:

A randomized, multi-center non-inferiority trial (phase IV RCT). The trial is unblinded. Investigational medicinal products (IMPs) will be "off-the-shelf" and administered in standard dosages and -intervals.

Trial population:

We aim to include 220 patients with severe, uncontrolled CRSwNP (110 patients in each treatment group).

Main inclusion criteria:

Age ≥18 and able to speak and read Danish language.
Furthermore, in accordance with the criteria set by the Danish Medicines Council (DMC):

Patients **must have**:

- Bilateral polyps in nose and sinuses
- ESS within the last three years (unless unfit for surgery - in this study defined as either a severe somatic disease, for which other specialist advise against surgery, e.g., cardiac disease, pulmonary disease, or coagulation disorder OR/AND severe anxiety which can either be due to previous traumatic experiences with surgery or the postoperative period, post-traumatic stress disorder or severe anxiety disorder. In cases of doubt, investigators can ask for a written statement from the general practitioner or a psychiatrists/psychologist)Optimal local treatment with saline irrigation and topical nasal steroids for at least three months (unless contraindicated)
- Evidence of type 2 inflammation (as per EPOS2020 – see table 3)

Furthermore, patients must fulfil **three out of the following five criteria:**

- Need for systemic corticosteroids (at least two courses/year OR long-term treatment >3 months) or contraindication to systemic steroids
- Significantly impaired QoL (SNOT-22 score≥50)
- Significant LoS (SSIT-16 score 0-8)

- NPS ≥5 (with a score of at least 2 on either side)
- Asthma diagnosis (requiring inhaled corticosteroid (ICS))

Patients who intend to achieve pregnancy within the one year follow up period are not eligible.

Main exclusion criteria:

- Systemic corticosteroid treatment within the last three months
- Endoscopic sinus surgery (ESS) within the last six months
- Non-adherent to medicine regimens
- Hypersensitivity to the active substance or any of the excipients in the two IMPs
- Not able to understand spoken and/or written Danish
- Participation—current or previous—in another investigational drug trial with monoclonal antibodies for asthma, CRSwNP, atopic dermatitis or allergic rhinitis.
- Pronounced fear of needles
- Pregnant or breastfeeding patients.

Methods:

Subjects fulfilling the inclusion criteria will be randomized 1:1 to either dupilumab or mepolizumab. After 24 weeks a halfway evaluation will decide if subjects are to stay in their current treatment arm, or cross-over to the opposite arm.

By including 220 participants (effectively 176 participants after 20% drop-outs) we will achieve a power of >95% to show non-inferiority of dupilumab to mepolizumab for both co-primary endpoints with the following criteria: Level of significance for both endpoints of a one-sided test, $p<0.025$ and including previously found *standard deviation* (SD) values 1.9 for NPS and 22 for SNOT-22, an expected superior effect of 0.7 for NPS and 7 on SNOT-22, a *minimal clinically relevant difference* (MCID) of 1 for NPS and 12 for SNOT-22, respectively.

Trial endpoints:

The **coprimary endpoints** are:

- Change in NPS-score from baseline to week 24
- Change in SNOT-22 score from baseline to week 24

Secondary endpoints

- Change in NPS-score from baseline to week 48
- Change in SNOT-22 score from baseline to week 48
- Proportion of subjects meeting the Danish Medicines Council response criteria (table 2) at 24 and 48 weeks
- Change in loss of smell (LoS) measured by Sniffin' Sticks Identification Test 16 (SSIT-16) at weeks 24 and 48
- Change in Asthma Control Questionnaire (ACQ) score at weeks 24 and 48
- Change in CRS visual analogue scale (VAS) score at weeks 24 and 48
- Change in perceived sense of smell - VAS score at weeks 24 and 48
- Change in lung fractional exhaled nitrous oxide at weeks 24 and 48
- Change in Tympanometry at weeks 24 and 48
- Change in allergy/N-ERD symptoms – VAS score at weeks 24 and 48
- Change in FEV1 at weeks 24 and 48

- Nasal Congestion Score at weeks 24 and 48
- The Lund-Mackay score at weeks 24 and 48
- Proportion of subjects requiring rescue treatment

Trial medication:
All trial medication will be "off the shelf" *i.e.* no special labelling. It will be provided by hospital pharmacies in accordance with GMP. The investigational medicinal products (IMPs) are dupilumab (Dupixent, Sanofi) and mepolizumab (Nucala, GSK). Dupilumab are given as subcutaneous injections of 300 mg every two weeks in the first 24 weeks. If the DMC response criteria (table 2) are met after 24 weeks, the dosing interval will be increased to every four weeks, in accordance with previous research (1,2). Mepolizumab is administered subcutaneously as 100 mg sc. every four weeks. Patients will continue their basic treatment of INCS and saline irrigation, unless contraindicated.
If rescue treatment is needed, a course of oral corticosteroids (Prednisolone) 37.5 mg once daily for 7 days will be given.
The treatment response will be evaluated after 24 weeks, and in case the criteria are not met, subjects will cross-over to the opposite treatment arm.

Trial schedule:

Planned first subject first visit	March 2023
Planned last subject randomized	March 2024
Planned last subject last visit:	June 2025
End of trial	October 2025

2. Trial schedule

Figure 1 – Trial Schedule (see details in section 10)

TORNADO trial	visit 1$	visit 2$	visit 3£	visit 4£	visit 5$	visit 6£	visit 7$	visit 7b$	visit 8£	visit 9£	visit 10£	visit 11£	visit 11##	visit 12£	visit 13$	visit 14##
Week no. (+/- 7 days)	**(-4)–0**	4	8	12	16	20	**24**	**26**	28	32	36	40	42	44	**48**	**50**
Informed consent	x															
Randomisation	x															
CRS and asthma history	x															
Asthma test*	x															
Clinical examination	x						x								x	x##
Medicine adherence check	x				x		x					x#	x##		x	x##
Smell test (SSIT-16)	**x**						**x**								**x**	x##
Nasal polyp score	**x**						**x**								**x**	x##
SNOT22	**x**				x		**x**					x#	x##		**x**	x##
ACQ	**x**				x		**x**					x#	x##		**x**	x##
VAS-scores ****	x				x		x					x#	x##		x	x##
Nasal congestion score	x				x		x					x#	x##		x	x##
STARR15	x															
FEV1	x						x								x	x##
FeNO	x						x								x	x##
Tympanometry	x						x								x	x##
Blood test (blood EOS)	x	x			x		**x**	**x##**	x#			x#	x##		x	x##
Allergy testing	x															
Polyp biopsy	x**															
Lund-Mackey Score	x								x#						x	x##
Evaluation of AE/SAE/SUSAR					x		**x**	**x**				x#	x##		x	x#/x##
Response evaluation/possible cross-over							x								x	x##
Injection w. biologic***	x	x	x	x	x	x	**x¤**	**x¤##**	x	x	x	x	x	x		
End of Study															X	X##

* = Carried out if not previously done. Diagnosis is to be made by a medical specialist.

** = unless one was already taken within <12 months

*** = Dupilumab will be administered every 2 weeks for the first 24 weeks of treatment

**** = VAS scores: Asthma, CRS, allergic rhinitis, smell

= Only necessary if participant crosses-over from mepolizumab to dupilumab

= Only necessary if participant crosses-over from dupilumab to mepolizumab

¤ = First injection with new drug if participant crosses-over.

Bold writing = evaluation criteria, <u>underlining</u> = primary endpoint, parentheses () = last injection with trial medication

$ = mandatory visit

£ = Visit not mandatory. Can be omitted if patient can self-administer injections

3. Background/Rationale

3.1 Disease background

Chronic rhinosinusitis with nasal polyps (CRSwNP) is an inflammatory disease of the nasal and paranasal mucosa leading to mucosa thickening and polyp formation from the ethmoid sinuses. The estimated prevalence of CRSwNP is 2-4% in European adults (3). Common symptoms include nasal obstruction, reduced sense of smell, nasal discharge, and sleep disturbances—resulting in a significantly decreased quality of life (4,5). In many cases, CRSwNP patients have co-existing asthma, allergic rhinitis and/or aspirin sensitivity (N-ERD) (6,7). This correlation is due to the fact that these diseases share a common inflammatory pathway—so-called type 2 inflammation—characterized by the presence of interleukins (IL) -4, -5 and -13 in combination with eosinophilic cells and immunoglobulin E (IgE) (8)

Danish studies have shown that 40% of patients with CRSwNP in primary ENT clinics and 65% of patients referred to a tertiary hospital for ESS surgery had co-existing asthma – a large proportion of them previously undiagnosed (9,10). This association between upper and lower airway disease has coined the term *Global Airways* and has led to the growing awareness that disease in both upper and lower airways should be treated simultaneously, preferably in a multidisciplinary effort (1–3) (11).

The current cornerstone of treatment for patients with CRSwNP is daily saline irrigation and topical steroids, sometimes supplemented by courses of antibiotic treatment. In cases where this treatment is insufficient, courses of systemic oral corticosteroid (OCS) and/or endoscopic sinus surgery (ESS) is added (8). The surgical treatment reduces the inflammatory load by removal of inflamed mucus membrane, as well as widening the natural drainage openings in the sinus system, thereby facilitating access for topical steroids. Furthermore, it reduces symptoms such as nasal congestion, reduced smell and facial pressure. By this combined treatment approach most patients can achieve a satisfactory result. However, for about 10% of patients with the most severe disease, repeated courses of OCS or surgery are needed, resulting in a severely reduced health-related quality of life (HRQoL) with many sick-days from work (*absenteeism*) as well as feelings of fatigue, depression and poor concentration (*presenteeism*) (5, 6).

3.2 Treatment of CRSwNP

Daily treatment with intranasal steroids is recommended in the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (8). They are generally well tolerated and have minor to no systemic effects. Systemic oral corticosteroids are effective but are associated with many unwanted systemic side effects (7). Endoscopic sinus surgery is generally a safe procedure and serious adverse effects are rare, however they lead to several sick days, and 40% of patients in an American study had polyp recurrence at 18 months follow-up (12,13).

Monoclonal antibodies (MABs)—also referred to as *biologics*—target various key drivers in the pathophysiological immunological response and have proven effective and safe for the treatment of CRSwNP caused by type 2 inflammation, with or without concurrent asthma (2,14).

3.3 Trial rationale

Biologics have been used to treat asthma for more than 15 years, but were recently approved for the treatment of CRSwNP, and only very recently were two different MABs approved in Denmark; mepolizumab (Nucala) and dupilumab (Dupixent). Both drugs have shown excellent efficacy and safety, with comparable improvements in both objective and subjective measures and low risk of

adverse effects (AEs) (2,14). However, the phase-III trials varied slightly, for example in the handling of missing data, and patients in the SYNAPSE study generally had a higher disease burden, thus making direct comparison of the two drugs difficult (15). To date, a few meta-analyses exist that seek to indirectly compare the different available biologics for CRSwNP (16–18). The conclusion in these studies is similar; dupilumab is superior to the rest (including mepolizumab) on most subjective and objective parameters, including improvements of olfaction. However, due to the before-mentioned uncertainties and differences, the Danish Medicines Council (DMC) concluded that the differences between mepolizumab and dupilumab were insignificant, and hence a recommendation to the five health regions of Denmark to primarily prescribe the cheapest (mepolizumab) was made (15). It was noted that in some cases clinicians may wish to prescribe dupilumab—for example in cases where olfactory improvements are of special significance—and hence it was recommended to use mepolizumab over dupilumab in an 80/20-fashion (15). In the report, the DMC also encourages that an RCT is performed to enable direct comparison between the two, and it also states that it will re-assess the recommendations in two-three years based on the observational data.

The positive effects of mepolizumab and dupilumab on both upper and lower airway disease are well documented, and the introduction of biologics are commonly regarded as *game-changers* for patients with uncontrolled CRSwNP and healthcare providers. Their high price, however, warrants cost-effective use of them. There is international controversy whether their use is cost-effective compared to basic supportive care (BSC) in combination with ESS. One US study found that dupilumab was ten times costlier and slightly less effective than ESS (8.95 quality-adjusted life years (QALY) vs. 9.80 QALYs with ESS)—regardless of revision surgery rates (19). However, this study only considered direct costs of treatment in relation to health benefit and did not bring into the equation the indirect costs associated with decreased productivity due to absenteeism, presenteeism and later in life; costs of treating long-term adverse effects of repeated courses of systemic corticosteroids (osteoporosis, diabetes, cataracts, obesity, hypertension, and glaucoma). In contrast, a recent Italian study concluded that dupilumab as an add-on to conventional BSC was cost-effective in gained quality-adjusted life-years compared to BSC alone (20). The true costs of uncontrolled disease are difficult to estimate, as several factors such as absenteeism, presenteeism and indirect costs of long-term adverse effects of OCS tend to be underestimated. A recent European study, however, estimated that total direct costs pr. Patient year for CRSwNP patients were €1501 whereas indirect costs were almost four times as high (€5659). Direct costs were mainly attributable to hospitalization and outpatient visits, whereas indirect costs were due to *absenteeism* and *presenteeism* (21). The study shows that indirect costs far exceed direct costs, even without including the costs of treating the long-term complications of repeated courses of systemic steroid.

We aim to perform a randomized, prospective, multi-centre, head-to-head study in real-world Danish patients. To our knowledge, this will be the first of its kind in the world, and it will provide much-needed knowledge to healthcare workers and policy makers all around the world, and aid them in making rational, cost-effective decisions on how to use these new promising—but very costly—biologic drugs. The knowledge gained will be of benefit not only to healthcare providers and taxpayers, but particularly to CRSwNP patients. A major strength of our study is that it is investigator-initiated and 100% uninfluenced by financial interests of the pharmaceutical industry. The trial is exclusively funded by the public health system and a non-profit organization. Furthermore, the

healthcare system in all regions of Denmark is completely reimbursed by the state, so inclusion of participants in our study will be free from economic bias.

3.4 Benefit-risk assessment and ethical considerations

This will be an RCT where all study participants will be randomized to one of two effective drugs (*i.e.* no placebo group), and therefore all participants stand to gain from participating in the study. When the DMC allowed the prescription of biologics for CRSwNP in Denmark, it was strongly encouraged that an observational study be undertaken to measure effects and adverse effect to enable an analysis after two-three years. This quality assessment study was already planned before the second biologic (mepolizumab) was approved in Denmark thereby laying the ground for this RCT, meaning that there was already a strategy for the number and types of diagnostic tests before treatment and at follow-up visits. The number and types of tests and follow-up visits in our study are identical, so participants will not be exposed to extra testing or discomfort by joining our trial.
The adverse effects of both drugs are generally very mild, and in phase III studies data actually showed that adverse events were slightly more common in the placebo group than in the treatment group (2,14). The most common adverse events in both studies were nasopharyngitis, headache, nose bleeding, and irritation or tenderness at the site of injection. In the LIBERTY NP SINUS 52-study seven cases of non-severe conjunctivitis was reported in the treatment group, and one in the placebo group. Four patients experienced eosinophilia along with clinical symptoms that were reported as treatment-emergent adverse events: one patient experienced eosinophilic granulomatosis with polyangiitis (EGPA) while receiving dupilumab; one patient experienced eosinophilia along with arthralgia, asthma exacerbation, and insomnia while receiving dupilumab; one patient experienced EGPA more than 300 days after receiving. In the SYNAPSE study, there was no difference in adverse events between the treatment group and placebo group.

4. Hypothesis

This is a non-inferiority study where we expect to find no clinically relevant difference in treatment outcome between dupilumab and mepolizumab for the treatment of severe, uncontrolled CRSwNP.

5. Objectives

5.1 Primary objective

The primary objective is to compare the efficacy of mepolizumab versus dupilumab on objective and subjective symptoms of CRSwNP and related comorbidities in an attempt to determine non-inferiority between the two, or possibly; superiority of dupilumab over mepolizumab.

5.2 Secondary objective

The secondary objective is to explore any other relevant differences between mepolizumab and dupilumab in terms of frequency of AEs, need for rescue treatments, diversity in outcome based on endotype or comorbidity or other factors, that can lead to a patient-centred approach, when choosing treatment for CRSwNP.

5.3 Primary endpoints

The coprimary endpoints are:

- Change in NPS-score from baseline to week 24
- Change in SNOT-22 score from baseline to week 24

Baseline values will be recorded at randomization.
The null hypothesis will be proven if we find a difference of ≥1 on NPS-score and ≥12 points on SNOT-22.

The Nasal polyp score is a grading system for polyp size ranging from 0 to 4 in each nostril, thus giving a total score ranging from 0 to 8. The polyp size is assessed by the examiner and graded as follows; 0 = no polyps, 1 = polyps confined to the middle meatus, 2 = multiple polyps occupying the middle meatus, 3 = polyps extending beyond middle meatus, 4 = polyps completely obstructing the nasal cavity.

SNOT-22 is a patient-reported measure of outcome (PROM) consisting of 22 individual questions for use in CRS with or without nasal polyposis. The SNOT-22 covers a broad range of disease-specific HRQOL topics including physical complaints, functional limitations, and emotional consequences. The SNOT-22 has shown to be reliable and valid in clinical practice to assess the impact of CRSwNP on disease-specific HRQOL and to measure treatment-related change. The minimal clinically relevant difference is 8.9 points (22)

5.4 Secondary endpoints

- Change in NPS-score from baseline to week 48
- Change in SNOT-22 score from baseline to week 48
- Proportion of subjects meeting the Danish Medicines Council response criteria (table 2) at 24 and 48 weeks
- Change in loss of smell (LoS) measured by Sniffin' Sticks Identification Test 16 (SSIT-16) at weeks 24 and 48
- Change in Asthma Control Questionnaire (ACQ) score at weeks 24 and 48
- Change in CRS visual analogue scale (VAS) score at weeks 24 and 48
- Change in perceived sense of smell - VAS score at weeks 24 and 48
- Change in lung fractional exhaled nitrous oxide at weeks 24 and 48
- Change in Tympanometry at weeks 24 and 48
- Change in allergy/N-ERD symptoms – VAS score at weeks 24 and 48
- Change in FEV1 at weeks 24 and 48
- Nasal Congestion Score at weeks 24 and 48
- The Lund-Mackay score at weeks 24 and 48
- Proportion of subjects requiring rescue treatment

6. Trial design

6.1 Summary of trial design

A randomized, multi-centre non-inferiority trial (phase IV RCT). The trial is unblinded since patients, caregivers and local investigators can guess which group the patient is in due to differences in treatment interval. We decided to not inject placebo every other time in the mepolizumab due to ethical and practical reasons.

We will seek to get the trial approved as a *low intervention clinical trial* (LICT) with the European *Clinical Trials Information System* (CTIS) under *European Medicines Agency* (EMA). We believe the trial qualifies as a LICT since the included pharmaceuticals are being used for their approved indications in either standard dosages and intervals, or dosage intervals that are well founded in the scientific literature, and since participants will undergo no additional discomfort compared to standard clinical practice for biologics in Denmark[1].

We expect to include 220 subjects with a drop-out rate of 20%, leaving 176 patients for statistical analysis.

Patients with severe, uncontrolled CRSwNP with/without concomitant asthma referred for evaluation and possible treatment with a biologic—and who fulfil the inclusion criteria (see section 7.1)—will be invited to participate in the study. At the first visit they will be screened for disease severity and possible comorbidity with several diagnostic tests and standardized questionnaires (see section 10).

Following inclusion in the study, participants will be stratified by smell loss (SSIT-16 0-8 and 9-16), gender and geographic location and then randomized 1:1 to receive treatment with either

- dupilumab (Dupixent) 300 mg injection every two weeks, or
- mepolizumab (Nucala) 100 mg injection every four weeks

The trial subjects will receive treatment for 24 weeks by which time treatment response will be evaluated based on the response criteria (table 2). Depending on the results, patients will either change dosage intervals, switch-over to the other drug or stay on the drug there are on. This will take place in the following way (see also figure 2):

- dupilumab-group:
    - If the response criteria are fulfilled (table 2): participants will change to a prolonged dosage interval, *i.e.* every 4 weeks[2] from week 24.
    - If the response criteria are not met: participants will switch to mepolizumab 100 mg every four weeks.
- mepolizumab-group:
    - If the response criteria are fulfilled: participants will continue same treatment regimen until week 48
    - If the response criteria are not met: participants will switch to dupilumab 300 mg every two weeks

In addition to the trial medicine, patients will continue basic treatment of INCS and saline irrigation, unless contraindicated.

In cases where participants cross-over to the opposite treatment arm, a CT scan of the sinuses will be repeated.

[1] Since biologics are being introduced on a trial period of 2-3 years, their use and effect is strictly monitored by the Danish Medicines Council.

[2] This dosage interval was proven in the LIBERTY NP SINUS-52 study to be effective for patients who had responded in the first 24 weeks(2), and was recently supported in a real-world study from the Netherlands (42). It was recommended by the DMC to switch to this interval after 24 weeks in dupilumab-responders(15).

Figure 2 – trial design

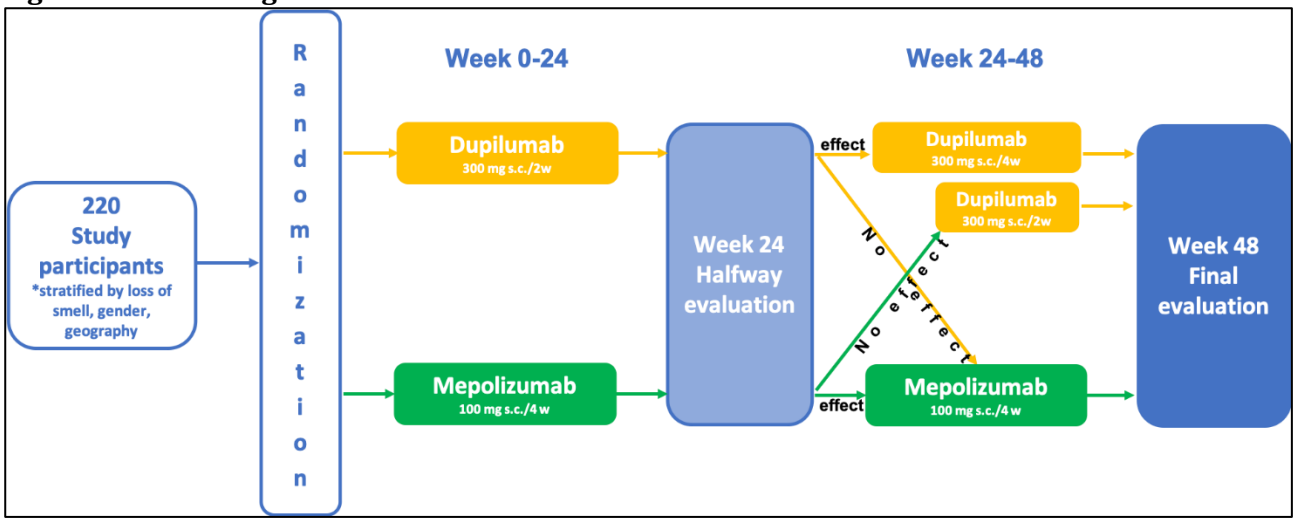

Table 2 – Minimal response criteria (as stated by the Danish Medicines Council)

	24 weeks	52 weeks*
NPS	≥ 1 point	≥ 2 points
SNOT-22	≥ 12 points	≥ 12 points
Evaluation of sense of smell	Depends on the value at the start of treatment. Either - normal sense of smell (i.e. SSIT-16 >8) Or - If the sense of smell was good before biological treatment, it must not deteriorate.	
Improvement of comorbidity	The desired minimum improvement is 0.5 points on the Asthma Control Questionnaire (ACQ) .	

- If patients do not achieve an improvement of 2 out of 4 items the treatment is discontinued
- If there is effect of treatment, reduction in treatment (e.g., 1 injection per month) should be contemplated

***For the sake of equally long observation periods in cases of cross-over, the final evaluation takes place after 48 weeks of follow-up, and not 52 weeks in this study.**

6.2 Discussion of trial design

This is a head-to-head, real-world study directly comparing two relatively new drugs for the indication CRSwNP. We therefore decided on a design with two active arms and no placebo arm, as the intention is to test the hypothesis by the DMC that the two drugs are non-inferior to each other. Participants will start treatment in the standard dosage and -interval, but the cross-over design enables switching to the other drug in the case of absence of treatment response. This gives us the opportunity to investigate if some patients might benefit from one drug, and not the other. By comparing non-responders to their endotype (tissue biomarkers obtained from tissue biopsies) we are hoping to learn how to better predict who will gain most from one drug, and not the other—and thereby move one step closer to personalized medicine.

Furthermore, we decided to increase injection intervals for participants in the dupilumab-arm, to see if the previously found sustained benefit in the LIBERTY NP SINUS-52 will hold true in these real-

world Danish patients. If symptoms return/worsen, the dosage interval will be returned to every two weeks.

Lastly, we will stratify patients into two groups based on their LoS; patients who are anosmic (score 0-8 in SSIT-16) and patients with normal or only mild loss of smell (SSIT-16 score 9-16). We decided this approach since LoS is one of the most significant effectors of HRQoL for CRSwNP-patients, and because we wish to include change in LoS as one of the most important secondary endpoints (7). There are suspicions that dupilumab is mepolizumab superior in terms of improvement on smell, and with this direct comparison we expect to be able to add knowledge to this suspicion.

6.3 Trial schedule

Planned first subject first visit	March 2023
Planned last subject randomized	March 2024
Planned last subject last visit:	March 2025
End of trial	November 2025

7. Trial population

7.1 Inclusion criteria

Subjects must be 18 or over and be able to speak and read Danish language. Furthermore, the inclusion criteria follow the criteria determined for treatment with biologics by the DMC, *i.e.:*

Patients **must have**:

- **Bilateral polyps** in nose and sinuses
- **ESS within the last three years** (unless unfit for surgery - in this study defined as either a severe somatic disease, for which other specialist advise against surgery, e.g., cardiac disease, pulmonary disease, or coagulation disorder OR/AND severe anxiety which can either be due to previous traumatic experiences with surgery or the postoperative period, post-traumatic stress disorder or severe anxiety disorder. In cases of doubt, investigators can ask for a written statement from the general practitioner or a psychiatrists/psychologist)**Optimal local treatment** with saline irrigation and topical nasal steroids for at least three months (unless contraindicated)
- Evidence of **type 2 inflammation** (as per EPOS2020 – see table 3)

Furthermore, patients must fulfil **three out the following five criteria:**

- Need for systemic corticosteroids (at least two courses/year OR long-term treatment >3 months) or contraindication to systemic steroids
- Significantly impaired QoL (SNOT-22 score≥50)
- Significant LoS (SSIT-16 score 0-8)
- NPS ≥5 (with at least 2 on either side)
- Asthma diagnosis (requiring inhaled corticosteroid (ICS))

Table 3 – Criteria for evidence of type 2 inflammation (as stated by EPOS2020) (8)

Type 2 inflammation (at least one of the following)
– Current blood eosinophilia (≥250 10^6 cells/L / ≥0,25 10^9cells/L) – Previous blood eosinophilia (>0,30 x 10^9 cells/L during last 12 months) – Polyp eosinophilia (cell count in at least 2 out of 3 hotspots with x40 magnification) ≥10 cells/high power field – Total serum IgE ≥100 IU/mL – Late onset eosinophilic asthma – FeNO ≥ 25 ppb

7.2 Exclusion criteria

- Systemic corticosteroid treatment within the last three months
- Endoscopic sinus surgery (ESS) within the last six months
- Non-adherent to medicine regimens
- Hypersensitivity to the active substance or any of the excipients in the two IMPs
- Not able to understand spoken and/or written Danish
- Participation—current or previous (within the last year)—in another investigational drug trial with monoclonal antibodies for asthma, CRSwNP, atopic dermatitis or allergic rhinitis.
- Pronounced fear of needles
- Pregnant or breastfeeding patients (see further explanation in section 9).

7.3 Recruiting

Eligible subjects, either from the out-patient clinic or hospitalized, will be identified by medical professionals (MD or nurse) involved in their treatment. The subjects will be asked if they are interested in information about the trial. If they accept, they will be informed about the trial by either that same medical professional or specific trial personnel. Written consent from an eligible subject must be obtained before any transfer of information on the subject from a medical professional involved in the treatment to trial personnel. Written consent must be obtained by a medical doctor. Furthermore, the author group will send out a letter to all private ENT practices in Denmark informing them about the study and the new possibility of referring patients with severe, uncontrolled CRSwNP to treatment with biologics and possible enrolment in this trial, or one of the other trials investigating the effects of biologics in Denmark.

7.4 Discontinuation

Subjects will be informed about the possibility of discontinuing the trial at any time and without giving a reason. We will encourage subjects to inform the investigator as soon as they have decided to discontinue the trial whereby the last administration of trial medication will be registered. In case of discontinuation, we will ask the subject to indicate a reason for the discontinuation which will be registered

Subjects will be discontinued from the trial in case of failure to adhere to the trial. If subjects fail to meet for treatment i.e., not receiving two or more injections, they are discontinued.

In cases of discontinuation, subjects will be booked for a final check for AEs/SAEs four weeks after the last treatment injection.

7.5 Pregnancy and anticonception

No teratogenic/foetal adverse effects have been reported in the literature and no formal contraindication due to pregnancy has been made for neither mepolizumab nor dupilumab (23–25). However, since scarce data exists, especially in the case of dupilumab, pregnant or breastfeeding subjects will be excluded if pregnancy is present or occurs during the run-in period before the CT scan

and first injection. Women in the fertile age will take a pregnancy test before entering the study. Fertile women included in the study shall use safe contraception (intrauterine contraception or hormonal contraception). This treatment shall be continued for minimum six weeks after terminating the treatment (see section 9.2).
If pregnancy occurs after treatment has started, subjects will be discontinued in the study, and their data will be included in the intention to treat analysis in a manner of last observation carried forward (see also section 7.4). Finally, patients who wish to become pregnant during the study period will not be eligible.

7.6 Rescue treatment

If participants need to receive rescue treatment (for example due to intolerable symptoms/intolerable adverse events) they will be offered rescue-treatment in the form of tablet Prednisolone 37.5 mg once daily for 7–10 days (injections are contraindicated in this trial due to their longer-lasting effect).

Surgery will be reserved for acute and threatening disease complications such as intra-orbital or intra-cranial infections, in accordance with normal clinical practice.

Results from the subject will be excluded in the "protocol analysis" but will be included in the "intended to treat (ITT)" analysis. Data will be analysed in a "last observation carried forward" (LOCF) fashion. Patients needing rescue treatment will be encouraged to stay on the prescribed drug until week 24, where they will be offered to cross-over to the other treatment arm.

If the reason for discontinuation is treatment failure and the subject is determined to discontinue in the study, time of treatment failure will be registered, and the participant will be offered rescue treatment (in the form of OCS or ESS in case of severe, acute complications such as intra-orbital or intra-cranial infections) following normal treatment guidelines (see also section 7.4).

Asthma exacerbations:

Subjects experiencing asthma exacerbations during the trial period will be guided to increase the ICS treatment, in accordance with normal clinical practice as per the Global Initiative for Asthma (GINA)-guidelines (26).

8. Randomization, blinding and sample size

8.1 Randomization

Subjects will be randomized in a 1:1 ratio and stratified by sense of smell (SSIT-16 0-8 and >8), geography (national multi-centre study) as well as gender.
Randomization will be performed with the built-in randomization module in REDCap. The method will be variable block randomization in blocks of 4-8 subjects. This design is to reduce bias of being able to guess/predict randomization patterns.

8.2 Blinding

The IMPs are off-the-shelf, and not specially labelled. Participants and caregivers will therefore be unblinded. The final data analysis will, however be performed with the investigator/statistician blinded to the treatment given.

8.3 Sample size

Based on the estimate by the DMC, we expect to be able to include 220 patients within 18 months (27)

By including 220 participants (effectively 176 participants after dropouts) we will achieve a power of >95% to show non-inferiority of dupilumab to mepolizumab for both co-primary endpoints with the following criteria:

- Level of significance for both endpoints of a one-sided test, $p<0.025$ and
- including the previously found *standard deviation* (SD) values 1.9 for NPS and 22 for SNOT-22 (14,28),
- an expected superior effect of 0.7 for NPS 7 on SNOT-22 (17) and
- a *minimal clinically relevant difference* (MCID) of 1 for NPS and 12 for SNOT-22, and
- assuming no negative correlation between the two co-primary endpoints, respectively (29).

We do not expect the study to have power to show superiority or equality between mepolizumab and dupilumab, but superiority analyses will be performed if the null hypothesis for non-superiority is rejected for both co-primary outcomes.

9. Trial products

9.1 Administration of trial products

Each subject will be randomly assigned to receive either dupilumab (investigational medicinal product (IMP) 1) or mepolizumab (IMP2). Please refer to figure 1 for a visual on the trial design. Trial medication will be provided by local hospital pharmacies in accordance with Good Manufacturing Practice (GMP). Trial medicine will not be specially labelled.
At visit 3 on day "0" each subject will be injected with one of the two; IMP1 or IMP2.
The first time the participant is injected, he/she will remain in the department for at least 30 minutes for observation of acute adverse events. Here the participant will be under constant supervision by a nurse or doctor. This also applies to subjects who have crossed-over and is injected with the new IMF for the first time.
In case of serious/life-threatening adverse events such as anaphylaxis, the patient will be already located at a tertiary hospital with quick access to advanced resuscitation, including anti-anaphylactic drugs, and in severe cases intubation or emergency crico-thyroidectomy.

The first three to five injection will take place at the hospital department, but after this there will be the possibility of the patient injection them self at home

9.1.1 Compliance/adherence with the trial medicine

Participants will be asked at each appointment if they are adhering to the treatment plan. An "injection diary" (see appendix 1) will be provided once participants switch to home-injections. Furthermore, FMK-online.dk will be checked in some cases, to check whether the patient has collected their medicine from the pharmacy (in cases where this is applicable).

9.2 Dupilumab: IMP1 (25)

Dupilumab (Dupixent, Sanofi) is a recombinant, monoclonal antibody that inhibits signalling by IL-4 and IL-13, cytokines that are key drivers of type 2 inflammation. Dupilumab is approved in several countries for the treatment of type 2 inflammation-derived diseases such as severe asthma, ectopic dermatitis and CRSwNP.

The EMA approved dosage is 300 mg s.c. every two weeks, but in the phase-III trial an increased dosage interval of every 4 weeks proved efficient to sustain clinical response after the initial 24 weeks of treatment (2). Based on these finding it was recommended by the DMC, that patients meeting response criteria (see table 2) after week 24 can try the prolonged dosage interval (30).

Dupilumab is administered subcutaneously. Median times to maximum serum concentration is 3-7 days. The absolute bioavailability ranges from 61-64%. Steady concentration is reached by week 16 (standard dose interval) and ranges across different clinical trials from 69.2±36.9 mcg/mL to 80.2±35.3 mcg/mL for 300 mg dose.
Elimination happens by parallel linear and non-linear pathways. Time to non-detectable concentrations for 300 mg s.c./2 weeks were 6-7 weeks (25).

Pregnancy: There is little data available for safety in pregnancy. Animal studies have shown no direct or indirect harmful effects. The EMA recommends use of dupilumab in pregnancy only if the benefits outweigh the risks.
Breastfeeding: It is unknown if dupilumab is excreted in breast milk. As for pregnancy, it must be assessed if the potential benefits justify the potential risks to the child.

In this trial it was decided to not include pregnant or breastfeeding women, as well as women planning to get pregnant within the study period. See section 7.5 for more details.

9.2.1 Undesired effects:

The following is an exert from (25). The section about paediatric populations have been removed since this study only includes adults. For full text and reference list, please refer to (25).

Summary of the safety profile
The most common adverse reactions are injection site reactions (includes erythema, oedema, pruritus, pain, and swelling), conjunctivitis, conjunctivitis allergic, arthralgia, oral herpes, and eosinophilia. Rare cases of serum sickness, serum sickness-like reaction, anaphylactic reaction, and ulcerative keratitis have been reported (see section 4.4).

Tabulated list of adverse reactions
The dupilumab safety data presented in Table 4 were predominantly derived from 12 randomised, placebo-controlled trials, including atopic dermatitis, asthma, and CRSwNP patients. These studies involved 4,206 patients receiving dupilumab and 2,326 patients receiving placebo during the controlled period are representative of the overall safety profile for dupilumab.

Listed in Table 4 are adverse reactions observed in clinical trials and/or postmarketing setting presented by system organ class and frequency, using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4: List of adverse reactions

MedDRA System Organ Class	Frequency	Adverse Reaction
Infections and infestations	Common	Conjunctivitis* Oral herpes*
Blood and lymphatic system disorders	Common	Eosinophilia
Immune system disorders	Uncommon Rare	Angioedema# Anaphylactic reaction Serum sickness reaction Serum sickness-like reaction
Eye disorders	Common Uncommon Rare	Conjunctivitis allergic* Keratitis*# Blepharitis*† Eye pruritus*† Dry eye*† Ulcerative keratitis*†#
Skin and subcutaneous tissue disorders	Uncommon	Facial rash#
Musculoskeletal and connective tissue disorders	Common	Arthralgia#
General disorders and administration site conditions	Common	Injection site reactions (includes erythema, oedema, pruritus, pain, and swelling)

*eye disorders and oral herpes occurred predominately in atopic dermatitis studies. † the frequencies for eye pruritus, blepharitis, and dry eye were common and ulcerative keratitis was uncommon in atopic dermatitis studies. # from postmarketing reporting.

Description of selected adverse reactions

Hypersensitivity
Cases of anaphylactic reaction, angioedema, and serum sickness/serum sickness-like reaction have been reported following administration of dupilumab (see section 4.4).

Conjunctivitis and keratitis related events
Conjunctivitis and keratitis occurred more frequently in atopic dermatitis patients who received dupilumab compared to placebo in atopic dermatitis studies. Most patients with conjunctivitis or keratitis recovered or were recovering during the treatment period. In the long-term OLE atopic dermatitis study (AD-1225) at 3 years, the respective rates of conjunctivitis and keratitis remained similar to those in the dupilumab arm in the placebo controlled atopic dermatitis studies. Among asthma patients frequency of conjunctivitis and keratitis was low and similar between dupilumab and placebo. Among CRSwNP patients the frequency of conjunctivitis was higher in dupilumab than placebo, though lower than that observed in atopic dermatitis patients. There were no cases of keratitis reported in the CRSwNP development program (see section 4.4).

Eczema herpeticum
Eczema herpeticum was reported in < 1% of the dupilumab groups and in < 1 % of the placebo group in the 16-week atopic dermatitis monotherapy adult studies. In the 52-week atopic dermatitis

dupilumab + TCS adult study, eczema herpeticum was reported in 0.2 % of the dupilumab + TCS group and 1.9 % of the placebo + TCS group. These rates remained stable at 3 years in the long-term OLE study (AD-1225).

Eosinophilia
Dupilumab-treated patients had a greater mean initial increase from baseline in eosinophil count compared to patients treated with placebo. Eosinophil counts declined to near baseline levels during study treatment and returned to baseline during the asthma open-label extension safety study (TRAVERSE). The mean blood eosinophil levels decreased to below baseline by week 20 and was maintained up to 3 years in the long-term OLE study (AD-1225). Treatment-emergent eosinophilia (≥ 5,000 cells/mcL) was reported in < 2 % of dupilumab-treated patients and < 0.5 % in placebo-treated patients (SOLO1, SOLO2, AD-1021, DRI12544, QUEST, SINUS-24 and SINUS-52 studies) (see section 4.4).

Infections
In the 16-week atopic dermatitis monotherapy clinical adult studies, serious infections were reported in 1.0 % of patients treated with placebo and 0.5 % of patients treated with dupilumab. In the 52-week atopic dermatitis CHRONOS adult study, serious infections were reported in 0.6 % of patients treated with placebo and 0.2 % of patients treated with dupilumab. The rates of serious infections remained stable at 3 years in the long-term OLE study (AD-1225).

No increase was observed in the overall incidence of infections with dupilumab compared to placebo in the safety pool for asthma clinical studies. In the 24-week safety pool, serious infections were reported in 1.0% of patients treated with dupilumab and 1.1% of patients treated with placebo. In the 52-week QUEST study, serious infections were reported in 1.3% of patients treated with dupilumab and 1.4% of patients treated with placebo.

No increase was observed in the overall incidence of infections with dupilumab compared to placebo in the safety pool for CRSwNP clinical studies. In the 52-week SINUS-52 study, serious infections were reported in 1.3 % of patients treated with dupilumab and 1.3 % of patients treated with placebo.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity with dupilumab.

Anti-Drug-Antibodies (ADA) responses were not generally associated with impact on dupilumab exposure, safety, or efficacy.

Approximately 5 % of patients with atopic dermatitis, asthma, or CRSwNP who received dupilumab 300 mg Q2W for 52 weeks developed ADA to dupilumab; approximately 2 % exhibited persistent ADA responses and approximately 2 % had neutralizing antibodies. Similar results were observed in paediatric patients (6 to 11 years of age) with atopic dermatitis who received dupilumab 200 mg Q2W or 300 mg Q4W for 16 weeks and patients (6 to 11 years of age) with asthma who received dupilumab 100 mg Q2W or 200 mg Q2W for 52 weeks. Similar ADA responses were observed in adult patients with atopic dermatitis treated with dupilumab for up to 3 years in the long-term OLE study (AD1225).

Approximately 16 % of adolescent patients with atopic dermatitis who received dupilumab 300 mg or 200 mg Q2W for 16 weeks developed antibodies to dupilumab; approximately 3 % exhibited persistent ADA responses, and approximately 5 % had neutralizing antibodies. Approximately 9 % of patients with asthma who received dupilumab 200 mg Q2W for 52 weeks developed antibodies to dupilumab; approximately 4 % exhibited persistent ADA responses and approximately 4 % had neutralizing antibodies.
Regardless of age or population, approximately 2 to 4 % of patients in the placebo groups were positive for antibodies to dupilumab; approximately 2 % exhibited persistent ADA response and approximately 1 % had neutralizing antibodies.

Less than 1 % of patients who received dupilumab at approved dosing regimens exhibited high titer ADA responses associated with reduced exposure and efficacy. In addition, there was one patient with 11 serum sickness and one with serum sickness-like reaction (< 0.1 %) associated with high ADA titers.

9.3 Mepolizumab: IMP2 (24)

Mepolizumab (Nucala) is a recombinant, human, monoclonal antibody that selectively bind to IL-5 thereby inactivating it. In Europe it is approved for the treatment of severe eosinophilic asthma, CRSwNP, eosinophilic granulomatosis with polyangiitis (EGPA) and hyper eosinophilic syndrome.

The EMA recommended dose for CRSwNP is 100 mg s.c. every four weeks. In this trial we intend to keep participants at this dose and dosage interval, unless cross-over to dupilumab is warranted.

Mepolizumab is administered subcutaneously. Median time to maximum serum concentration is 4-8 days. The absolute bioavailability ranges from 74-80% if injected in the arm, and slightly lower if administered in the thigh or abdomen.
Elimination happens at a mean terminal half-life of 16-22 days (24)

Pregnancy: mepolizumab was shown to cross the placental barrier in monkeys, but studies do not indicate reproductive toxicity. The potential for harm to a human foetus is unknown. The EMA discourages the use of mepolizumab unless the benefits are considered to outweigh the risks.
Breastfeeding: It is unknown if mepolizumab is excreted in human breast milk. However, it was found in breast milk of monkeys. As for pregnancy, it must be assessed if the potential benefits justify the potential risks to the child.

In this trial it was decided to not include pregnant or breastfeeding women, as well as women planning to get pregnant within the study period.

9.3.1 Undesired effects:

The following is an exert from (24). The section about paediatric populations have been removed since this study only includes adults. For full text and reference list, please refer to (24).

Summary of the safety profile

Severe eosinophilic asthma
In placebo-controlled studies in adult and adolescent patients with severe refractory eosinophilic asthma, the most commonly reported adverse reactions during treatment were headache (20%), injection site reactions (8%) and back pain (6%).
CRSwNP
In a placebo-controlled study in patients with CRSwNP, the most commonly reported adverse reactions during treatment were headache (18%) and back pain (7%).

EGPA
In a placebo-controlled study in patients with EGPA, the most commonly reported adverse reactions during treatment were headache (32%), injection site reactions (15%) and back pain (13%). Systemic allergic/hypersensitivity reactions were reported by 4% of EGPA patients.

HES
In a placebo-controlled study in patients with HES, the most commonly reported adverse reactions during treatment were headache (13%), urinary tract infection (9%), injection site reactions and pyrexia (7% each).

Tabulated list of adverse reactions
The table below presents the adverse reactions from placebo-controlled severe eosinophilic asthma studies from patients receiving mepolizumab 100 mg subcutaneously (SC) (n=263), from a randomised, double-blind placebo-controlled 52-week study in patients with CRSwNP receiving mepolizumab 100 mg SC (n=206), in patients with EGPA receiving mepolizumab 300 mg SC (n=68), in a double-blind placebo-controlled 32-week study in patients with HES receiving mepolizumab 300 mg SC (n= 54), and from spontaneous post-marketing reports. Safety data is also available from open-label extension studies in severe refractory eosinophilic asthma patients (n=998) treated for a median of 2.8 years (range 4 weeks to 4.5 years). The safety profile of mepolizumab in HES patients (n=102) enrolled in a 20-week open label extension study was similar to the safety profile of patients in the pivotal placebo-controlled study.

The frequency of adverse reactions is defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10), uncommon (≥1/1 000 to <1/100); rare e (≥1/10 000 to <1/1000); very rare (<1/10.000) and not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System Organ Class	Adverse reactions	Frequency
Infections and infestations	Lower respiratory tract infection Urinary tract infection Pharyngitis	Common
Immune system disorders	Hypersensitivity reactions (systemic allergic)* Anaphylaxis**	Common Rare
Nervous system disorders	Headache	Very common
Respiratory, thoracic and mediastinal disorders	Nasal congestion	Common
Gastrointestinal disorders	Abdominal pain upper	Common

Skin and subcutaneous tissue disorders	Back pain	Common
General disorders and administration site conditions	Administration-related reactions (systemic non allergic)*** Local injection site reactions Pyrexia	Common

* Systemic reactions including hypersensitivity have been reported at an overall incidence comparable to that of placebo in the severe eosinophilic asthma studies. For examples of the associated manifestations reported and a description of the time to onset, see section 4.4. **From spontaneous post marketing reporting. *** The most common manifestations associated with reports of systemic non-allergic administrationrelated reactions from patients in the severe eosinophilic asthma studies were rash, flushing and myalgia; these manifestations were reported infrequently and in <1% of patients receiving mepolizumab 100 mg subcutaneously.

Description of selected adverse reactions

Systemic reactions, including hypersensitivity reactions, in CRSwNP

In the 52-week placebo-controlled study, systemic allergic (type I hypersensitivity) reactions were reported in 2 patients (<1%) in the group receiving mepolizumab 100 mg and in no patients in the placebo group. Other systemic reactions were reported by no patients in the group receiving mepolizumab 100 mg and in 1 patient (<1%) in the placebo group.

Systemic reactions, including hypersensitivity reactions, in EGPA

In the 52-week placebo-controlled study the percentage of patients who experienced systemic (allergic and non-allergic) reactions was 6% in the group receiving 300 mg of mepolizumab and 1% in the placebo group. Systemic allergic/hypersensitivity reactions were reported by 4% of patients in the group receiving 300 mg of mepolizumab and 1% of patients in the placebo group. Systemic non-allergic reactions (angioedema) were reported by 1 (1%) patient in the group receiving 300 mg of mepolizumab and no patients in the placebo group.

Systemic reactions, including hypersensitivity reactions, in HES

In the 32-week placebo-controlled study, 1 patient (2%) reported a systemic (other) reaction in the group receiving 300 mg of mepolizumab (multifocal skin reaction) and no patients in the placebo group.

Local injection site reactions

Severe eosinophilic asthma
In placebo-controlled studies the incidence of local injection site reactions with mepolizumab 100 mg subcutaneous and placebo was 8% and 3%, respectively. These events were all non-serious, mild to moderate in intensity and the majority resolved within a few days. Local injection site reactions occurred mainly at the start of treatment and within the first 3 injections with fewer reports on

subsequent injections. The most common manifestations reported with these events included pain, erythema, swelling, itching, and burning sensation.

CRSwNP

In the placebo-controlled study, local injection site reactions (e.g., erythema, pruritus) occurred in 2% of patients receiving mepolizumab 100 mg compared with <1% in patients receiving placebo.

EGPA

In the placebo-controlled study, local injection site reactions (e.g., pain, erythema, swelling) occurred at a rate of 15% in patients receiving mepolizumab 300 mg compared with 13% in patients receiving placebo.

HES

In the placebo-controlled study, local injection site reactions (e.g., burning, itching) occurred at a rate of 7% in patients receiving mepolizumab 300 mg compared with 4% in patients receiving placebo.

9.4 Rescue treatment: Systemic corticosteroid or FESS

9.4.1 Systemic corticosteroid (prednisolone)

Short courses of moderate to high dose OCS are standard treatment for severe, uncontrolled CRSwNP, and recommended in EPOS2020 with grade 1a evidence (8).
Standard dosage in Denmark is 37.5 mg Prednisolone orally for 7–10 days.
Prednisolone has been added as an auxiliary product in the CTIS file.

Adverse effects:

The list of adverse effects for corticosteroids is long, and the risks well-known. The risk of adverse effects generally increases with repeated use, *i.e.* there is a dose-response relation for the frequency of events. Below is a list based on frequency of their appearance and in order of seriousness (33)

>10%:	leucopoenia, lymphopenia, growth retardation (in children), increased intraocular pressure, cataracts, dampening infections, infections, adrenal insufficiency, decreased glucose tolerance, myopathy, osteoporosis, lung abscess.
1-10%:	Thrombocytosis, heart-failure (worsening), hypogonadism, decreased wound healing, candidiasis, hypercholesterolemia, hypercortisolism, hypertriglyceridemia, hypokalaemia, natrium-retention, depression, euphoria, psychosis, dermatitis, erythema, purpura, hypertension, oedema, leucocytosis, weight increase, increased appetite, nycturia, hirsutism, skin atrophy, rashes, striation, telangiectasia, increased sweating,
0.1-1%:	Peptic ulcers, allergic reactions, worsening of diabetes, porphyria, myopathy, osteonecrosis, hallucinations, mood-swings, mania, personality changes, urolithiasis, sleep disturbances.
0.01-0.1%:	Thyroid imbalance, glaucoma, tendon rupture, epidural lipomatosis, cognitive dysfunction, thrombosis, falsely negative skin-prick test, affected thyroid hormone-test.
<0.01%:	Serious cardiac events (bradycardia, cardiomyopathy, infarction), central serous chorioretinopathy, exophthalmos, blurry vision, pancreatitis, Steven-Johnson syndrome, hyperosmolar coma, hyperparathyroidism, ketoacidosis, sclerodermic renal crisis, tumor lysis syndrome, benign intracranial hypertension, loss of consciousness, epilepsy, toxic epidermal necrolysis, circulation collapse, dyspepsia, tendinopathy.

9.4.2 Endoscopic Sinus Surgery

Endoscopic sinus surgery (ESS) is a safe and effective procedure with good short-term effects on

symptoms and quality of life. However, recurrence rates are high and are generally reported to range between 20–60% (7,34)

Adverse events:
Serious adverse events are generally uncommon for benign ESS. There is a 5% risk of minor complications, and a 0.5–1% risk of major/serious complications (13,35)
Peri-/post-operative complications will be treated following normal clinical practice.
The list of complications includes the following:

>5%:	Post-operative pain, bleeding, nasal blockage, fatigue, nausea, reduced sleep quality
1-5%:	Post-operative infection, orbital emphysema, ecchymosis of the eyelid, minor peri-operative bleeding, hyposmia, synechia, hypoesthesia of the infraorbital nerve, slight exacerbation of asthma symptoms.
0.1-1%:	CSF-leak, orbital injury, peri-operative haemorrhage requiring transfusion,
<0.1%:	Death

9.5 IMP accountability

There will be an accountability log on subject level in the electric patient journal (SP/EPJ/MidtEPJ/NordEPJ) to aid in traceability and compliance. This log will contain

- Drug name
- Dispensed by: date and initials
- Batch number

10. Methods/Procedures

10.1 Visit schedule

Below is a list of procedures to be performed at various times during the trial. To account for possible problems with meeting exact dates due to weekends, public holidays etc., dates may be exceeded or preceded with +/- 7 days. However, baseline screening data can be collected up to 4 weeks before first injection. The different clinical tests are discussed in detail later in this section. See also Figure 1 for trial schedule.

Visit ID	Procedures to be performed at the visit
Screening Visit(s) Week (-4)–0	Obtain written informed consent for the trial before any other trial procedures are performed Assess inclusion and exclusion criteria Obtain demographic data Record medical history Record use of relevant previous medications and concomitant medications Obtain STARR-15, ACQ, SNOT-22, VAS-nose score Perform clinical examination including basic ENT examination + nasal endoscopy (rhinoscopy) + tympanometry Perform asthma tests: FEV1, FeNO, provocation test (if not previously done) Perform allergy test (skin prick/blood test) if not previously done Perform smell test (SSIT-16) Collect blood samples (EOS and differential count) Collect polyp biopsy (if not previously done within 12 months) CT scan of the paranasal sinuses is performed, unless a scan maximum 12 months old exist. The Lund-Mackey score is assessed.

Visit ID	Procedures to be performed at the visit
	Possibly re-test of asthma provocation. Endotype determined (pathology department)
Randomization And first injection Week 0 (+/- 7 days)	Randomization **First injection of treatment** (both groups) Check for acute hypersensitivity reaction for 30 mins at department.
Week 2 (+/- 7 days)	Treatment injection (dupilumab group)
Week 4 (+/- 7 days)	Blood sample (EOS) – check for hypereosinophilia. Treatment injection (both groups)
Week 6(+/- 7 days)	Treatment injection (dupilumab group)
Week 8(+/- 7 days)	Treatment injection (both groups)
Week 10(+/- 7 days)	Treatment injection (dupilumab group)
Week 12(+/- 7 days)	Treatment injection (dupilumab group)
Week 12–24* (+/- 7 days)	Treatment injection (both groups) Treatment injections are self-administered or study nurse-administered every two- or four weeks depending on treatment group
Week 16 (+/- 7 days)	Obtain ACQ, SNOT-22 score, VAS scores, NCS Check for compliance and possible side effects. Blood sample (EOS)
- Halfway evaluation - Week 24 (+/- 7 days) **Possible cross-over**	Obtain ACQ, SNOT-22, VAS-nose score Check for AEs/SAEs Perform clinical examination including basic ENT examination + nasal endoscopy (rhinoscopy) + tympanometry + smell test (SSIT-16) Perform asthma tests: FEV1, FeNO Perform allergy test (skin prick/blood test) Perform smell test (SSIT-16) Collect blood samples (EOS) Check for response criteria Possible cross-over or increased dose interval. • Dupilumab group: +Effect: increased dose interval to every four weeks -effect: switch over to mepolizumab in standard dosing (treatment starts after a four-week treatment pause, and following a check for side effects, see below). • Mepolizumab group: +Effect: continue standard dosing and dose interval. -effect: switch over to dupilumab in standard dose First injection with new IMF if cross-over is from mepolizumab to dupilumab** CT scan paranasal sinuses in subjects who are crossing-over** (to allow for evaluation of 24w effect of the first drug)
Week 26* **	First injection with new IMF (if crossed-over from dupilumab to mepolizumab)
Week 24–48* (+/- 7 days)	Treatment injections are self-administered or study nurse-administered every two- or four weeks depending on treatment group Blood sample (EOS) after 8 days (+/- 3 days) for patients who have crossed over.
Week 40 (+/- 7 days) ** **(Week 42 +/- 7 days)*** **	Obtain ACQ, SNOT-22 score, VAS scores, NCS Check for compliance and possible side effects.
- Endpoint evaluation- **Week 48 (+/-7 days) (Week 50 +/- 7 days)**/*** **	Obtain ACQ, SNOT-22, VAS-nose score Perform clinical examination including: basic ENT examination + nasal endoscopy (rhinoscopy) + tympanometry + smell test (SSIT-16) Perform asthma tests: FEV1, FeNO Perform allergy test (skin prick/blood test) Perform smell test (SSIT-16) Collect blood samples (EOS)

Visit ID	Procedures to be performed at the visit
	CT scan paranasal sinuses (all subjects) Check for response criteria Final check for adverse effects End of trial
* From week 12 most participants are expected to be able to auto-inject the medication. Those who are not able will continue injections at the study site by a study nurse. ** This applies only to subjects who have crossed-over from mepolizumab to dupilumab *** This applies only to subjects who have crossed-over from dupilumab to mepolizumab.	

10.2 Trial procedures

This section outlines the procedures that will be performed during the trial. For further details on the specific timing of the procedures please refer to the visit schedule above.

The tasks listed below must be performed by a physician:

- Obtainment of informed consent
- Evaluation of in- and exclusion criteria
- Assessment of AEs/SAEs
- Assessment of CT scans and other laboratory results (including EOS counts).
- Physical examination

The remaining below may be performed by a physician or an appropriately trained nurse to whom the local investigator has delegated the tasks:

- Tests of lung function, smell and allergy tests and smell tests
- Observation for acute anaphylactic adverse events after the first injections.

10.3 Informed Consent

Before any trial activities are performed the written informed consent-form must be obtained (i.e. signed and dated by the subject). The written consent form will be uploaded to the e-CRF (REDCap).

Each participant will be informed that participation in the trial is voluntary and that he/she may withdraw from the trial at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

Subjects will be made aware that they can bring with them a relative to any appointment in relation to the trial.

Subjects meeting the inclusion criteria for the trial will be given thorough verbal and written information about the trial (see "Patientinformation"). This information will be given by a trial authorized physician or nurse directly affiliated with the trial. Information must take place in an undisturbed room. The subject will be given time to ask questions and allowed sufficient time (minimum 24 hours) to consider the trial before deciding whether to participate.

If subjects so desire, they may make a later appointment with the site investigator after having reviewed the written information about the trial, at which they can meet and discuss participation in the trial. Such a meeting must take place in an undisturbed room and the subject may bring a family member or friend to aid the decision-making. After this meeting, the subject may deliberate on trial participation for up to seven days.

The subjects will be informed of any potential risks associated with the trial.

It is the responsibility of the principal investigator or a sub-investigator to obtain the written informed consent from the subject.

After completion of the trial, all participating subjects will be informed of the overall results. Information of individual data and the interpretation hereof will be provided by the investigator. The individual subject's right not to know of own data will be respected.

10.4 Future contact

When subjects are asked to consent to participation in the trial, they will be asked specifically if they will accept possible future contact for the purpose of further research regarding biologics for CRSwNP. The answer to this question will be recorded on the informed consent form as well as on the e-CRF. Subjects will be able to participate in the trial without giving consent to future contact and they can withdraw their consent at any time.

10.5 Consent for long-term storage of blood samples and tissue in a biobank

Subjects will also be asked specifically if they can accept the storage of their biologic samples in a biobank. The answer to this question will be recorded on the informed consent form as well as on the e-CRF. Subjects will be able to participate in the trial without giving consent to long-term storage of biologic samples. Subjects may withdraw this consent at any time, and any samples stored in the biobank will then be destroyed.

10.6 Subject ID and e-CRF inclusion

The subject's social security number (CPR number) will be entered in the e-CRF (REDCap) at the first visit. A subject ID will be created, by which the subject will be pseudo-anonymized. An identification log containing the name and CPR-number linked to the subject ID will be created in an encrypted file in the Trial Master File (TMF). The TMF will be inaccessible to the sponsor or third parties. The anonymization can be lifted in case of AEs/SAEs/SUSARs.

10.7 Demography

The following data will be recorded directly in REDCap:

- Age
- Sex
- Educational background (no. of years)

10.8 Medical history and concomitant disease

Medical history is a medical event that the subject has experienced in the past. Only medical history considered relevant by the Investigator should be reported.

Concomitant disease is any illness that is present at the start of the trial (i.e at the screening visit or found as a result of the screening procedure).

Smoking status, *i.e.* current smoking or previous smoking, type of tobacco and number of "pack years" (i.e. years of smoking 20 cigarettes daily).

This will be recorded directly in the e-CRF.

10.9 Concomitant and previous medication

All medication related to asthma or CRS will be recorded, including medicine the subject is taking currently, as well as medication (related to CRS or asthma) including OCS courses within the last year.

Subjects will be interviewed about their adherence to medication, whereby the e-CFR (REDCap) will automatically calculate a Foster-score (Score ranging from 0-7 based on the question: "how many days out of a week do you take your medication as it is prescribed?" – the score should be minimum 80%)

At each visit the Investigator or delegate should ask the subject about use of concomitant medication including rescue medication. All concomitant medication and changes hereto must be documented in the subject's medical records and directly in the e-CRF.

10.10 Vital signs and weight

Blood pressure (BP) and pulse will be measured.

Weight and height will be measured according to local procedures, and BMI automatically calculated.

This will be recorded directly in the e-CRF.

10.11 Physical Examination

A physical examination will be performed by a local investigator.

Significant findings that are present at screening must be recorded as medical history in the e-CRF. Significant findings found at the following visits, which meet the definition of an AE, must be recorded on an AE page in the e-CRF.

The physical examination includes:

Examination of the nose and paranasal sinuses including polyp biopsy:

- **Basic ENT-examination** with inspection of the ears, nasal- and oral cavity, and palpation if mandated.
- Test of middle ear pressure (**tympanometry**).
- **Nasal endoscopy** with a rigid or flexible endoscope of the nasal cavity (preceded by local anaesthesia with lidocaine-adrenaline 2%, if the patient wishes it). The examination takes about two minutes, and is slightly uncomfortable, but not painful. An assessment of the "nasal polyp score" (NPS) will be made:
    - **The NPS** is a score ranging from 0–4 on either side (total score range: 0–8) with 0 representing no polyps, 1=polyps confined to the middle meatus, 2=polyps extending below the inferior border of the middle turbinate, 3=polyps extending beyond the middle meatus, *i.e.* either inferiorly below the lower border of the middle turbinate to the lower border of the inferior turbinate, or in the anterior/posterior direction beyond the (normal) placement of the middle turbinate and/or medial to the middle turbinate, and 4=complete obstruction of the nasal cavity.
- **Polyp biopsy** (approximate size 0.5x0.5x0.5 cm) with small forceps under direct vision from the endoscope. This too can be somewhat uncomfortable to some subjects, however not painful. There can be a small bleeding, which usually subsides spontaneously. If not, they are easily controlled by compression for a few minutes with a cotton swap. Polyp tissue will be

microscopically analysed for eosinophilic cell count in accordance with EPOS2020 guidelines (8).

*Polyp tissue might be further analysed for specific biomarkers via flow-cytometry or another assay testing (TBD).

- **Sniff'n Sticks-evaluation Identification test 16 (SSIT-16):** The sense of smell will be evaluated using identification test 16 (Sniffin' Sticks® Burghartt, Germany) (36). The test consists of 16 odour pens with household odours (orange, cinnamon, garlic, etc.). The patient must identify the odour by a forced multiple-choice of four written descriptors. The maximum score of the test is 16 points. A score 0-8 indicates anosmia, a score between 9 and 11 indicates hyposmia, and a score >11 indicates normosmia.

Lung examination and asthma provocation tests:

- **Lung auscultation** with a stethoscope
- **Pulmonary function test**: Lung function will be measured with the usual spirometer. The expected values (% pred) will be calculated from reference values for healthy Caucasian adults. In the case of airway obstruction, with a FEV1/FVC ratio less than 70%, a reversibility test will be performed after inhalation of four puffs of salbutamol. An increase of 200 mL and 12% is diagnostic for asthma.
- **Asthma-provocation test (Methacholine or mannitol challenge)**: Patients with an FEV1% pred < 60% will be excluded from the airway hyperresponsiveness (AHR) test (at baseline). Inhalation of methacholine will be done from 0 to 8.0 microg. The test is positive if there is a 20% or more decrease in lung function (PD20) from baseline. The inhalation of mannitol capsules from 0 to 635 mg will be performed in a standardised stepwise method. The test is positive if lung function drops 15% or more from baseline (PD15, mannitol) and 20% from baseline (PD20, methacholine), depending on the bronchial challenge agent. The two tests will be done on two different days or, if possible, on the same day with mannitol first followed by methacholine (37). The dose-response ratio will be calculated for all patients (38). Withholding of medication prior to provocation will be carried out (ICS/LABA 24 hours, UltraLABA 48 hours, ICS 12 hours, SABA and SAMA 6 hours and LAMA 48 hours).
- **FeNO** (fractional expired nitrous oxide). The FeNO level will be measured before spirometry (NIOX VERO or MINOR; Circassia UK). The patient will be instructed to inhale NO-free air to total lung capacity and immediately exhale fully into the device, keeping a steady flow rate of 50 ml/s. It usually takes 1–2 minutes and is not uncomfortable.

Additional tests:

CT scan of the paranasal sinuses: Will be carried out with enrolment in the study, unless one was already performed within the previous three months. Furthermore, the CT scan will be repeated at 24 weeks if a patient crosses over to the other treatment arm. A CT scan involves a low dose of radiation. The risk of radiation-induced damages are low due to modern technology. The first CT scan of the sinuses will be part of the routine assessment of these patients. Females will undergo a pregnancy test prior to the CT scan. All patients will

give informed consent, here with an emphasis on the additional yet small dose of radiation from the CT scans (<2 mSv).
CT scans will be scored in accordance with the Lund-Mackey score, see below.

- The **Lund-Mackey score** is a widely used radiologic reference for staging CRS (39). By assigning a score ranging from 0=no opacification to 2=complete opacification, to each of the six segments; frontal sinus, anterior ethmoid cells, posterior ethmoid cells, maxillary sinus, sphenoid cells, ostio-meatal complex on either side, a total sum-score of 0–24 is calculated.

- **Allergy test (blood or skin prick):** The standard panel of birch (Betula), grass (phl. praetense), mugwort, dog, cat (fel d), house dust mites (Der p1. og Der f2) and mould (Alternaria, Cladosporium and aspergillus fumigatus) will be used in testing atopy. A positive response can be viewed as a blood IgE measurement > 0.35 or positive skin prick test.
- **Blood samples:** Blood will be continuously sampled (4 weeks after starting a new treatment, and hereafter at 16 weeks and 24 weeks) as a measure of safety, as there is a risk of hypo- or hyper-eosinophilia. On-treatment eosinophil counts >3000 cells/µL (3.0 G/L) are to be reported as AEs. Eosinophilia ≥1500 will warrant closer observation of eosinophilic blood count, and more frequent blood testing (for example every 14 days) will be considered by local investigators (doctors).

10.12 Questionnaires

Questionnaires will be answered digitally, directly in the e-CRF via subjects' mobile phones. If this is not possible the questionnaire will be answered either via a tablet provided by the department, or alternatively on a piece of paper, which is subsequently entered in the e-CRF.

Sino-nasal Outcome Test 22 (SNOT-22) (22): The SNOT-22 is a 22-item questionnaire covering aspects related to sino-nasal disease and HRQoL. Each item is scored on Likert-scale ranging from 0 ("No problem") to 5 ("Problem as bad as it can be"), thus producing a score ranging from 0 to 110. The recall period is two weeks. A score of up to 8 is normal, 8-20 is mild disease, 21-50 moderate, and >50 is severe disease. Completion time is about 5–10 minutes.

Visual analogue scales (VAS) asthma/ASA-intolerance/CRS/sense of smell: subjects are asked to place a marker on a visual analogue scale, indicating how much they are bothered by their asthma/ASA-intolerance/chronic rhinosinusitis. The range is from "very much" to "not at all".

Standard Test for Asthma, Allergic Rhinitis and chronic Rhinosinusitis (STARR-15)(40): The STARR-15 is newly developed *global airways* PROM, designed as a screening tool to raise clinicians' awareness of coexisting double (or triple) disease in patients suspected of type 2 inflammation disease. There are three disease sub-domains; allergic rhinitis, CRS and asthma. Each of the 15 items are scored on a 3-point Likert scale ranging from 0=no problem to 2=severe problem. No sum-score is obtained. Completion time is about 2 minutes.

Asthma Control Questionnaire (ACQ) (41)**:** The original ACQ evaluation tool contains five patient-reported items scored on a seven-point Likert scale, with levels of control ranging from 0 (no impairment) to 6 (extreme impairment), using the past seven days as a recall period, and with all items equally weighted. The remaining two items is one concerning medical use and one is reserved

for an objective measure of FEV1. A score of ≤1.5 points means well-controlled asthma. Completion time is 2–4 minutes.

10.13 Treatment failure

Treatment failure will be registered if a subject decides to discontinue the trial because of insufficient symptom relief. Time of treatment failure will be registered directly in the e-CRF by the investigator or a delegate.
Failure to meet treatment response will not be considered a failure. The subject will be encouraged to stay on the treatment until 24 weeks, where they can cross-over.
As mentioned in section 7.4 subjects will be evaluated for AEs/SAEs four weeks following their last treatment injection.

10.14 Electronic medical record (Sundhedsplatformen, EPJ SYD, MidtEPJ, NordEPJ, FMK-online)

The electronic medical records will be viewed in the process of recruiting subjects and assessing compliance with in- and exclusion criteria. The subjects will have to confirm compliance with these criteria prior to starting the trial.
The subjects are all patients at the departments, so regardless if they participate in the study or not, investigators will assess their electronic medical information.

The following data will be obtained from the subject's electronic medical record and entered in the e-CRF (REDCap) (if available):
Prior to enrolment:

- Number of ESS'es and date of latest ESS
- Number of courses with systemic corticosteroids and date of latest course
- Type of INCS and ICS as well as other medication related to treatment of asthma, CRS, atopy, allergic rhinitis, and medicine related to eosinophilic, rheumatoid or autoimmune disease.
- Result (Lund-MACKEY score) of CT-scan performed prior to enrolment.
- Pathology report from any pre-existing polyp biopsies.
- Pre-existing diagnosis of relevant chronic disease
- Surgery/out-patient reports from any previous ESS/out-patient visits in the ENT or pulmonology department.

11. Assessment of Safety

Information about Adverse Events (AEs), whether reported by the subject, discovered by the investigator, detected through physical examination, laboratory test or other means, must be collected and recorded on the AE form and followed up as appropriate.

Evaluation of AEs including severity, causality, outcome and seriousness assessments must be performed by a physician.

Any AE occurring from the time of the first IMP injection and until the day of the last control visit (week 48or week 50 if the subject has crossed-over) must be recorded and reported on an AE page in the e-CRF.

If the subject discontinues, registration of AEs will continue until 30 days after the last injection.

Standardized report forms for AEs and SAEs will be provided as part of the e-CRF.

11.1 Definitions – Adverse Event (AE)

An AE is any unexpected medical occurrence in a subject treated with a medicinal product/device even if it does not necessarily have a causal relationship with this treatment. It can be a symptom, diagnosis, or a change in a laboratory value or any other measure of health status.

The following events should not be recorded as AEs:

- A pre-planned procedure, e.g. a surgical intervention, unless the condition for which the procedure was planned has worsened since the informed consent form was signed.
- Pre-existing conditions documented as medical history. Any worsening in severity or frequency of a pre-existing condition during the clinical trial period must be regarded as an AE.

11.2 Definitions – Serious Adverse Event (SAE) / Serious Adverse Reaction (SAR) / Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse event (**SAE**)/reaction (**SAR**) is an AE that at any dose results in any of the following:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Leads to a congenital anomaly or birth defect
- Is otherwise medically significant (this refers to an event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed above).

A suspected unexpected serious adverse reaction (**SUSAR**) is defined as:
A SAR that was unexpected based on previous knowledge/experience.

11.3 Assessments of AEs and SAEs/SUSARs

When assessing AEs and SAEs/SUSARs the investigator will refer to the product resumés (24,25)

Severity:

The severity of an AE/SAE is a clinical observation assessed by the investigator using the following definitions:

- Mild: Transient symptoms, not interfering with the subject's daily activities
- Moderate: Marked symptoms, moderate interference with the subject's daily activities
- Severe: Considerable interference with the subject's daily activities, unacceptable

Potential AEs/SAEs will be treated according to standard practice and if relevant follow-ups will be scheduled with relevant specialists.

Causality / Causal Relationship to IMP:

The following terms and definitions are used when assessing the relationship between an AE/SAE and the relevant trial product (IMP):

- Probable: good reason for sufficient documentation to assume a causal relationship
- Possible: a causal relationship is conceivable and cannot be dismissed

- Unlikely: the event is most likely related to an etiology other than the trial product

Final outcome:
The outcome of an AE/SAE is assessed by the investigator using the following definitions:

- Recovered/resolved: Fully recovered or has returned to baseline
- Recovered with sequelae: As a result of the AE the subject suffered persistent and significant disability/incapacity
- Not recovered: The condition has not returned to baseline, however symptoms may have improved
- Fatal: Event that results in death – An AE with fatal outcome must be reported as an SAE
- Unknown: The outcome is unknown. This term should only be used when no other definition is possible e.g. the subject is lost to follow-up

11.4 Reporting

SAEs/SARs/SUSARs will be reported the e-CRF and reviewed by the sponsor. In case of IT breakdown/power shortages/other emergencies, printed versions of the SAE form will be available at all study sites.
Both the sponsor and the primary investigator must be notified of SAE/SAR/SUSARs via e-mail or phone within 24 hours:

Sponsor:	Christian von Buchwald
Email address:	Christian.von.buchwald@regionh.dk
Primary investigator:	Christian K. Pedersen
Email address:	Christian.korsgaard.pedersen.01@regionh.dk
Emergency phone:	(+45) 25 30 11 86

Serious Adverse Events:
SAEs must be reported to the above-mentioned persons immediately (within 24 hours of awareness). Any follow-up data must be detailed in a subsequent SAE form in due time.
The initial SAE report must contain as much information as possible including relevant information from the e-CRF (e.g., medical history, concomitant medication) and must be provided via the e-CRF system. If the reporter does not have access to the e-CRF, e-mail may be used.

The SAE report will remain open as long as the trial is active. Should new relevant data on the event emerge, a follow-up report will be sent.

Suspected unexpected serious adverse reaction (SUSAR):
Definition: An unexpected serious adverse reaction where source or severity is not consistent with information in the current Summary of Product Characteristics (SmPC).

It is the responsibility of the Sponsor to determine whether a reported SAE is a SAR and whether a SAR is a SUSAR. A SUSAR resulting in death or life threatening must be reported within 7 days after the Sponsor becomes aware of the reaction. Within 8 days after reporting, the sponsor must enter the

information in the EudraVigilance-database. Any other SUSAR must be reported to the above-mentioned agencies within 15 days after the Sponsor becomes aware the reaction. SUSARs must also be reported to all local investigators on all study sites.

Pregnancy

- If a pregnancy is reported, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor and/or primary investigator within 24 hours of learning about the pregnancy. Although pregnancy itself is not considered an AE/SAE/SUSAR, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an SAE/SUSAR
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participants will be followed up to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and neonate, and the information will be forwarded to the sponsor.

11.5 Annual reporting

The Sponsor is responsible for creating an annual subject safety report and list of SARs and submit it in the EUclinicaltrials database (CTIS) as well as to all local investigators on the involved study sites. The sponsor is responsible for notifying the EMA, the Danish Health authorities as well as all local investigators in case the safety profile of one of the IMP changes.

12. Data handling / Data Management

Data will be handled according to the General Data Protection Regulation (EU) 2016/679 (GDPR, or "persondataforordningen").
The trial e-CFR has been reported to 'Datatilsynet' via the Danish central region's (Region Hovedstaden) data centre (Pactius). Approval is pending.

The trial will be reported to all involved regions ahead of initiating the trial in each region.
Data will be stored for 25 years, after which they will be transferred to "Dansk Data Arkiv" or deleted or anonymized.

12.1 Case Report Form (CRF)

All data related to the trial will be recorded in an electronic CRF (REDCap) which will thus provide the basis for a central database.

Source data will be recorded and kept for minimum 25 years, as per requirement in Denmark.

The e-CRF is to be completed by the investigator or a delegate at the time of the subject's visit to the clinic so that it always reflects the latest observations on the subject.
At the subject's final visit, the e-CRF should be verified and signed off by the responsible investigator or delegate at the site.

12.2 Laboratory Data

Values from previous blood samples, tissue biopsies, and CT scans will be obtained from the medical journal and be entered manually into the e-CRF.

13. Statistical evaluation

The primary analysis will consist of a linear mixed effects model taking the full longitudinal design into account. The model will be adjusted for olfactory function and site (categorical variable) due to the stratified design. Subjects will be included in the intention to treat analysis irrespectively of their adherence to the protocol. The treatment effect for the co-primary outcomes will be presented as the average difference between the dupilumab and mepolizumab groups in changes in SNOT-22 score and NCS from baseline to week 24. These comparisons will be based on the standard errors from the linear mixed model. Sensitivity analyses will be performed using multiple imputation where the imputation model will include all available baseline variables.

Note: Since this trial investigates two IMPs that have already been proven comparable in effectivity, no real control group exists. In the two phase 3 studies (SINUS 24/52 and SYNAPSE) the drop-out rates were similar (<10%), and hence, we estimate that the risk of bias due to differences in discontinuation rates is low.

Before the randomization code will be added to the cleaned dataset, a prespecified statistical analysis plan (SAP) will be elaborated and accepted by the statistician and investigators.

All data will be described including data-incompleteness as well as reasons for data-incompleteness. Data will be analyzed blinded by the statistician. Any changes to the statistical analysis plan will be described in any future publications.

13.1 Analysis populations

The primary analyses will be performed on all subjects randomized in the trial (intention to treat). Sensitivity analyses will be performed on the per protocol population.

14. End of trial

Within 15 days after the trial completion (*I.e.* the last patient's last visit (LPLV)) the sponsor must report the completion of the trial in CTIS. Trial results will be submitted to CTIS within 12 months from LPLV (see also section 15.9).

14.1 Early termination of the trial

The sponsor reserves the right to terminate the trial under the following conditions:

- Safety concerns

If the trial is prematurely terminated or suspended, the investigator should promptly inform the subjects and ensure appropriate therapy and follow-up. Furthermore, the investigator and/or Sponsor should promptly inform the pertinent ethics committee and regulatory authorities.

14.2 Subject Discontinuation

The subject will be advised in the informed consent form that he/she has the right to withdraw from the trial at any time without prejudice. Where discontinuation from the trial is initiated by the subject, the investigator is to ascertain the primary reason for discontinuation from the list below:

- An AE for which the investigator did not consider discontinuation from the trial necessary
- Co-existing disease
- Withdrawal of consent
- Other reasons including treatment failure

The subject may at any time be discontinued from the trial at the discretion of the investigator.

Subjects must be discontinued from the trial under the following circumstances:

- If a criterion equivalent to an exclusion criterion occurs
- If, in the investigator's opinion, continuation in the trial would be detrimental to the subject's well-being
- Occurrence of intolerable AE(s) as determined by the investigator and/or subject
- Subject lost to follow-up
- If informed consent is withdrawn

In all cases, the primary reason for discontinuation must be recorded in the e-CRF and in the subject's medical records. Follow-up on the subject is necessary to establish whether the reason was an AE. If so, this must be reported in accordance with the appropriate procedures.
As far as possible, all examinations scheduled for the final visit must be performed on subjects who receive the IMP but do not complete the trial according to the protocol.
Data obtained until discontinuation will be entered in the clinical database and used for statistical analyses.

15. Administrative procedures

15.1 Source data and subject data protection

Source data will be registered in patient records or on source data sheets or directly in the e-CRF.

Prior to start of data recording from subjects, the investigator will prepare a Source Data Location Agreement to document where the first recording of data is done.

As a minimum requirement, the following data must be source data-verifiable in source documentation other than the e-CRF:

- Subjects informed consent
- Date of informed consent
- List of randomised subjects

A common e-CRF will be constructed and provide the basis for a central database. Data will in the central database will be stored in coded form according to the rules of the Danish Data Protection Agency (Datatilsynet) with whom the trial is registered.

In accordance with the Danish Data Protection Agency data processing will be completed within 25 years of this submission.
Afterwards, data in paper form will be destroyed and electronic data will be transferred and stored at the Danish Data Archives (Statens Arkiver).
Christian K Pedersen will be responsible for data collection and processing.
In addition, Christian von Buchwald, Vibeke Backer, Kasper Aanæs, and Tonny Studsgaard Petersen will be involved in data processing.

The investigator will have direct access to source data and documents in case of monitoring, auditing or inspection from health authorities (Lægemiddelstyrelsen, Videnskabsetisk komité, GCP-enhederne).

15.2 Quality control and assurance

The trial will be carried out according to the EU Clinical trials regulation (regulation (EU) no. 536/2014), the protocol, ICH-GCP principles (https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-6-r2-guideline-good-clinical-practice-step-5_en.pdf) and current national and international law. Furthermore, it will follow the Declaration of Helsinki.
Quality control and assurance will be carried out in accordance with ICH-GCP and standard procedures will be followed including monitoring, auditing or inspection from health authorities (Lægemiddelstyrelsen, Videnskabsetisk Komité, GCP-enhederne).

15.3 Monitoring (Good clinical practice, GCP)

Regular monitoring visits will be performed according to ICH-GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. The GCP monitor will verify that the clinical trial is conducted, and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.
The local-regional GCP units will conduct the monitoring, regulatory compliance, and review of e-CRFs to source documents. The monitoring will be coordinated from the GCP-unit at Bispebjerg-Frederiksberg University Hospital, Copenhagen, Denmark. It is the responsibility of the Sponsor that the trial is monitored.

15.4 Research Biobank

Although permission for a biobank was initially applied for and permission was granted by The Danish National Centre for Ethics, the plans to collect samples for a biobank was abandoned. Hence, no biobank exists for this trial

15.5 Financing

The initiative for this trial was taken by the sponsor, investigator and advisors, none of whom have any financial interest in the trial.
Financial support in the form of a salary grant for the principal investigator CKP for the conduct of this study has been made to sponsor's research account at Rigshospitalet (PSP-account F-22214-35) from a private non-profit organization (Mauritzen La Fontaine Family Fond). The foundation has donated 723.000 DKK. This will cover salary expenses for the principal investigator during the first 11 months

of the trial period. Further applications will be made to cover the full salary expenses during the trial period just as an additional application will be made to cover running expenses for the primary investigator such as travel expenses, a laptop, admission fee to scientific congresses etc.
The remaining trial expenses such as salaries of involved physicians and nurses, test and equipment costs, laboratory costs, radiology costs, medicine expenses, costs of treatment of possible SAEs etc. are all part of standard running costs and will be covered by the relevant involved region belonging to the hospital.

15.6 Financial compensation to subjects
The trials subjects will not be financially compensated for participating in the trial.

15.7 Insurance
Patients will be covered according to current regulations. Trials in the Danish regions are covered by the patient-insurance (Patienterstatningen).

15.8 Ethical Considerations
Irrespective of the outcome of the trial it will provide useful information on biologic treatment of CRSwNP. The result of the trial will thereby provide physicians and patients with new relevant information guiding their choice of treatment. To date, no direct comparison between mepolizumab and dupilumab exists, and since the treatments are both very costly, however with one being less expensive than the other, there is a huge global interest in learning more of cost-effectiveness of these new drugs.
Based on already solid clinical experience with both agents, we consider both treatments safe to use, especially in comparison with the best available alternatives (OCS or ESS).
Both groups will be allowed to ask for corticosteroids as rescue medication so no subjects are completely excluded from effective treatment. Furthermore, both treatment arms contain drugs that have already proven effective and safe, and they are given in scientifically proven doses and intervals.

15.9 Publication
The trial is investigator-initiated, and data are owned by Region Hovedstaden. As soon as possible and no later than one year after the trial has ended, the trial results will be submitted to the CTIS portal. Subsequently, data will be published on clinicaltrialsregister.eu. Furthermore, results will be published in an international peer-reviewed scientific journal. Christian K. Pedersen will draft the first manuscript. Christian von Buchwald will be last author. Local investigators who aids in including subjects and also contributed in the planning of the trial, or in data analysis or other academic work will be offered a co-authorship.

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