English title: Tapering of biologics in CRSwNP

Subtitle: Tapering of Mepolizumab or Dupilumab after 12 months of partly controlled disease in patients with severe chronic rhinosinusitis with nasal polyposis – a national Danish RCT

Danish title: Delvis sygdomskontrol ved nedtrapning af biologisk behandling af kronisk bihulebetændelse med polypper

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Trial ID:

CTIS: 2024-519758-35
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It is hereby declared that the trial will be performed according to the latest approved trial protocol, ICH-GCP Guidelines and local regulatory requirements and legislation

08/05/2025

Signature Date

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Monitor, Study Sites and Local Investigators

The sites, investigators and GCP-units are listed in CTIS.

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1. Introduction, rationale and hypothesis

Introduction

Type-2 high inflammation (T_2H) represents a critical disease aspect that is responsible for an extensive disease burden, especially for patients who remain unresponsive to standard treatment regimens. The state-of-the art endotypes among respiratory diseases are related to both T_2H and ILC2 cells; this is called Type-2 inflammation. In Type-2 inflammation, there are specific circulating cytokines, such as interleukin (IL)-4, 5 and 13 and potent innate effector cells, such as eosinophilic cells (1, 2). Eosinophil cells are the major players in the action and disease burden among patients with Type-2 chronic rhinosinusitis with nasal polyps (CRSwNP), as well as in asthma.

The hallmark of CRSwNP is nasal obstruction, nasal discharge, facial pain, and loss of smell for at least 12 weeks. In severe cases the symptoms last and significantly decrease quality of life despite standard medical treatment, surgical intervention, and lifestyle modifications (e.g., tobacco cessation), as well as treatment of co-morbidities such as asthma. The new monoclonal antibodies (biologics) are used for treating Type-2 diseases such as CRSwNP; reducing acute rhinology exacerbations, reducing polyp size, reducing smell deficiency, increasing airflow, decreasing nasal secretions and improving comorbidities as asthma and aspirin intolerance and thereby increasing quality of life (QoL). In most phase III trials, the effects of biologics on CRswNP have been substantial (3, 4).

When treated, the response varies substantially between patients and can, as suggested by EPOS/EUFOREA(5), be categorized as follows:

Uncontrolled CRSwNP: "Patient reported lack of control" and the presence of clinically relevant sinonasal symptoms of active disease (defined as overall symptom severity, nasal obstruction and smell)

Controlled CRSwNP: "Patient reported control" with the absence of clinically relevant sinonasal symptoms of active disease (defined as overall symptom severity, nasal obstruction and smell). Control can be with or without ongoing / past treatment.

Remission: Sustained control (as defined above) for ≥ 12 months combined with the absence of signs of active disease evaluated by nasal endoscopy. Remission can be reached with or without treatment (not including systemic steroids and/or sinonasal surgery in the last 12 months)

Cure: Sustained remission without treatment for at least 5 years.

However, in order to account for nuances in response we propose the below categorization based on the current evidence(6):

True remission: no or few symptoms without medicine.

Complete remission: no or few symptoms on treatment. Also called controlled disease or remission under treatment.

Partial remission: Improvement of initial symptoms. Patients have some on-treatment symptoms but are somewhat well-controlled called partly disease control.

Poor disease control or uncontrolled disease: Many symptoms despite treatment.

Achieving remission in severe CRSwNP requires systematic assessment, and a thorough approach addressing treatable traits (7, 8). Mepolizumab was developed for treatment of type-2 eosinophilic asthma (9, 10) however, has also shown to significantly improve CRS symptoms in CRSwNP irrespective of blood eosinophil count (3, 11). A sustained effect of mepolizumab in CRSwNP has even been demonstrated after discontinuation of treatment (12). In asthma, a study has shown that the majority of patients in complete remission could be reduced (tapered) in

treatment and 32 % of these patients could later cease treatment(13). Further, a substantial proportion of patients achieving remission of their asthma while treated with Omalizumab (a biologic used in allergic asthma and in CRSwNP independent of allergy) can maintain remission after discontinuation of treatment (14). Besides Mepolizumab and Omalizumab, the drug Dupilumab can be used for CRSwNP and asthma as well(15) and can in some CRS patients successfully be tapered(16).

Rationale: Development of CRSwNP is associated with an overshoot of Type 2 inflammatory cells and cytokines. In patients with Type-2 inflammation and symptoms of CRSwNP, treatment with biologics targeting the Type 2 inflammatory components can control disease in both upper and lower airways. The disease control induced by the monoclonal antibodies is often very effective, thereby reducing patients' needs for standard care of nasal corticosteroids (nCS) and inhaled corticosteroids (ICS). It could be hypothesized that patients achieving remission due to the combined therapy of standard care and monoclonals antibodies, may reset or modulate their type-2 inflammatory disease and possibly gain effective inflammatory control along with symptom control, which could continue after tapering or even discontinuation of monoclonal antibodies, but with continuation of standard care. It is further unknown whether a specific endotype of CRSwNP patients have a higher risk of relapse after tapering or discontinuation of monoclonal antibodies, this would be important knowledge for future treatment strategies.

Hypothesis: A significant proportion of patients with CRSwNP, who have had at least 12 months of partial remission after treatment with either mepolizumab or dupilumab will continue partial remission after tapering of treatment.

Overall aim: The aim of this randomized controlled trial (RCT) is to investigate the proportion of CRSwNP patients in continued partial remission after tapering of mepolizumab or dupilumab, and to investigate whether this group is non-inferior to the standard-dosing group in terms of symptom control.

Novelty: Diseases based on inflammation of the mucosal layer of the nose, lungs and intestine, either Type 2 or non-Type2, are at risk of being treated continuously with biologic drugs. It is unknown when to taper or discontinue treatment, however if a proportion of patients can be tapered and continue having partial or complete remission, that would be very helpful information in the decision-making of clinicians.
Biologic treatment is expensive, but of high importance for the wellbeing of the patients treated. Those who have achieved (only) partial inflammatory control after 12 months of treatment, might be able to continue this partial control with less frequent biologic treatments and continued standard care. This gives the patients more freedom, less attachment to the hospital system, and enables availability and funds for other patients still uncontrolled and/or waiting for access to treatment. Patients who experience worsening of symptoms and lack of disease control after tapering, will resume treatment at the longest previous effective dosing interval, and this event might in fact indicate the ideal length of treatment intervals for disease control/partial remission.
In contrast, some patients who achieve complete remission could be candidates for complete cessation of biologic treatment (such study is under construction by our research group).

Expected outcome: This project will provide unique and valuable information on disease control in patients with CRSwNP and treatment with monoclonal antibodies – including information on what endotypes of CRSwNP need continuation of treatment vs. the endotypes being able to taper off biologicals without experiencing worsening of symptoms. The importance of co-morbid asthma will also be evaluated. The above-mentioned study is actually mentioned as a wanted study by the European Rhinology Society(17).

2. Background

Patients with chronic rhinosinusitis (CRS) have a large disease burden and low health-related QoL. The overall frequency of CRS in Denmark is 8% (18) and of these individuals, 25% have CRSwNP. In patients with severe CRSwNP, there is a tendency to have comorbid disease with severe asthma and/or aspirin insensitivity. These

patients often have an intractable disease, meaning that, despite optimal medical treatment and sinus surgery, their disease is not under control. The current standard care for CRSwNP is a combination of nasal steroids, nasal saline irrigation, a short course of systemic corticosteroid and sinus surgery. However, because the treatment might be considered symptomatic, the long-lasting effect of the currently available treatment is modest for patients with severe CRSwNP (19). Even more extensive surgery (DRAF 3), often only prolongs recurrence time and only relieves symptoms temporarily (20).

In 2019, a novel treatment was introduced: monoclonal antibodies, which is also called biologic treatment in the current proposal. Two products (Dupilumab and Mepolizumab) have been approved for treatment in Denmark in 2022. Both are modulators of the immune system and the treatment is very promising but expensive. Several studies have shown that approximately 80% of patients with severe CRSwNP will significantly benefit. Yet there remains a lack of selection and consensus on the correct timing of these medications. In particular, the role of these medications and timing of surgical intervention remains unanswered. With this new treatment option, it is crucial to thoroughly follow the patients receiving the treatment and determine who will obtain the best benefits from the treatment, hence being able to find out how to optimize it. Many countries in Europe have started to offer biologic treatment to patients with severe CRS, with varying criteria for when to use it. However, they are all based on the recommendations made by the European guidelines, stating that biologic drugs are indicated in patients fulfilling all the following four criteria(5): 1. Bilateral nasal polyposis 2. Previous ESS (sinus surgery) (In Denmark ESS within the last three years) 3. Evidence of Type-2 disease 4. Satisfactory adherence to local steroid treatment and 5. Asthma in ICS treatment.
Furthermore, in Denmark the patients offered biologic drugs should also fulfil at least three of the following five criteria: 1. Need of (and received) systemic corticosteroids, 2. Significantly impaired QoL (SNOT-22≥50), 3. Smell dysfunction, 4. Nasal polyp score ≥ 5 (out of 8), 5. a diagnosis of comorbid asthma using ICS. Criteria that all support the likelihood of efficacy of treatment (21).

Upper airways: Patients may suffer from CRSwNP or CRS without polyps (CRSsNP). Most patients with CRSwNP suffer from Type-2, whereas Type-2 is only found in 20% of those with CRSsNP (6). Surgery removes inflamed tissue in the sinuses and nasal cavities, thus improving airflow, with a long-lasting success rate between 40% and 60% (22); in other studies, the use of monoclonal antibodies has been shown to have a success rate of 50% (23). The closure of the airflow in the nasal cavity leads to a low QoL, disturbed sleep, snoring and, perhaps, and in some patients hearing disability, due to closure of the Eustachian tube and eosinophilic cells in the middle ear. In patients with severe CRSwNP who display severe nasal obstruction (21), the effects of the currently available treatment options are modest, and the trajectory of these individuals is defined by a higher morbidity, high disease burden and very poor QoL (24). Overall, QoL in patients with CRSwNP is lower than QoL in patients with back pain, heart failure, asthma, and migraines (25, 26).

Lower airways: Airway inflammation is a specific feature in patients with asthma, in which the lumen of the small airways may be occluded by mucous plugs (which can be related to mucus hypersecretion) and may lead to the development of goblet cell metaplasia. The airway wall becomes thickened with an increase in basal membrane thickness and airway smooth muscle hypertropia, with airway obstruction of the smaller airways as well as airway hyper responsiveness. The management of severe asthma follows the 'treatable traits approach' (27, 28), and treatment selection is based on the type of inflammation (29, 30). In asthma patients, with Type-2, several different biologic drugs have been used (22, 31, 32). Interestingly, no head-to-head studies exist, but clinical experience reveals that not all patients benefit in the same way from different monoclonal antibodies. These differences may be based on the airway pathology, inflammatory cell responsiveness and/or cytokine levels produced.

Global airways: Epidemiologically, 60% of patients with CRSwNP suffer from asthma; similarly, 60% of those with asthma suffer from CRSwNP (33, 34). Some patients exhibit severe upper and non-severe lower airway diseases and vice versa. Global disease results in significant impairment, with a high disease burden, which is worse than either disease alone (35). One-tenth of patients with CRSwNP require FESS more than once within 12 months, and the need

for sinus surgery is more common among those with asthma (36–38). In severe CRSwNP and severe asthma (39, 40), additional treatment with systemic corticosteroids (SCS) is frequently prescribed, even though SCS has many undesirable systemic side effects (39, 41, 42).

Treatment with the new monoclonal antibodies reduce asthma exacerbations and increase QoL while reducing the need for SCS; the treatment is offered to those with overweight of Type 2 inflammation in patients with CRSwNP, asthma or global airway disease—with the last one being the least investigated endotype. It is unknown whether and how those biologics change the immunological appearance in the tissue and improve tissue remodelling simultaneously; for example, does the use of anti-IgE lead to a parallel decline in both serum IgE and tissue IgE in both the upper and lower airways, and is this true for anti-IL5 and anti-IL4/13 as well?

Mepolizumab and Dupilumab are administrated subcutaneously and are human monoclonal (IgG) antibodies that targets IL5 and IL4/13, respectively, thus, reducing type 2 inflammatory markers in the tissue e.g. eosinophil granulocytes. Mepolizumab and Dupilumab are currently approved for treating CRSwNP. The outcomes in previous RCTs are expressed as health-related quality of life (HRQL) measurements, such as SNOT-22, sense of smell disease severity, including symptom scores performed by, for example, the Visual analogue scale (VAS) scale or others and, finally, adverse events (AEs) or serious adverse events (SAEs). Secondary outcomes include the avoidance of surgery, avoidance of systemic steroid, change in nasal polyp scores (NPS) and changed CT scan score. Both drugs have shown to improve both disease specific and generic HRQL and improve NPS – importantly, showing insignificant or no side effects. Hence, this has the potential to be a 'game-changer' in the management of patients with severe disease, allowing them to avoid other treatments associated with higher risk (3, 11). In previous international RCTs, all patients were treated with nasal steroids and saline irrigation, which remained unchanged throughout the studies. However, this local treatment did only have modest effect.

Dosing intervals and discontinuation of biological drugs.

When initiating biological treatment in CRSwNP patients in Europe in 2019, the guidelines did not state any recommendations on dosing intervals or overall duration of treatment, however, it was strongly recommended to make such guidelines. So, when the treatment was initiated in Denmark in 2022 the Danish Medicines Council noted that reduction of dose by prolongation of dosing intervals could be considered in patients with response to the therapy after 24 weeks of treatment (https://medicinraadet.dk/media/wruoqmyf/medicinr%C3%A5dets-opstarts-monitorerings-og-stopkriterier-for-biologiske-l%C3%A6gemidler-til-sv%C3%A6r-crswnp.pdf).

3. Design

3.1 Study design

Nine hospitals in Denmark have ENT-Departments. All departments have out-patients with severe CRSwNP treated with biologics. These patients attend regular out-patient controls including classification of symptoms based on standardised questionnaires using the 'Sino-Nasal outcome test' (SNOT22), VAS score of CRS symptoms, STARR15 questionnaire, asthma symptoms with asthma control questionnaire (ACQ), and Smell Identification Test (16stix). Furthermore, clinical examinations focus on nasal endoscopy, ear examination and treatment adherence. Paraclinical data such as CT scans, blood work and lung function tests are also part of the standard initial evaluation.

The treatment of Mepolizumab is 100 mg given every four weeks.

The treatment of Dupilumab is 300 mg given every two weeks. If response is achieved, the dose is, according to the Danish Medicines Council guidelines, reduced to treatment with 300 mg every 4th week – therefore all patients with response to therapy are currently receiving this dose.

3.2 Type of study
A randomized, investigator-initiated, multi-center, controlled trial. The trial is un-blinded and investigational medicinal products (IMPs) will be given at standard doses at increased dosing intervals.

The rationale behind choosing the RCT design is the aim of determining a causal relationship between dosing intervals and effect of biologic treatment for CRSwNP. To minimize the risk of selection bias we chose a 1:1 block randomization method, using REDCap's randomization module. The unblinded design is a result of the available resources, as one of the trial medication manufacturers does not provide a "dummy" injector pen and thereby patients would have to go to the out-patient clinic, be blindfolded and receive the medication by a nurse injector every few weeks, which is not feasible for this investigator-initiated trial that is planned and funded without financial ties to the pharmaceutical industry. Choosing to investigate increased dosing intervals is inspired by other studies (13, 16) of which Søndergaard et. al. investigated increased dosing intervals in asthma patients receiving IL5 inhibitors (mepolizumab being one of them) in a RCT design, and van der Lans et. al. investigated increased dosing intervals of dupilumab in CRSwNP as an observational study – both studies found that tapering was feasible in approximately ¾ of patients.

3.3 Randomization
The REDCap database will randomize the patients 1:1 into two groups:

1: Unchanged biologic treatment every fourth week (control group).

2: Gradually prolonged dosing interval with biologics (intervention group).

Further, we will stratify for what biologic the patient is receiving (Mepolizumab or Dupilumab), diagnosis of asthma, age below 40 years, and geographical region of the trial site, so variables are similar in each group.

The reason for stratifying is as follows: Naturally, we would like to observe if one of the two drugs is better at ensuring continued partial remission. It is known that having asthma as a comorbidity worsens your disease. In the same way it is hypothesized that the duration of your illness might worsen your chances of continued partial remission, nevertheless, it is our experience that the patients have difficulties remembering how long they have had the disease, thus, second best is to stratify for age. Due to potential differences in patient population, investigator expertise, and resources available across regions, we choose to stratify for geographical region as well.

3.4 Bias
The randomization is done by REDCap using block randomization. We are aware that there is a risk of bias due to few patients and four stratifications. However, this bias is significantly reduced by the fact that inclusion, and therefore randomization, of patients occurs at 9 different trial sites. Further, we cannot imagine a situation where the physician would choose to not ask a patient to participate even if that physician could have an idea of the randomization outcome.
Further, to avoid selection bias the PI will go through our global airway database (where all patients receiving biologics for CRSwNP are registered) to ensure that all eligible patients get the opportunity to participate in the study.

4. Objective

The objective is to evaluate the impact of prolonged dosing intervals of biologic therapy in patients with CRSwNP who have demonstrated stable, partly controlled disease. Specifically, the study will assess partly controlled disease after 52 weeks of prolonged dosing intervals in patients who have received treatment with Mepolizumab or Dupilumab for at least 18 months, with consistent partly controlled disease for a minimum of 12 months.

4.1 The primary outcome: is to find the percentage of patients achieving sustained partly controlled disease after tapering of biologics for CRSwNP. This will be evaluated by comparison of disease control assessments at weeks 0 and 52.

The primary endpoint being presence of 1-2 of the following 7 items:

1. Nasal blockage[1]: present on most days of the week[3]
2. Rhinorrhoea/postnasal drip[1]: mucopurulent on most days of the week[3]
3. Facial pain/pressure[1]: present on most days of the week[3]
4. Sense of smell[1]: impaired[3]
5. Sleep disturbance or fatigue[1]: present[3]
6. Nasal endoscopy: diseased mucosa[4]
7. Rescue treatment (systemic corticosteroids, ESS, antibiotics): need of 1 course of rescue treatment

[1]symptom of CRS, [3]meassured by VAS score, [4]showing nasal polyps, mucopurulent secretions or inflamed mucosa

4.2 The secondary outcomes are 1: changes in health-related outcomes from baseline to 52 weeks, 2: to compare the two drugs in order to determine if one is better suited for prolonged dosing intervals. 3: lastly, identifying any factors associated with continued disease control.

These will be evaluated by the secondary endpoints: 1) changes in SNOT-22, WPAI, ACQ and smell test scores from baseline to 52 weeks; 2) changes in disease control assessments from baseline to 52 weeks by given drug; and 3) baseline and demographic data such as: age, sex, comorbidities, BMI, level of education, duration of biologic treatment.

4.3 Applicability

The proposed study will investigate whether patients having sustained partial remission for at least 12 months during treatment with biologics can continue this partial remission with gradually prolonged dosing intervals. This will help rhinology societies establish treatments guidelines.

4.4 Study drug

The IMPs are dupilumab (Dupixent, Sanofi) and mepolizumab (Nucala, GSK). Both administered as subcutaneous injections of 300 mg and 100 mg, respectively. During the 3 months before inclusion in the study the drugs will have been administered every 4 weeks as standard treatment. To ensure compliance throughout the trial, patients will be asked hereof at each visit, and will be asked to take home and fill out an "injection form" (please see *form 1* in section 6.1) in which they will note each injection throughout the duration of the trial.

4.5 Labelling

All trial medication will be "off the shelf" *i.e.,* no special labelling. It will be provided by hospital pharmacies in accordance with Good Manufacturing Practice (GMP). The indication and dosing of both Mepolizumab or Dupilumab will be consistent with the manufacturers' instructions, only the dosing intervals will vary from these instructions. Please note that the dosing interval of Dupilumab in Denmark is already varying from the manufacturers' instructions as it is currently 4 weeks (as opposed to the 2 weeks described by the manufacturer).

5. Materials

The study population is patients with severe CRSwNP already receiving biologics at Danish ENT departments – and therefore fulfill the EPOS criteria for biologic treatment of CRSwNP(17) :

- Fulfill the criteria for CRSwNP
- Presence of bilateral polyps
- Have had ESS (sinus surgery) (exceptional circumstances excluded)
- Fulfill at least three of the following five criteria:
    - Evidence of type 2 inflammation
    - Need for (and treated with) systemic corticosteroids or contraindication to these
    - SNOT-22 score of 40 or above
    - Significant loss of smell
    - Asthma needing regular inhaled corticosteroids

5.1 Inclusion criteria

- ≥18 years of age.
- Currently receiving treatment with either Dupilumab (300 mg) or Mepolizumab (100 mg) every four weeks.
- Having received the biologic at unchanged dosing interval for at least three months.
- For at least 1 year during treatment with biologics, the patients' CRSwNP must be categorized as "partly controlled" as defined by presence of 1-2 of the following 7 items (see EPOS 2020 table below):
    1. Nasal blockage[1]: present on most days of the week[3]
    2. Rhinorrhoea/postnasal drip[1]: mucopurulent on most days of the week[3]
    3. Facial pain/pressure[1]: present on most days of the week[3]
    4. Sense of smell[1]: impaired[3]
    5. Sleep disturbance or fatigue[1]: present[3]
    6. Nasal endoscopy: diseased mucosa[4]
    7. Rescue treatment (systemic corticosteroids, ESS, antibiotics): need of 1 course of rescue treatment

Table 1: EPOS 2020 assessment of current clinical control of CRS

EPOS 2020: Assessment of current clinical control of CRS (in the last month)

	Controlled (all of the following)	**Partly controlled** (**at least 1** present)	**Uncontrolled** (**3 or more** present)
Nasal blockage[1]	Not present or not bothersome[2]	Present on most days of the week[3]	Present on most days of the week[3]
Rhinorrhoea / Postnasal drip[1]	Little and mucous[2]	Mucopurulent on most days of the week[3]	Mucopurulent on most days of the week[3]
Facial pain / Pressure[1]	Not present or not bothersome[2]	Present on most days of the week[3]	Present on most days of the week[3]
Smell[1]	Normal or only slightly impaired[2]	Impaired[3]	Impaired[3]
Sleep disturbance or fatigue[1]	Not present[2]	Present[3]	Present[3]
Nasal endoscopy (if available)	Healthy or almost healthy mucosa	Diseased mucosa[4]	Diseased mucosa[4]
Rescue treatment (in last 6 months)	Not needed	Need of 1 course of rescue treatment	Symptoms (as above) persist despite rescue treatment(s)

[1] Symptoms of CRS; [2] For research VAS ≤ 5; [3] For research VAS > 5; [4] Showing nasal polyps, mucopurulent secretions or inflamed mucosa

5.2 Exclusion criteria

- Patients with excellent response to biologics ("controlled" in table above)
- Patients with no or limited response to biologics ("uncontrolled" in table above)
- Patients with a cancer diagnosis deemed by the investigator to preclude participation in the trial
- Patients who, because of language barriers, are not able to understand Danish written information and, thus, are not able to answer questionnaires
- Patients who currently receive biologics for any other disease (asthma not included)
- Patients who are not able to give informed consent (i.e., patients who are permanently incapable)
- Patients who are not eligible because of the investigator's judgement
- Patients who experience pregnancy during the study will be excluded after an unscheduled visit – active IVF treatment (please see below)
- Unwillingness to follow the study procedure

5.3 Recruiting

Eligible subjects from the out-patient biologics clinics, will be identified by the medical professional involved in their treatment (medical doctor or nurse). The subjects will be asked if they are interested in information about the trial. If they accept, they will be informed about the trial either by the 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.

5.4 Pregnancy

It has been decided by the Danish Medicines Council that patients who are or wish to become pregnant should not receive biologic treatment for CRSwNP, thus none of our patients will be pregnant at inclusion. Pregnancy tests will be conducted in all fertile women before inclusion in the study. Fertile women included in the study shall use safe contraception (intrauterine or hormonal contraceptives) throughout the trial period and until a minimum of 6 weeks after termination of treatment. Any women who wish to or becomes pregnant during the study will be discontinued without receiving more study medication, and the data from the last follow-up visit will be used in the analyses. A report will be submitted to the pharmaceutical sponsor within 24 hours after learning the participant has become pregnant. Male participants with partners who become pregnant can participate in the study.

5.5 Other medication

All patients continue nasal steroids at the same frequencies as before. Any patients who have been prescribed reduced dosage of both nCS and/or ICS, during the follow-up period, should continue with this dosage of local steroid for both upper and lower airways. However, changing the medication is not an exclusion criterion, including prescription of montelukast which is a drug with action on allergic rhinitis and asthma, but must be done by or in consultation with the doctor responsible for the asthma treatment (usually GP or pulmonologist) according with the Global Initiative for Asthma's (GINA) recommendations.

6. Methods

6.1 Patient visits

During standard out-patient visits in the months leading up to the study, patients will be notified about the study and the potential to join. Patients may take as long as they wish to consider participation in the trial.

Visit 1: Week 0. Disease control assessment. Inclusion and exclusion criteria are evaluated. Informed consent obtained. This is a standard scheduled out-patient visit including questionnaires (SNOT-22, WPAI and ACQ), smell test, eos blood sample and nasal endoscopy. Randomization (1:1) to either continue standard dosing or to gradual prolonged dosing interval in which +2 weeks are added to the current dosing interval.

Visit 2: Week 12. Project specific out-patient visit with disease control assessment, SNOT-22, WPAI and nasal endoscopy.

Visit 3: Week 26. Standard scheduled out-patient visit including questionnaires (SNOT-22, WPAI and ACQ), smell test, eos blood sample and nasal endoscopy. If continued partial remission in the intervention group: +2 weeks are added to the current dosing interval.

Visit 4: Week 38. Project specific out-patient visit with disease control assessment, SNOT-22, WPAI and nasal endoscopy.

Visit 5: Week 52. Standard scheduled out-patient visit including questionnaires (SNOT-22, WPAI and ACQ), smell test, eos blood sample and nasal endoscopy. Marks end of study.

The scheduling of visits is allowed within a +/- 2-week period from the above-mentioned schedule.

Table 2: drug administration

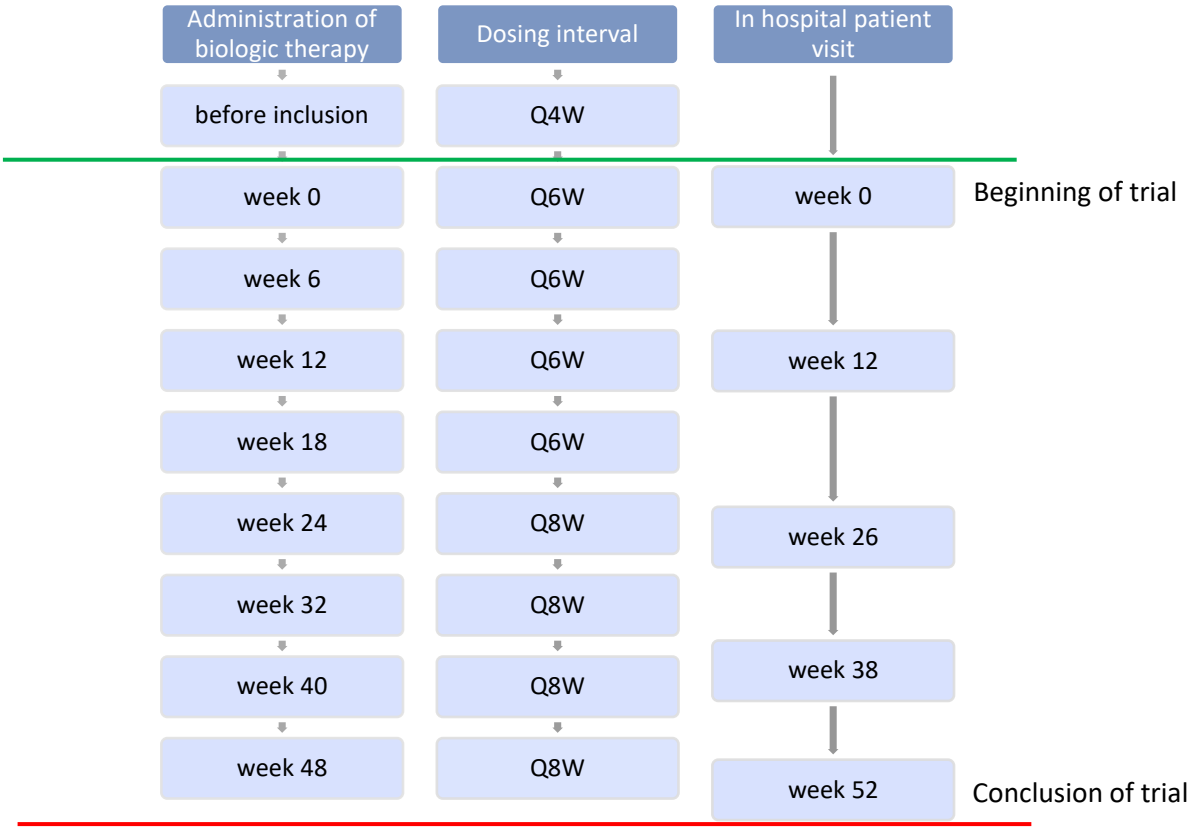


Table 3: tests during patient visits

Tests/examinations	Patient visits				
	1 (week 0)	2 (week 12)	3 (week 26)	4 (week 38)	5 (week 52)
Disease control assessment	X	X	X	X	X
SNOT-22	X	X	X	X	X
WPAI	X	X	X	X	X
ACQ	X		X		X
Smell test	X		X		X
Eos blood sample	X		X		X
Nasal endoscopy	X	X	X	X	X
Registration of adverse events	X	X	X	X	X

Registration of data: All data points generated from the abovementioned tests and examinations will be registered in the electronic case report form at each visit.

6.2 Other medication

If the patient is receiving either asthma treatment, nasal corticosteroid treatment and/or nasal irrigation, these treatments must continue unchanged.

6.3 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, on a piece of paper, which is subsequently entered in the e-CRF, or alternatively together with the health care professional directly in the e-CRF.

Sino-nasal Outcome Test 22 (SNOT-22): The SNOT-22 is a 22-item questionnaire covering aspects related to sino-nasal disease and health related quality of life. 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 approximately 5–10 minutes. Please see the questionnaire as it will be used (in Danish) in appendix 1.

Asthma Control Questionnaire (ACQ): 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 indicates well-controlled asthma. Completion time is 2–4 minutes. Please see the questionnaire as it will be used (in Danish) in appendix 2.

Work Productivity and Activity Impairment Questionnaire (WPAI): The WPAI questionnaire contains 6 patient-reported items related to activities at and outside of work and how these are affected by the patient's CRSwNP. Completion time is 2–5 minutes. Please see the questionnaire as it will be used (in Danish) in appendix 3.

6.4 Worsening of symptoms

In case a patient experiences worsening of symptoms they will contact the department for at clinical evaluation and if the CRS symptoms are uncontrolled (3 or more symptoms on the EPOS 2020 chart) they will return to the previous effective dosing interval. In case patients experience worsening of symptoms while receiving the biologic medication

at the previous effective dosing interval, the medication will be adjusted identical to patients not participating in the trial, that is following The Danish Medicines Councils guidelines.

6.5 Compliance and adverse effects

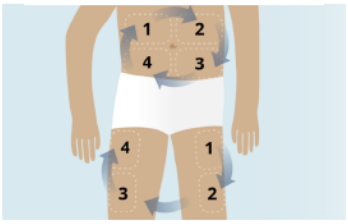
As has been routine before inclusion, the patients will at every visit be asked about compliance and whether they experience any adverse effects of the medication. To further ensure compliance patients will be asked to take home and fill out an "injection form" (please see *form 1 below*) in which they will note each injection throughout the duration of the trial.

Form 1: injection form

Stikkeskema - Behandling med biologisk medicin for svær næsepolypsygdom

REDCap ID# _____

Du skal skifte indstikssted, hver gang du stikker dig for at undgå dannelse af arvæv i hudområdet. Du må ikke stikke i hud, som er øm, har blå mærker, har ar eller er beskadiget. Du kan med fordel gøre som på figuren til højre.



Vi ser meget gerne at du medbringer skemaet til din kontrol på sygehuset om 12, 26, 38 og 52 uger. Alternativt kan du tage et billede af skemaet og sende det til forsøgsansvarlig læge Elizabeth Stevens på:

EMAIL: este0027@regionh.dk

Planlagt dato (d.d. + 4/6/8 uger) (udfyldes af sundhedspersonale)						
Faktisk dato for indsprøjtning (udfyldes af patienten)						
Indstikssted Mave = M Lår = L Skulder = S						
Side Højre = H Venstre = V						
Eventuelle bivirkninger siden sidste stik? (udfyldes af patienten)						

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6.6 Control group

When patients in the control group have finished the study period of 52 weeks, they will return to standard scheduled visits and depending on the study results, potentially be offered to receive treatment at prolonged dosing intervals.

6.7 Home Administration of Mepolizumab and Dupilumab

Most patients have before study start administrated the medication at home by themselves and received medicine to take home (usually approx. four doses at a time) This procedure will be maintained. It will also still be available for participants to have the medication administered by a nurse at the hospital, which is always available for patients receiving the biologics regardless of trial participation, and therefore is standard of care.

6.8 Objective measurements

Height, weight, sex, smoking habits, allergies, alcohol habits, asthma and other co-morbidities have previously been noted in our original so-called "Global Airways" REDCap database, however, we will ask if any of these data have changed and the data will also be registered in the new "Tapering study" REDCap database. The patients will be informed that this data will be used when writing the final article.

Nasal endoscopy: Nasal inspection will be done with either a flexible or rigid scope, and the participants will be examined for signs of CRS: 1. nasal polyps, 2. swollen mucosa and 3. character of secretion (nothing, clear or purulent). NPS will be measured as 0, 1, 2, 3 and 4 based on the size and location of the polyps.

6.9 Collection of biological material

No tissue or blood samples are kept for future research.

7. Ethical considerations:

7.1 Overall

We have very few ethical concerns by conducting this study. Though it is a pharmacological study, the patients are already in treatment with the drug the study concerns, thus, it is unlikely that any new side effects will occur and if they do, they would most likely have shown anyhow. There is no indication that prolonging dosing intervals of biologics increases the risk of side effects.
Further, examinations and questionnaires are all part of the current monitoring that the patients partake in when being on biologic treatment – only one extra questionnaire (WPAI) will be administered. No extra blood samples are taken. There will only be two additional out-patient visits.

Our main concern is that some patients will experience worsening of some sino-nasal symptoms when extending the dosing interval of the biologic medicine. In these cases, the patients will quickly be offered to return to the previous dosing interval. Further, some patients might experience worsening of their asthma symptoms – in that case we will promptly contact a pulmonologist to optimize the patient's treatment, however it should be kept in mind that the patients' asthma treatments have been unchanged from before they started the biologic treatment. Lastly, it should also be noted that the Danish Medicines Council recommends trying to prolong the dosing interval in patients after 24 weeks of treatment, thus we find it better to do this under RCT conditions as to gain a better understanding of potential risks and benefits.

We believe the potential for benefits to the patients is great, as patients in the intervention group - and more patients long term if the study finds that prolonged dosing intervals in non-inferior to standard dosing - will receive the medication less frequently and thereby experience less discomfort due to fewer injections, less dependency on the hospital and health care system due to fewer controls long term, and long-term lower medication costs for the individual and society. There is also the potential for even fewer adverse reactions with less frequent dosing, but this is not documented.

7.2 Criteria for discontinuing parts of the clinical trial or the entire clinical trial

In the hypothetical situation that patients experience severe adverse reactions resulting from tapering the medicine and that the reaction is irreversible despite starting the medicine again the trial will be discontinued.

In case all the first 34 patients randomized to receive the medication at increased dosing intervals (half of the approximately 68 patients projected to be randomized to the intervention) experience worsening of symptoms within the first three months after tapering, no further patients are included.

In case all the first 17 patients receiving the same drug (half of the approximately 34 patients projected to receive each of the two drugs in the intervention group) experience worsening of symptoms within the first three months after tapering, no further patients are included.

8. Statistical analysis

8.1 Power calculation

The study includes 135 participants with an expected 10% dropout rate, providing 90% power to demonstrate non-inferiority of dose reduction compared to standard dosing with a significance threshold of 0.05 and a non-inferiority margin of 20%. The expected proportion of patients with sustained response is 90% and 95% in the dose reduction and standard dose arms, respectively.

Secondary analyses will be conducted on the success rate of prolonged dosing intervals of dupilumab versus mepolizumab, but the study is not expected to have sufficient power to make any conclusive statements about this.

All participants who are included will be part of an intention-to-treat analysis.

8.2 Analysis plan

The aim is to analyse the proportion of patients able to sustain partial remission while tapering of biologics.

Normally distributed data will be analysed with the use of parametric statistics, such as t-test, mean and standard deviation (SD). In the regression analysis, one-way ANOVA will be used, and in variables with p=0.2 or less, they will be included in a multivariate regression analysis with backward elimination. In variables where logarithmic transformation will make them normally distributed, this will be performed, and the above-listed analysis will be used. In the case of a non-normal distribution, parametric analysis will be performed using Wilcoxon or Spearman correlations. Serial analysis will be done (0, 9, 12) using mixed models or others.

Imputation: will be used in cases of major protocol deviations, missing drug adherence, missed visit windows, lost to follow-up, treatment cessation due to intolerability, and pregnancy.

Last observation carried forward (LOCF): will be done in cases of lack of response to biologic therapy despite following the Danish Medicines Council's guidelines for treatment failure (i.e. returning to standard dosing and trying the other biologic product if needed).

8.3 Primary output

At the 52nd week evaluation, with the Chi-square test (sustained partial remission vs lack thereof) will be performed. The time to event analyses and safety analyses were based on all patients who underwent random assignment and had one year of partial remission using ITT analysis. Binary end points will be analysed both using ITT and PP (only including the patients with continued partial remission) – and will be depicted in Kaplan-Meier plots as well as using Cox proportional Hazard regression analysis.

8.4 Study administration

The study coordinator, Elizabeth M. Stevens Saporito, MD, is responsible for notifying relevant authorities including but not limited to: De Videnskabsetiske Medicinske Komiteer (VMK) via CTIS (CITIS 2024-519758-35), the Regional

GCP Unit, the Danish Data Protection Agency, the regional research inventory system “Privacy” (P-2024-28002) regarding this investigator-initiated collaborative pharmaceutical study.

All regulations concerning the data protection of the patients (General Data Protection Regulation (GDPR) and Danish Data Protection Act will be kept.
All patients will be informed by one of the medical staff engaged in the current study. GCP training of the medical staff is required. The staff involved have either experience with ENT or lung diseases, and substantial knowledge in the area of CRSwNP and asthma.

Patients will be offered an unlimited consideration period, they will be given the opportunity of having a co-sitter if needed, otherwise they will be given the opportunity to accept and sign for participation at the visit in the out-patient clinic. The visit is carried out in a room in the out-patients clinic, where the ordinary clinical visits take place.

The patients are already in the out-patient clinic care and will be included consecutively, when in the clinic. At previous visits, all patients have consented to data collection in the current so-called “Global airways” REDCap database, including giving consent to further contact from the departments. Patients will be notified of the project before their scheduled appointment. Data collected in the study, will not be transferred into the electronic medical records.

8.5 Budget and economics.

The medicine is already paid for and handed out by the ENT departments, which individually have requested their region for the extra economy to cover the medicine costs. Funds have been awarded by the Danish national joint regional organization “Regionernes Medicin og Behandlings pulje” towards 1 year’s full-time salary for the study coordinator, Elizabeth M. Stevens Saporito, and 1 year’s part-time salary for a nurse to assist in running the study. We will apply to non-profit organizations for additional capital towards funding for the following 2 years and for funds towards publication fees and GCP costs.

8.6 Timeline

Biological treatment of CRSwNP was launched in 2022, and the first patients to be included in the proposed study are ready for inclusion in November 2024.
Administrative work with the Ethical Committee, CTIS and regional research inventory system (Privacy), as well as contact with other sites clinicians and with the GCP Unit, will start as soon as possible.

8.7 Milestones

- January 2024: protocol finalized
- January 2024: submission to CTIS, clinicaltrial.gov, Privacy
- Estimated March 2025: first patient’s initial visit – beginning of study
- Estimated March 2028: final patient’s last visit – conclusion of study

9. Risks and adverse drug reactions

9.1 Safety concerns

The biologic drugs have very few adverse effects, none of which are persistent, nevertheless, it should be noted that it is still unknown whether the drugs can have any long-term adverse effects, which the patients also are

informed of when initiating the treatment. The past year, we at Rigshospitalet together with Odense University Hospital have treated approximately 185 patients and have not registered any serious adverse drug reactions (SAR), and only few adverse reactions (AR). No patients so far have wished to stop using the drugs due to AR. The patients will be covered by the hospital system in case of any significant adverse effect in agreement with the Danish patient compensation. To our knowledge there is no theory hypothesizing that prolonging dosing intervals should increase the risks of adverse effects. The potential adverse effects can be viewed at: https://www.drugs.com/sfx/dupixent-side-effects.html and https://www.drugs.com/sfx/nucala-side-effects.html

Safety will be monitored throughout the study in accordance with GCP guidelines. Trained and experienced staff will always be available. The procedures used in the study are all considered safe. At the primary study site (Department of Otorhinolaryngology, Head & Neck Surgery and Audiology, Rigshospitalet, Copenhagen, Denmark), we have a routine and training for all procedures. Rigshospitalet also provides sufficient back-up in terms of a full-scale department of emergency medicine and an intensive care unit in the unlikely case of emergencies. Similarly, this is the case at all other ENT departments in Denmark, who already joined the treatment of CRSwNP with biologic drugs.

We will use the internationally acknowledge template of the GCP unit, which will be included in the REDcap database. At every visit we will ask for, evaluate and register, smaller adverse effects, as decided by the PI, or furthermore any adverse event (AE), serious adverse event (SAE), serious adverse reaction (SAR) or suspected unexpected serious adverse reaction (SUSAR). If any SAE/SAR or SUSAR occur during the trial the patients are carefully instructed to contact the local PI. In case of any SUSAR they will immediately be directly reported to the European EudraVigilance database.

The sponsor shall notify the Danish authorities about any serious breach of this Regulation or of the version of the protocol applicable at the time of the breach through CTIS without undue delay but not later than seven days of becoming aware of that breach.

9.2 Safety definitions

Adverse events: The definition of AEs and SAEs follows the CT-3 (detailed guidance on the collection verification and presentation of AEs/reactions arising from clinical trials on medicinal products for human use) by the European Commission. Furthermore, SUSAR will be collected and reported as needed to the authorities.

AE: Any unwanted medical occurrence in a patient or clinical trial subject administered a medicinal product that does not necessarily have a causal relationship with the treatment.

SAE: Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity or is congenital anomaly or birth defect.

SAR: An SAE that occurs during research with a medicinal product if there is a certain degree of probability that the SAE is a harmful and undesired reaction to the investigational medicinal product, regardless of the administered dose.

SUSAR: An unexpected SAR**.** In this case 'unexpected' means that the nature and severity of the SAR do not match the reference safety information (RSI) as included in the summary of product characteristics (SPC) or Investigator's Brochure.

Safety reporting

All AEs will be recorded in REDCap. All reported adverse events will be followed up until resolved or as clinically required.

The investigator is responsible for causality assessment of AEs and SAEs and reports the SAE/SAR to the sponsor within 24 hours of first becoming aware of the event.

The sponsor will immediately (within 7 days if deadly/life-threatening; within 15 days if not) report the SUSAR in the EudraVigilance database. In Region Hovedstaden the reporting will be performed through Region Hovedstadens Apotek. https://www.apoteket-regionh.dk/medicin-for-sundhedsprofessionelle/sider/susar-indberetning.aspx

The sponsor submits an annual safety report that summarizes all SARs and SUSARs for the two trial drugs, along with a report regarding the safety of study participants, to the CTIS system. The final reporting will occur once the last participant has completed the trial (last patients' final visit).

9.3 Participant discontinuation

Participants will be informed about the possibility of discontinuing the trial at any time, without giving a reason, and without their future medical care being influenced. We will encourage participants to inform the investigator as soon as they have decided to discontinue the trial, thereby allowing the registration of the last administered dose of trial medication. A participant may also be withdrawn at any time at the discretion of the investigator. In case of discontinuation, we ask the physician and/or the participant to indicate a reason for discontinuation, if they wish – this will be documented in the electronic case report form (eCRF) and summarized in trial reports. Adverse events resulting in discontinuation are anticipated to be uncommon because the individuals have already received biologic therapy for at least 18 months at the time of inclusion. However, the following factors could lead to discontinuation:

- Development of serious or unexpected adverse events
- Treatment failure despite following the Danish Medicines Council's treatment guidelines
- Persistent or substantial non-adherence to the study protocol or medication (e.g., <80% adherence to dosing, repeated missed visit windows)
- Participant request or loss of willingness to continue
- Investigator's clinical judgment for any other reason affecting participant safety or data integrity

Patients who prematurely discontinue the study will be asked to attend an early study discontinuation (ESD) visit at the earliest convenience, with all procedures planned as listed for the end of the study. Adverse events will be registered until withdrawal or discontinuation from the study. On the participant's requests, any data collected will be deleted, whereas, in all other cases, all data and tests collected before discontinuation will be included in the database and used in the analysis.

9.4 Participants who become pregnant

- The investigator will attempt to collect any history of pregnancy in the participants who become pregnant during the study using Mepolizumab and Dupilumab.
- A report will be submitted to the pharmaceutical sponsors (GSK and Sanofi) within 24 hours after learning the participants has become pregnant
- The outcome of the pregnancy will be followed. The follow-up period will be 6-8 weeks after the delivery
- Any termination of the pregnancy will be reported, independent of the outcome (the fetus)
- Any pregnancy complication of elective termination for medical reasons will be reported as AE or SAE.
- Any spontaneous abortion within 22 weeks or still born birth occurring after 22 weeks is always recorded as SAE, and needs to be reported to the pharmaceutical industry and health authorities as such.

- Any post-study abnormalities of the pregnancy outcome should be considered as a possible SAE, and the investigators are obliged to collect information of these circumstances.
- Women who become pregnant during the study will be discontinued, will not receive more study medication, and the data from the last follow-up visit will be used in the analysis.

10. Publication, Collaboration and Scientific statement

As soon as possible and no later than one year after the trial has ended, the summary of the results will be submitted to the CTIS portal.

All results will be published, both positive and negative results in National and international Journals, at congresses and webinars. Inconclusive results, which can be difficult to publish will be published in clinicaltrial.gov

The collected data will be aggregated in anonymized form with other international databases on the same subjects; nasal polyps, asthma and biological treatment.

The study is carried out in accordance with the Declaration of Helsinki. If the Helsinki criteria is fulfilled, each site that includes a patient for the study will be entitled to one co-author and if more than nine patients are included from the site two co-authorships are offered. The listed co-supervisors are automatically offered a co-authorship.

11: Protocol Synopsis

11.1 EU trial number and full trial title

CTIS: 2024-519758-35

English title: Tapering of biologics in CRSwNP

Subtitle: Tapering of Mepolizumab or Dupilumab after 12 months of partly controlled disease in patients with severe chronic rhinosinusitis with nasal polyposis – a national Danish RCT.

Dansk titel: Delvis sygdomskontrol ved nedtrapning af biologisk behandling af kronisk bihulebetændelse med polypper

11.2 Rationale: Specify background and hypothesis of the trial

The Danish Medicines Council has recommended that patients with CRSwNP and a good response to biologics should try prolonged dosing intervals of the medication (Mepolizumab or Dupilumab) after 24 weeks of treatment. We find it better doing so in a RCT setting.

11.3 Objective: Specify the main and secondary objectives of the trial

The objective is to evaluate the impact of prolonged dosing intervals of biologic therapy in patients with CRSwNP who have demonstrated stable, partly controlled disease. Specifically, the study will assess partly controlled disease after 52 weeks of prolonged dosing intervals in patients who have received treatment with Mepolizumab or Dupilumab for at least 18 months, with consistent partly controlled disease for a minimum of 12 months.

The primary outcome is to find the percentage of patients achieving sustained partly controlled disease after tapering of biologics for CRSwNP. This will be evaluated by comparison of disease control assessments at weeks 0 and 52.

The secondary outcomes are 1: changes in health-related outcomes from baseline to 52 weeks, 2: to compare the two drugs in order to determine if one is better suited for prolonged dosing intervals. 3: lastly, identifying any factors associated with continued disease control.

11.4 Main trial endpoints
The primary endpoint is presence of 1-2 of the following 7 items:

1. Nasal blockage[1]: present on most days of the week[3]
2. Rhinorrhoea/postnasal drip[1]: mucopurulent on most days of the week[3]
3. Facial pain/pressure[1]: present on most days of the week[3]
4. Sense of smell: impaired[3]
5. Sleep disturbance or fatigue[1]: present[3]
6. Nasal endoscopy: diseased mucosa[4]
7. Rescue treatment (systemic corticosteroids, ESS, antibiotics): need of 1 course of rescue treatment

11.5 Secondary trial endpoints
The secondary endpoints are: 1) changes in SNOT-22, WPAI, ACQ and smell test scores from baseline to 52 weeks; 2) changes in disease control assessments from baseline to 52 weeks by given drug; and 3) baseline and demographic data such as: age, sex, comorbidities, BMI, level of education, duration of biologic treatment.

11.6 Trial design
Non-blinded, prospective RCT. Half the included patients will continue their current treatment (control-group), the other half will receive the biological treatment at gradually increased dosing intervals (everything else unchanged). Every individual patient will have a 52-week follow-up period. If a patient in the active group experience worsening of symptoms, they will resume the last effective dosing interval.

11.7 Trial population
Patients over 18 years of age with severe CRSwNP, who have been on hospital administrated biologic treatment for at least 1.5 years and have had partial remission of CRSwNP for at least 1 year.

11.8 Interventions
The patients are randomized 1:1 into two groups: one group will be the control group with no change to their treatment, the other group will receive the biological treatment at gradually increased dosing intervals.

11.9 Ethical considerations
We have very few ethical concerns by conducting this study. It is unlikely that any new side effects will occur, since patients are already receiving the treatment and there is no suspicion that prolonging dosing intervals of biologics raises the risk of side effects. Further, none of the examinations or questionnaires are add-on to the examinations that the patients must already go through when receiving biologic treatment.

Our only concern is that some patients will experience worsening of symptoms when tapering the biologic medicine. However, we have a plan for handling this safely. Lastly, it should also be kept in mind that the Danish Medicines Council recommends tapering the treatment, thus we find it better doing so under RCT conditions.

12. References

1. Pavord ID. Blood Eosinophil-directed Management of Airway Disease. The Past, Present, and Future. *Am J Respir Crit Care Med* 2020;202:637–639.

2. Takabayashi T, Schleimer RP. Formation of nasal polyps: The roles of innate type 2 inflammation and deposition of fibrin. *J Allergy Clin Immunol* 2020;145:740–750.

3. Bachert C, Sousa AR, Han JK, Schlosser RJ, Sowerby LJ, Hopkins C, *et al.* Mepolizumab for chronic rhinosinusitis with nasal polyps: treatment efficacy by comorbidity and blood eosinophil count. *J Allergy Clin Immunol* 2022;doi:10.1016/J.JACI.2021.10.040.

4. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, *et al.* Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet* 2019;394:1638–1650.

5. Fokkens WJ, De Corso E, Backer V, Bernal-Sprekelsen M, Bjermer L, von Buchwald C, *et al.* EPOS2020/EUFOREA expert opinion on defining disease states and therapeutic goals in CRSwNP. *Rhinology* 2024;62:287–298.

6. Caminati M, De Corso E, Ottaviano G, Pipolo C, Schiappoli M, Seccia V, *et al.* Remission in Type 2 Inflammatory Diseases: Current Evidence, Unmet Needs, and Suggestions for Defining Remission in Chronic Rhinosinusitis with Nasal Polyps. *Curr Allergy Asthma Rep* 2024;24:11–23.

7. Castillo JA, Plaza V, Rodrigo G, Juliá B, Picado C, Fernández C, *et al.* Chronic rhinosinusitis with nasal polyps and allergic rhinitis as different multimorbid treatable traits in asthma. *The journal of allergy and clinical immunology Global* 2023;2:.

8. Heffler E, Malvezzi L, Pirola F, Zieba N, Paoletti G, Mercante G, *et al.* Treatable traits in chronic rhinosinusitis with nasal polyps. *Curr Opin Allergy Clin Immunol* 2019;19:373–378.

9. Klimek L, Förster-Ruhrmann U, Olze H, Beule AG, Chaker AM, Hagemann J, *et al.* Monitoring mepolizumab treatment in chronic rhinosinusitis with nasal polyps (CRSwNP): Discontinue, change, continue therapy? *Allergol Select* 2024;8:26–39.

10. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, *et al.* Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651–659.

11. Han JK, Bachert C, Fokkens W, Desrosiers M, Wagenmann M, Lee SE, *et al.* Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med* 2021;doi:10.1016/S2213-2600(21)00097-7.

12. Desrosiers M, Diamant Z, Castelnuovo P, Hellings PW, Han JK, Peters AT, *et al.* Sustained efficacy of mepolizumab in patients with severe chronic rhinosinusitis with nasal polyps: SYNAPSE 24-week treatment-free follow-up. *Int Forum Allergy Rhinol* 2024;14:18–31.

13. Soendergaard MB, Bjerrum A-S, Rasmussen LM, Lock-Johansson S, Hilberg O, Hansen S, *et al.* Titration of anti-IL-5 biologics in severe asthma: an open-label randomised controlled trial (the OPTIMAL study). *Eur Respir J* 2024;64:.

14. Zierau L, Walsted ES, Thomsen SF, Backer V. Response to omalizumab in patients with severe allergic asthma: A real-life study. *Respir Med* 2017;131:109–113.

15. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE, *et al.* Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet* 2019;394:1638–1650.

16. van der Lans RJL, Otten JJ, Adriaensen GFJPM, Hoven DR, Benoist LB, Fokkens WJ, *et al.* Two-year results of tapered dupilumab for CRSwNP demonstrates enduring efficacy established in the first 6 months. *Allergy* 2023;78:2684–2697.

17. Fokkens WJ, Viskens A-S, Backer V, Conti D, De Corso E, Gevaert P, *et al.* EPOS/EUFOREA update on indication and evaluation of Biologics in Chronic Rhinosinusitis with Nasal Polyps 2023. *Rhinology* 2023;61:194–202.

18. Thilsing T, Rasmussen J, Lange B, Kjeldsen AD, Al-Kalemji A, Baelum J. Chronic rhinosinusitis and occupational risk factors among 20- to 75-year-old Danes-A GA(2) LEN-based study. *Am J Ind Med* 2012;55:1037–43.

19. Alanin MC, Hopkins C. Effect of Functional Endoscopic Sinus Surgery on Outcomes in Chronic Rhinosinusitis. *Curr Allergy Asthma Rep* 2020;20:27.

20. Southwood JE, Loehrl TA, Poetker DM. Advances in Surgery: Extended Procedures for Sinonasal Polyp Disease. *Adv Otorhinolaryngol* 2016;79:148–57.

21. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, *et al.* European Position Paper on Rhinosinusitis and Nasal Polyps 2020. *Rhinology journal* 2020;0:1–464.

22. Bachert C, Han JK, Wagenmann M, Hosemann W, Lee SE, Backer V, *et al.* EUFOREA expert board meeting on uncontrolled severe chronic rhinosinusitis with nasal polyps (CRSwNP) and biologics: Definitions and management. *J Allergy Clin Immunol* 2021;147:29–36.

23. Gallo S, Castelnuovo P, Spirito L, Feduzi M, Seccia V, Visca D, *et al.* Mepolizumab Improves Outcomes of Chronic Rhinosinusitis with Nasal Polyps in Severe Asthmatic Patients: A Multicentric Real-Life Study. *J Pers Med* 2022;12:1304.

24. Lange B, Holst R, Thilsing T, Baelum J, Kjeldsen A. Quality of life and associated factors in persons with chronic rhinosinusitis in the general population: a prospective questionnaire and clinical cross-sectional study. *Clin Otolaryngol* 2013;38:474–80.

25. Sundh J, Johansson G, Larsson K, Lindén A, Löfdahl C-G, Janson C, *et al.* Comorbidity and health-related quality of life in patients with severe chronic obstructive pulmonary disease attending Swedish secondary care units. *Int J Chron Obstruct Pulmon Dis* 2015;10:173–83.

26. Sahlstrand-Johnson P, Hopkins C, Ohlsson B, Ahlner-Elmqvist M. The effect of endoscopic sinus surgery on quality of life and absenteeism in patients with chronic rhinosinuitis - A multi-centre study. *Rhinology* 2017;55:251–261.

27. Hiles SA, Gibson PG, Agusti A, McDonald VM. Treatable Traits That Predict Health Status and Treatment Response in Airway Disease. *J Allergy Clin Immunol Pract* 2021;9:1255-1264.e2.

28. McDonald VM, Osadnik CR, Gibson PG. Treatable traits in acute exacerbations of chronic airway diseases. *Chron Respir Dis* 2019;16:1479973119867954.

29. McDonald VM, Fingleton J, Agusti A, Hiles SA, Clark VL, Holland AE, *et al.* Treatable traits: a new paradigm for 21st century management of chronic airway diseases: Treatable Traits Down Under International Workshop report. *European Respiratory Journal* 2019;53:1802058.

30. Menzies-Gow A, Bafadhel M, Busse WW, Casale TB, Kocks JWH, Pavord ID, *et al.* An expert consensus framework for asthma remission as a treatment goal. *J Allergy Clin Immunol* 2020;145:757–765.

31. Hellings PW, Verhoeven E, Fokkens WJ. State-of-the-art overview on biological treatment for CRSwNP. *Rhinology* 2021;59:151–163.

32. Peters AT, Han JK, Hellings P, Heffler E, Gevaert P, Bachert C, *et al.* Indirect Treatment Comparison of Biologics in Chronic Rhinosinusitis with Nasal Polyps. *J Allergy Clin Immunol Pract* 2021;doi:10.1016/j.jaip.2021.01.031.

33. Håkansson K, Bachert C, Konge L, Thomsen SF, Pedersen AE, Poulsen SS, *et al.* Airway Inflammation in Chronic Rhinosinusitis with Nasal Polyps and Asthma: The United Airways Concept Further Supported. In: Cormier SA, editor. *PLoS One* 2015;10:e0127228.

34. Frendø M, Håkansson K, Schwer S, Rix I, Ravn AT, Backer V, *et al.* Asthma in ear, nose, and throat primary care patients with chronic rhinosinusitis with nasal polyps. *Am J Rhinol Allergy* 2016;30:.

35. Pearlman AN, Chandra RK, Chang D, Conley DB, Tripathi-Peters A, Grammer LC, *et al.* Relationships between Severity of Chronic Rhinosinusitis and Nasal Polyposis, Asthma, and Atopy. *Am J Rhinol Allergy* 2009;23:145–148.

36. Alsharif S, Jonstam K, van Zele T, Gevaert P, Holtappels G, Bachert C. Endoscopic Sinus Surgery for Type-2 CRS wNP: An Endotype-Based Retrospective Study. *Laryngoscope* 2019;129:1286–1292.

37. Rix I, Håkansson K, Larsen CG, Frendø M, von Buchwald C. Management of Chronic Rhinosinusitis with Nasal Polyps and Coexisting Asthma: A Systematic Review. *Am J Rhinol Allergy* 2015;29:193–201.

38. Eriksen PRG, Jakobsen KK, Backer V, von Buchwald C. The potential role of biological treatment of chronic rhinosinusitis with nasal polyps: a nationwide cohort study. *Rhinology* 2021;doi:10.4193/Rhin20.480.

39. Hox V, Lourijsen E, Jordens A, Aasbjerg K, Agache I, Alobid I, *et al.* Benefits and harm of systemic steroids for short- and long-term use in rhinitis and rhinosinusitis: an EAACI position paper. *Clin Transl Allergy* 2020;10:1.

40. Sweeney J, Patterson CC, Menzies-Gow A, Niven RM, Mansur AH, Bucknall C, *et al.* Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. *Thorax* 2016;71:339–46.

41. Sahlstrand-Johnson P, Holmström M, Ehnhage A. Does the oral steroid treatment of patients with nasal polyposis cause osteopenia or osteoporosis? *Clin Otolaryngol* 2019;44:1011–1016.

42. Thomas AJ, Alt JA. Oral Therapeutics for Rhinosinusitis with Nasal Polyposis. *Adv Otorhinolaryngol* 2016;79:138–147.

Appendix 1: SNOT-22

Vigtigste emner (5)	Du bedes vurdere hvert enkelt spørgsmål nedenfor i forhold til alvorlighed og hyppighed ved at sætte kryds i den boks der svarer til beskrivelsen ovenfor	Ikke noget problem	Et meget let problem	Et let eller mindre problem	Et moderat problem	Et svært problem	Det værst tænkelige problem
		0	1	2	3	4	5
	1. Behov for at pudse næse						
	2. Nysen						
	3. Løbenæse						
	4. Tilstoppede næsebor						
	5. Manglende lugte- eller smagssans						
	6. Hoste						
	7. Slim fra næsen løber ned bagtil i halsen						
	8. Tykt sekret i næsen						
	9. Trykken i ørerne						
	10. Svimmelhed						
	11. Ørepine						
	12. Ansigtssmerter/trykken						
	13. Vanskeligheder ved at falde i søvn						
	14. Opvågnen om natten						

	15. Manglende god søvn om natten						
	16. Vågner op og er træt						
	17. Træthed						
	18. Nedsat produktivitet						
	19. Nedsat koncentrationsevne						
	20. Frustreret/rastløs/irritabel						
	21. Trist						
	22. Flov						

Appendix 2: ACQ

Besvar spørgsmål 1 - 6.

Sæt cirkel om tallet ud for det svar, som bedst beskriver hvordan du har haft det i løbet af den sidste uge.

1.	I løbet af den sidste uge, hvor ofte er du i gennemsnit **vågnet om natten på grund af din astma?**	0 Aldrig 1 Næsten aldrig 2 Nogle få gange 3 Flere gange 4 Mange gange 5 Rigtig mange gange 6 Ikke i stand til at sove på grund af astma
2.	I løbet af den sidste uge, hvor **svære var dine astmasymptomer** i gennemsnit, **når du vågnede** om morgenen?	0 Ingen symptomer 1 Meget milde symptomer 2 Milde symptomer 3 Moderate symptomer 4 Ret svære symptomer 5 Svære symptomer 6 Meget svære symptomer
3.	I løbet af den sidste uge, **hvor hæmmet** har du generelt **været i dine aktiviteter** på grund af din astma?	0 Slet ikke hæmmet 1 Meget lidt hæmmet 2 Lidt hæmmet 3 Noget hæmmet 4 Meget hæmmet 5 Yderst hæmmet 6 Fuldstændig hæmmet
4.	I løbet af den sidste uge, **hvor forpustet** har du generelt været på grund af din astma?	0 Slet ikke 1 Meget lidt 2 Lidt 3 Noget 4 En del 5 Meget 6 Rigtig meget

5.	I løbet af den sidste uge, hvor meget af tiden havde du generelt **piben i brystet?**	0 Ikke noget af tiden 1 Næsten ikke noget af tiden 2 Lidt af tiden 3 Noget af tiden 4 En hel del af tiden 5 Det meste af tiden 6 Hele tiden
6.	I løbet af den sidste uge, hvor mange **pust/sug af en korttidsvirkende astmamedicin** (f.eks. Ventoline/Bricanyl) har du i gennemsnit taget hver dag? *(Hvis du ikke er sikker på, hvordan du skal svare på dette spørgsmål, så spørg om hjælp)*	0 Ingen 1 1 - 2 pust/sug de fleste dage 2 3 - 4 pust/sug de fleste dage 3 5 - 8 pust/sug de fleste dage 4 9 - 12 pust/sug de fleste dage 5 13 - 16 pust/sug de fleste dage 6 Mere end 16 pust/sug de fleste dage

Udfyldes af personalet

7.	FEV_1 før bronkodilatator: ..... FEV_1 forventet:..... FEV_1% af forventet:..... (Notér de faktiske værdier på de stiplede linjer og angiv FEV_1 som % af det forventede i den næste kolonne)	0 > 95% af forventet 1 95 - 90% 2 89 - 80% 3 79 - 70% 4 69 - 60% 5 59 - 50% 6 < 50% af forventet

Appendix 3: WPAI

Hvordan er dine arbejdsforhold ?

* must provide value

I de sidste 7 dage, hvor mange timer har du forsømt arbejdet på grund af symptomer fra din kroniske bihulebetændelse (næsepolypper)?
(Medtag timer du forsømte på sygedage, samt de timer du evt. mødte sent, gik tidligt osv.) (Medtag ikke den tid du har brugt på denne undersøgelse.)

* must provide value

I de sidste 7 dage, hvor mange timer har du forsømt arbejde af andre årsager som fx. ferie, helligdage eller tid hvor du fik fri til at deltage i denne undersøgelse?

* must provide value

I de sidste 7 dage, hvor mange timer arbejdede du rent faktisk?

* must provide value

I de sidste 7 dage, hvor meget påvirkede din kroniske bihulebetændelse (næsepolypper) din produktivitet i mens du arbejdede?
Tænk på de dage hvor du evt. var begrænset i mængden eller typen af arbejde som du kunne udføre, dage hvor du udrettede mindre end du gerne ville, eller dage hvor du ikke kunne udføre dit arbejde så omhyggeligt som sædvanligt. Hvis dine næsepolypper kun påvirkede dit arbejde lidt, skal du vælge et lavt tal.
Vælg et højt tal, hvis dine næsepolypper påvirkede dit arbejde meget.

* must provide value

Næsepolypper havde ingen indvirkninger på mit arbejde — Næsepolypper forhindrede mig fuldstændigt i at arbejde.

Change the slider above to set a response

I de sidste 7 dage, hvor meget påvirkede din kroniske bihulebetændelse (næsepolypper) din evne til at udføre almindelige daglige aktivitet, ud over at passe et arbejde?
Med almindelige aktiviteter mens de sædvanlige aktiviteter du udfører, som fx. husarbejde, indkøb, børnepasning, motion, lektielæsning, osv. Tænk på de gange hvor du var begrænset i mængden eller typen af aktiviteter som du kunne udføre, og de gange, hvor du udrettede mindre end du gerne ville.
Hvis dine næsepolypper påvirkede dine aktiviteter lidt, skal du vælge et lavt tal.
Vælg et højt tal, hvis dine næsepolypper påvirkede dine aktiviteter meget.

* must provide value

Næsepolypper havde ingen indvirkninger på mine daglige aktiviteter — Næsepolypper forhindrede mig fuldstændigt i at udføre mine daglige aktiviteter

Change the slider above to set a response