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Early View

Study protocol

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AROMA: Real-world Global registry of dupilumab for chronic rhinosinusitis with nasal polyps

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Take home message

AROMA, the first global registry to characterise patients with severe CRSwNP initiating dupilumab, will bridge the key evidence gap between efficacy and real-world effectiveness of dupilumab and generate evidence on long-term progression of severe CRSwNP

Abstract

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a predominantly type 2 inflammatory disease of the nasal and paranasal sinuses. Dupilumab is a monoclonal antibody that blocks the shared receptor component for interleukin-4 and interleukin-13, which are key and central drivers of type 2 inflammation. In clinical trials, dupilumab significantly improved objective and patient-reported measures of CRSwNP *versus* placebo and was well tolerated. Dupilumab is approved in the EU, USA, and Japan as add-on maintenance treatment for adults with inadequately controlled CRSwNP. There exists an important evidence gap between efficacy and effectiveness data for dupilumab in severe CRSwNP. In order to bridge this gap, the AROMA prospective global registry (NCT04959448) was established. AROMA will collect long-term data on the utilisation, effectiveness and safety of dupilumab for CRSwNP treatment in real-world clinical practice. AROMA will enrol approximately 1000 adults starting dupilumab for severe CRSwNP across 120 global sites. Baseline data will include patient demographics, medical/surgical history and presence of type 2 comorbidities. Effectiveness outcome assessments will include objective measures of CRSwNP assessed as part of routine clinical care and various patient-reported questionnaires. Treatment patterns, concomitant medications and long-term safety will also be recorded.

Results from AROMA, the first prospective, real-world, global registry to characterise patients with severe CRSwNP starting dupilumab, will provide evidence on the real impact of dupilumab in patients with CRSwNP and complement the data from the randomised clinical trials. The registry will also provide evidence on disease progression in patients with CRSwNP including those with co-existing diseases.

Key words: Adult, Biological agents, Chronic sinusitis, Nasal polyps, Study design

Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a predominantly type 2 inflammatory disease of the nasal and paranasal sinuses [1]. An estimated 1–4% of the adult population in Europe and the United States is living with the condition at any given time [2, 3]. CRSwNP is associated with a high symptom burden, significant impairment of health-related quality of life (HRQoL) and high economic burden [4, 5]. The detrimental effects of CRSwNP on HRQoL are greatest in those with higher disease severity, anosmia or treatment-refractory disease [3, 4, 6]. Patients commonly have additional co-existing type 2 inflammatory diseases such as asthma, non-steroidal anti-inflammatory drug-exacerbated respiratory disease and allergic rhinitis, which further contribute to the burden of disease and the impact on patients' lives and wellbeing [4, 7, 8].

The management of CRSwNP can be challenging. Moderate-to-severe CRSwNP is often refractory to standard medical therapies such as intranasal corticosteroid spray. Sinonasal surgery is recommended to remove nasal polyps in patients who have failed medical therapy. However, not all patients experience restoration of sense of smell following surgery and polyp recurrence is common, necessitating repeat surgery [9, 10]. Biological therapies have demonstrated efficacy in the clinical trial setting for the treatment of severe CRSwNP uncontrolled with standard of care therapy and/or surgery. The first of these to receive regulatory approval was dupilumab, a fully human VelocImmune®-derived monoclonal antibody [11-13]. Dupilumab blocks the shared receptor component for interleukin-4 and interleukin-13, which are key and central drivers of type 2 inflammation in CRSwNP and other diseases [14, 15]. In the SINUS-24 (NCT02912468) and SINUS-52 (NCT02898454) randomised controlled trials (RCTs) in patients with severe CRSwNP, dupilumab significantly improved multiple objective measures of CRSwNP, including endoscopic, radiological and clinical outcomes, and patient-reported symptoms and HRQoL compared with placebo [16, 17]. Dupilumab treatment also reduced the need for sinonasal surgery and systemic corticosteroid (SCS) use *versus* placebo [18].

There currently exists an important evidence gap between dupilumab efficacy observed over 52 weeks in the RCTs and its long-term effectiveness in real-world clinical practice. Patients treated with dupilumab in usual practice encompass a broader and more diverse population than those recruited for the RCTs, and effectiveness and safety may be affected by such factors as dosing, adherence, concomitant medications and co-existing diseases. Other possible contributing factors include healthcare provider choices of interventions, access and reimbursement, and contextual influences such as family and social support. In order to bridge the evidence gap between dupilumab outcomes observed in RCTs and those experienced in the real-world setting, the **A**ssessing Long-te**R**m **O**utcomes of Dupilu**MA**b (AROMA; NCT04959448) global registry has been established. AROMA will collect longitudinal data on the characteristics of patients newly starting dupilumab and on the utilisation and long-term effectiveness and safety of dupilumab for the treatment of patients with severe CRSwNP. The primary objectives of the study are 1) to longitudinally characterise the long-term effectiveness of dupilumab through assessment of patient-reported symptoms, HRQoL related to CRSwNP and other type 2 comorbidities, and their change over time and 2) to characterise patients who receive dupilumab for CRSwNP in a real-world setting with respect to medical history, demographic and disease characteristics, and type 2 comorbidities.

Methods

Study design, setting and participants

AROMA is a Phase 4, prospective, observational, multicentre, global registry study (figure 1) being conducted at approximately 120 global sites, around 75 in the US and 45 in Canada, Germany, Italy, Japan and The Netherlands. The study sites selected are representative of those routinely treating patients with severe CRSwNP. The registry will recruit adults ≥18 years of age who are initiating dupilumab for severe CRSwNP according to country-specific prescribing information. The target enrolment is 1000, which was chosen empirically based on an estimated dropout rate of 15% per year [19, 20] and to ensure that an adequate number of patients from different centres and countries would be enrolled to provide sufficient data to fulfil the study objectives. No formal statistical power or sample size calculation was performed. Patients with contraindications to dupilumab or who have been treated previously with dupilumab for any condition are not eligible. The full list of inclusion and exclusion criteria are shown in table 1.

Enrolled participants will receive dupilumab according to the dosing regimen recommended in the country-specific prescribing information and current local standard of care. All treatments during the study will be subject to costs per country-specific local prescribing information and country-specific local reimbursement/availability, as prescribed by local healthcare physicians as part of routine care. After enrolment in the registry, there are no protocol requirements regarding dupilumab or any other treatments. Participants can receive other medicines and treatments for CRSwNP or any comorbidities according to local standard of care. The study duration for each participant is up to 36 months, with study visits scheduled every 3 months from baseline through Month 24 and then every 6 months through Month 36, the planned end of the study. The schedule of visits, the acceptable windows for data collection around each scheduled visit and the allowable unscheduled clinic visits are intended to reproduce the real-world environment as much as possible, while maintaining

sufficient consistency to allow adequate analysis and interpretation of the data collected. Applicable Local Health Authority and Institutional Review Board and/or Ethics Committee approvals will be required, and all patients will provide informed consent before enrolment and any study-related procedure.

Study objectives

The primary objectives of the study are 1) to longitudinally characterise the long-term effectiveness of dupilumab through assessment of patient-reported symptoms, HRQoL related to CRSwNP and other type 2 comorbidities, and their change over time, and 2) to characterise patients who receive dupilumab for CRSwNP in a real-world setting with respect to medical history, demographic and disease characteristics, and type 2 comorbidities (table 2). Secondary objectives are to characterise the real-world utilisation of dupilumab for patients with CRSwNP, to collect global data on disease severity and patient satisfaction with treatment, and to collect long-term safety data on dupilumab in patients with CRSwNP. Exploratory objectives are listed in table 2.

Study endpoints

The study endpoints were defined to support the study objectives (table 2). Primary endpoints include a descriptive summary of symptoms, HRQoL and change over time, and a descriptive summary of patients and disease characteristics, including the presence of type 2 comorbidities. Secondary endpoints include descriptive summaries of dupilumab and other treatments for CRSwNP used during the study, including most-used treatments, dosage, adherence, interruption, location and frequency of administration (home or clinic). Reasons for initiation of new CRSwNP treatments, concomitant therapies, treatment durations and reasons for discontinuation and/or switching will also be recorded. Global assessments of disease severity and treatment satisfaction (patient and physician) will be performed and adverse events recorded. Endpoints supporting the exploratory objectives are listed in table 2.

Assessments

Baseline assessments will include patient demographics, disease characteristics and medical history, presence of type 2 comorbidities, age at CRSwNP diagnosis and baseline measurements of effectiveness variables. Any recent (within the previous 12 months) results from local laboratory testing for total immunoglobulin E (IgE), allergen-specific IgE and eosinophil counts will be recorded at the baseline visit and throughout the study.

Measures of dupilumab effectiveness will be assessed at baseline and at various visits throughout the study period. As part of the primary endpoint the 22-item Sino-Nasal Outcome Test, the Work Productivity and Activity Impairment Questionnaire for CRSwNP and the 12-item Short-Form will be assessed at baseline, every 3 months for the first 2 years, and every 6 months in the last year of the study (Table 2, Figure 1). Patients with coexisting allergic rhinitis will also be requested to complete the allergic rhinitis visual analogue scale on this schedule. Other measures of dupilumab effectiveness to be evaluated as part of the primary endpoint will be assessed at baseline and every 6 months, including the Standardized Rhinoconjunctivitis Quality of Life Questionnaire for patients 12 years of age and older, the European Quality of Life 5-Dimensions, 5-Level Questionnaire and the Healthcare Resource Utilization Questionnaire. Patients with coexisting asthma will be requested to complete the Mini Asthma Quality of Life Questionnaire and the 6-item Asthma Control Questionnaire, and those with coexisting eczema the Patient-Oriented Eczema Measure. Additional measures will be collected where available, including the University of Pennsylvania Smell Identification Test, the Sniffin Stick Test, Lund–Mackay computed tomography, peak nasal inspiratory flow, fractional exhaled nitric oxide and spirometry. Patient-reported outcomes (PROs) will be captured via electronic diaries, or other suitable media, or during clinic visits if assessed in conjunction with other clinic-based assessments. Total symptom score (including subscores for nasal congestion and loss of smell) will be completed daily after an initial four-week period from the screening/baseline visit, then daily over two-week time periods commencing at Weeks 10, 22, 46, 70, 94, 118,

and 142, and at any early termination visit. Secondary endpoints of the Global Impression for Symptom Severity – Treatment Satisfaction (Global Patient Assessment) will be assessed at baseline, every 3 months in first 2 years, and every 6 months in the last year of the study, and the Global Impression for Disease Severity (Global Physician Assessment) will be assessed at baseline and every 6 months.

Adverse events, including those attributed to dupilumab and/or to concomitant treatments or procedures, will be recorded throughout the study. Adverse events are to be recorded in the electronic data capture system from the time informed consent is signed until the end of study. All serious adverse events are to be recorded in the electronic data capture within 24 hours of becoming aware of the event occurrence and its seriousness. The pharmacovigilance group responsible for processing safety information may follow up to elicit additional information in each case. The investigator will be responsible for assessment of severity and treatment-related causality. Pregnancy will not be classified as an adverse event, but occurrence of pregnancy and pregnancy outcomes will be recorded in the electronic data capture system, along with any adverse events/serious adverse events affecting female study patients and foetus and/or newborns.

Concomitant steroid use (intranasal corticosteroids, oral corticosteroids, or SCS) and other treatments for CRSwNP during dupilumab treatment will be collected in detail at baseline, including previous historical use, and at each scheduled assessment throughout the duration of the study and will be recorded in the case report form. The primary source for this information will be the treating physician by all means available to them (electronic medical records or prescription database systems). Sites will verify with the patient the actual use of these medications for compliance and adverse events. Treatment adherence for all treatments, including dupilumab, will be determined at each scheduled visit by the principal investigator throughout the duration of the three years of each patient’s participation in the study. Descriptive summaries will be provided as part of the exploratory analyses.

Further detail of the assessments is provided in the supplementary materials.

Statistical analysis

As an observational registry study, the analysis of data from AROMA will be descriptive and no formal statistical hypotheses will be tested. Demographic and baseline characteristics will be summarised descriptively. An interim data review to summarise the baseline characteristics is planned after at least 15–20% of the planned patient population have been enrolled. Baseline and post-baseline data will be compared and collected. However, since this is observational and open label study, no formal statistical analysis can be done, and descriptive comparisons will be stated in an appropriate manner.

The summary of safety and tolerability will be performed in the registry safety analysis set (RSAF), which will include all eligible patients who received at least one dose of dupilumab and consented to participate in the study. The safety analysis will be based on reported adverse events, with data summarised descriptively.

The effectiveness variables will be summarised in the registry evaluation analysis set, which will include patients in the RSAF with at least one post-baseline evaluation of either effectiveness or safety. The assessment of PROs will include patients who have a baseline and at least one PRO measurement after receiving at least one dose of dupilumab. The effectiveness data analysis will be of a descriptive nature. All observed values, regardless of whether data are collected after withdrawal from dupilumab treatment, will be used for analysis. No missing values will be imputed. Categorical variables will be reported using frequency tables; for continuous variables, the mean, standard deviation and five-point summaries comprising minimum, lower quartile, median, upper quartile and maximum values will be provided.

Dropouts will be defined as patients who voluntarily withdraw from the study, or patients who are withdrawn by an investigator and/or sponsor if it is no longer in the interest of the patient

to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). Patients will have the right to withdraw from the study at any time, for any reason, and without repercussion, but will remain eligible and be encouraged to stay in the study if they discontinue treatment permanently or temporarily. Patients who are withdrawn from the study altogether before the end of study visit (month 36) will be asked to return to the clinic for an early termination visit consisting of the early termination assessments.

Potential biases and their handling in interpreting effectiveness and safety

To avoid selection bias, all patients meeting the eligibility criteria will be invited to participate, and those who agree, will be enrolled consecutively into the registry. To minimise attrition bias, participants who discontinue dupilumab, either temporarily or permanently, will be encouraged to remain in the study and complete all scheduled study visits. Those who leave the study before the final visit at Month 36 will be asked to complete an early termination visit. The characteristics of participants who discontinue dupilumab and/or leave the study, and the reasons for them doing so, will be described. The characteristics of those who discontinue and/or withdraw will also be compared with those of all participants to highlight any differences. No missing values will be imputed, either for those who withdraw or for those who continue in the study but miss assessments. However, where necessary, further participants will be enrolled to ensure sufficient numbers will be available for evaluation.

Discussion

AROMA is the first prospective, observational, global registry study to characterise patients with CRSwNP who are initiating a biological treatment in a real-world setting, with a primary objective of capturing effectiveness and safety data covering dupilumab treatment for up to 3 years. It is anticipated that data from AROMA will bridge the evidence gap between the efficacy and safety of dupilumab reported in the RCTs and the effectiveness and safety of dupilumab in everyday clinical practice. The 3-year duration of AROMA will also address

questions regarding the longer-term effectiveness and safety profile of dupilumab beyond the 52-week treatment periods of the SINUS trials. In addition, AROMA will provide data on the demographics, clinical characteristics and medical history of patients receiving dupilumab in routine practice, a population which is expected to be broader than that eligible for participation in the RCTs. Information should also be generated regarding the impact of real-world dupilumab treatment on factors such as long-term requirement for SCS and rates of sinonasal surgery, previously shown to be improved by dupilumab over 52 weeks in the clinical trial setting [18].

As well as generating data using objective measures of CRSwNP disease, AROMA will collect patient-reported data using a wide range of instruments capable of capturing information on the impact of dupilumab treatment from a patient perspective. The registry is also designed to collect longitudinal data regarding the impact of dupilumab on other type 2 comorbidities commonly associated with CRSwNP, which are known to adversely affect clinical outcomes as well as patient HRQoL [3, 4, 6]. Recent analyses of the SINUS trial populations have confirmed that the efficacy of dupilumab is maintained regardless of comorbid asthma [21], NSAID-ERD [22] or AR (Peters et al. manuscript in preparation). Additional real-world data from AROMA will provide valuable new information regarding the effectiveness of dupilumab in these difficult-to-treat subgroups.

As with any registry-based study, there are potential limitations including data availability and underreporting of outcomes if a patient leaves the study, factors other than the treatment of interest contributing to outcomes and the lack of a control arm. However, the comprehensive range of endpoints and assessments, including assessment of the most common comorbidities, should provide a broad picture of the clinical evolution of patients participating in the registry over the planned 3-year timeframe.

AROMA started enrolling patients at the US sites in August 2021 and the estimated primary completion date is August 2026.

Conclusion

AROMA is the first global, real-world, prospective, longitudinal registry to characterise patients with CRSwNP starting dupilumab treatment. Results from AROMA will complement data from dupilumab randomised clinical trials, generating clinical evidence to address gaps in knowledge and evidence regarding real-world treatment patterns and outcomes among patients with CRSwNP.

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Conflict of interest: S. Siddiqui, H. Zhang are former Regeneron employees and may hold stock and/or stock options from Regeneron Pharmaceuticals, Inc. C. Bachert reports advisory board fees and speakers' fees from Actobiotics, ALK, ASIT Biotech, AstraZeneca, GlaxoSmithKline, Intrexon, Novartis, Sanofi, Stallergenes Greer. A.M. Chaker reports research support, clinical study grants and advisory board fees/speaker honoraria (via Technical University Munich [TUM]) from Abello, ALK, Allergopharma, ASIT Biotech, AstraZeneca, Bencard/Allergen Therapeutics, European Institute of Technology (EIT Health), German Federal Ministry of Education and Research, GlaxoSmithKline, Immunotek, LETI, Lofarma, Novartis, Regeneron Pharmaceuticals Inc., Roche, Sanofi, Zeller. J.K. Han reports advisory board fees from AstraZeneca, Genentech, GlaxoSmithKline, Novartis, Regeneron Pharmaceuticals, Inc., Sanofi. P.W. Hellings reports advisory board fees from Sanofi, Regeneron Pharmaceuticals, Inc. A.T. Peters reports advisory board fees and research grants from Regeneron Pharmaceuticals, Inc., Sanofi, and consultant and research support from Optinose and GlaxoSmithKline. E. Heffler reports research grants from AstraZeneca, Boehringer Ingelheim, Circassia, GlaxoSmithKline, Nestlé Purina, Novartis, Sanofi, Teva, Valeas. S. Kamat, S. Nash, Y. Deniz are employees and may hold stock and/or stock options from Regeneron Pharmaceuticals, Inc. A.H. Khan, L. De Prado Gomez, J.A. Jacob-Nara, P.J. Rowe are employees, and may hold stock and/or stock options in the company from Sanofi.

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TABLE 1 AROMA inclusion and exclusion criteria

Inclusion criteria
• Patients ≥18 years at initiation • All patients who are newly initiated on dupilumab for the treatment of CRSwNP according to the country-specific prescribing information (product label or SmPC) • Willing and able to comply with clinic visits and study-related procedures as per protocol • Provide informed consent signed by study patient or legally acceptable representative • Able to understand and complete study-related questionnaires as per protocol
Exclusion criteria
• Patients who have a contraindication to dupilumab according to the country-specific prescribing information • Any previous treatment with dupilumab for any condition • Any condition that, in the opinion of the investigator, may interfere with the patient's ability to participate in the study, such as short life expectancy, substance abuse, severe cognitive impairment or other medical, social or personal conditions and circumstances that can predictably prevent the patient from adequately completing the schedule of visits and assessments • Participation in an ongoing interventional or observational study that might, in the treating physician's opinion, influence the assessments for the current study   ○ Parallel inclusion in another Sanofi-independent registry might be possible if the patient gives consent

CRSwNP: chronic rhinosinusitis with nasal polyps; SmPC: summary of product characteristics.

TABLE 2 AROMA objectives and endpoints

Objectives	Endpoints	Assessments
Primary		
• To longitudinally characterise the long-term effectiveness of dupilumab through assessment of patient-reported symptoms, HRQoL related to CRSwNP and other type 2 comorbidities, and their change over time • To characterise patients who receive dupilumab for CRSwNP in a real-world setting with respect to their medical history, demographic and disease characteristics, and type 2 comorbidities	• Descriptive summary of symptoms, HRQoL and change over time • Descriptive summary of patients and disease characteristics with CRSwNP and type 2 comorbidities	• ACQ-6[#], AR-VAS[¶], eDiary[+] (LoS, NC, TSS), EQ-5D-5L[#], HCRUQ[#], mini-AQLQ[#], mini-RQLQ(S)[#], POEM[#§], SF-12[¶], Sniffin Stick Test[#], SNOT-22[¶], UPSIT[#], WPAI-CRSwNP[¶] • Not mandated per protocol; data will be collected if available for: FeNO, LMK-CT, PNIF, and spirometry
Secondary		
• To characterise the real-world utilisation of dupilumab for patients with CRSwNP	• Descriptive summaries of dupilumab and other CRSwNP treatments used	• Global patient assessment[¶], global physician assessment[#]

• To collect patient and physician global assessment of disease severity and treatment satisfaction for patients receiving dupilumab for CRSwNP • To collect long-term safety data for patients receiving dupilumab for CRSwNP	during the study, including the most commonly used treatments, dosage, adherence, interruption, place and frequency of administration (home or clinic) • Reasons for initiation of new CRSwNP treatments, concomitant therapies, treatment durations, and reasons for discontinuation and/or switching • Global assessment of disease severity and treatment satisfaction (patient and physician) • Descriptive summary of adverse events	• Adverse events[†], including those attributed to dupilumab and/or to concomitant treatments or procedures • Not mandated per protocol; data will be collected if available for: blood eosinophils; IgE
Exploratory		
• To assess INCS/SCS/OCS treatment patterns in patients with CRSwNP • To assess the use of controller medications in overlap patients with comorbid asthma • To collect information regarding surgery for CRSwNP in patients treated with	• Descriptive summaries of INCS/SCS/OCS use in CRSwNP patients during both pre- and post-use of dupilumab • Descriptive summaries of the use of controller medications in patients with comorbid asthma	

dupilumab and recurrence of CRSwNP in these patients	• Descriptive summaries of the history of surgeries and recurrence rates of nasal polyposis post-initiation of dupilumab treatment	

[#]Assessed at baseline and every 6 months of study.

[¶]Assessed at baseline, every 3 months in the first 2 years, and every 6 months in the last year of the study.

[+]eDiary assessments will be completed daily after an initial four-week period from the screening/baseline visit, then daily over two-week time periods commencing at Weeks 10, 22, 46, 70, 94, 118, and 142, and at any early termination visit.

[§]To be completed by patients with concurrent atopic dermatitis.

[†]Assessed throughout the study.

ACQ-6: 6-item Asthma Control Questionnaire; AR-VAS, Allergic Rhinitis Visual Analogue Scale; CRSwNP: chronic rhinosinusitis with nasal polyps; EQ-5D-5L: European Quality of Life 5-Dimensions, 5-Level Questionnaire; FeNO: fractional exhaled nitric oxide; HCRUQ: Healthcare Resource Utilization Questionnaire; HRQoL: health-related quality of life; INCS: intranasal corticosteroid; IgE, immunoglobulin E; LMK-CT: Lund–Mackay computed tomography; LoS: loss of smell; miniAQLQ: Mini Asthma Quality of Life Questionnaire; miniRQLQ(S): Mini Standardized Rhinoconjunctivitis Quality of Life Questionnaire for patients 12 years of age and older; NC: nasal congestion; OCS: oral corticosteroid; PNIF: peak nasal inspiratory flow; POEM: Patient-Oriented Eczema Measure; SCS: systemic corticosteroid; SF-12: 12-item short form; SNOT-22: 22-item Sino-Nasal Outcome Test; TSS: total symptom score; UPSIT: University of Pennsylvania Smell Identification Test; WPAI-CRSwNP: Work Productivity and Activity Impairment Questionnaire for CRSwNP.

FIGURE 1 AROMA study design

[#]Assessed at baseline and every 6 months of study.

[¶]Not required per protocol. Data will be collected, if available.

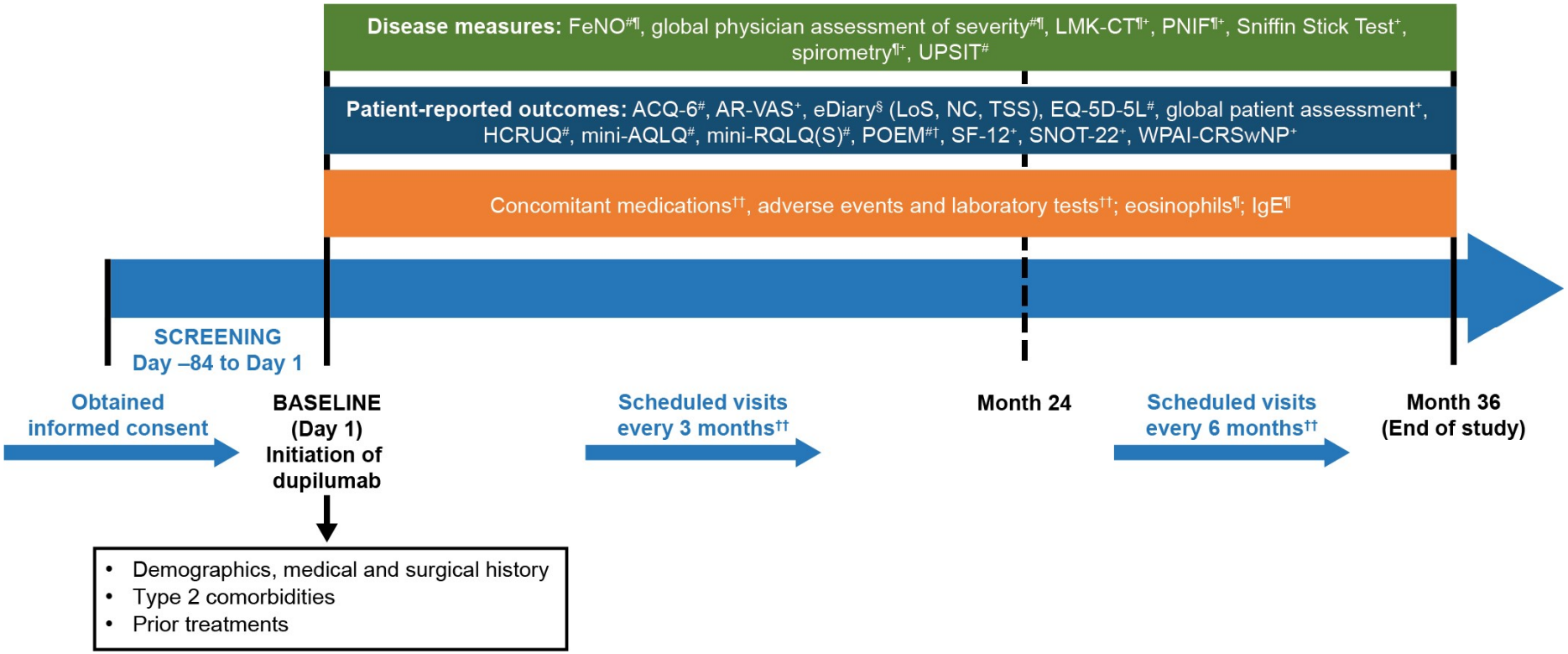
[+]Assessed at baseline, every 3 months in the first 2 years, and every 6 months in the last year of the study.

[§]eDiary assessments will be completed daily after an initial four-week period from the screening/baseline visit then daily over a two-week time period starting on: Week 10, Week 22, Week 46, Week 70, Week 94, Week 118, and Week 142, and at any early termination visit.

[†]To be completed by patients with concurrent atopic dermatitis.

[††]Assessed throughout the study.

ACQ-6: 6-item Asthma Control Questionnaire; AR-VAS, Allergic Rhinitis Visual Analogue Scale; CRSwNP: chronic rhinosinusitis with nasal polyps; EQ-5D-5L: European Quality of Life 5-Dimensions, 5-Level Questionnaire; FeNO: fractional exhaled nitric oxide; HCRUQ: Healthcare Resource Utilization Questionnaire; IgE: immunoglobulin E; LMK-CT: Lund–Mackay computed tomography; LoS: loss of smell score; miniAQLQ: Mini Asthma Quality of Life Questionnaire; miniRQLQ(S): Mini Standardized Rhinoconjunctivitis Quality of Life Questionnaire for patients 12 years of age and older; NC: nasal congestion/obstruction score; PNIF: peak nasal inspiratory flow; POEM: Patient-Oriented Eczema Measure; SF-12: 12-item short form; SNOT-22: 22-item Sino-Nasal Outcome Test; TSS: total symptom score; UPSIT: University of Pennsylvania Smell Identification Test; WPAI-CRSwNP: Work Productivity and Activity Impairment Questionnaire for CRSwNP.



#Assessed at baseline and every 6 months of study.

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+Assessed at baseline, every 3 months in the first 2 years, and every 6 months in the last year of the study.

Supplementary materials

Description of assessment

Allergic Rhinitis Visual Analogue Scale (ARS-VAS)

The AR-VAS is a validated measuring instrument for the documentation of symptoms and therapy monitoring in allergic rhinitis (AR). Patients with coexisting AR will be provided with an ungraduated VAS and will be asked to place a mark on the scale to indicate the severity of AR symptoms. Patients will be asked: “Overall how much are your allergic symptoms bothering you today?” The VAS extremities will be noted as “Not at all bothersome” to the left (score of 0) and “Extremely bothersome” to the right (score of 100).

Asthma Control Questionnaire, 6-Question Version (ACQ-6)

The 6-item version of the Juniper Asthma Control Questionnaire (ACQ-6) is a validated questionnaire to evaluate asthma control in registry patients with comorbid asthma. The ACQ-6 assesses the most common asthma symptoms: 1) frequency in past week awoken by asthma during the night; 2) severity of asthma symptoms in the morning; 3) limitation of daily activities due to asthma; 4) shortness of breath due to asthma; 5) wheeze; and 6) rescue bronchodilator use.

Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (where 0 = no impairment and 6 = maximum impairment), where a higher score indicates lower asthma control. Patients with a score <1.0 reflect adequately controlled asthma and patients with scores ≥1.0 reflect inadequately controlled asthma. The minimal clinically important difference (MCID) is a change in score of ≥0.5.

The European Quality of Life-5 Dimension, 5-Level Scale (EQ-5D-5L)

The EQ-5D-5L is a standardized health-related quality of life (HRQoL) questionnaire developed by the EuroQoL Group to provide a simple, generic measure of health for clinical and economic appraisal. The EQ-5D-5L is designed for self-completion by patients, and consists of 2 pages, the EQ-5D-5L descriptive system and the EuroQol-visual analogue scale (EQ-VAS). The EQ-5D-5L descriptive system comprises 5 dimensions: mobility; self-care; usual activities; pain/discomfort; and anxiety/depression. Each dimension has 5 levels: no problems; slight problems; moderate problems; severe problems; and extreme problems. The EQ-VAS records the respondent's self-rated health on a vertical VAS. The EQ-VAS 'thermometer' has endpoints of 100 (best imaginable health state) and 0 (worst imaginable health state).

Fractional Exhaled Nitric Oxide Levels (FeNO)

If consistent with the standard-of-care at the respective study center, FeNO (a marker of airway inflammation) should be measured prior to spirometry and following a fast of ≥1 hour.

Global Patient Assessment

The Global Patient Assessment is a 2-component questionnaire on symptom severity over the past week and the patient's overall satisfaction with their CRSwNP treatment.

The components are:

Please choose the response below that best describes the severity of your CRSwNP symptoms over the past week:

- No symptoms

- Mild
- Moderate
- Severe

Taking all things into account, how satisfied or dissatisfied are you with your current CRSwNP medications?

- Very satisfied
- Satisfied
- Undecided
- Dissatisfied
- Very dissatisfied

Global Physician Assessment

The Global Physician Assessment is a 1-item question asking physicians to rate the severity of their patient's CRSwNP:

Please answer this question based on your assessment of the patient today.

Overall, how severe is your patient's CRSwNP?

- Mild
- Moderate
- Severe
- Very severe

Healthcare Resource Utilization Questionnaire (HCRUQ)

The HCRUQ is a questionnaire filled out by the participating study site. At baseline, the past 1-year of data are collected from the physician's charts. The investigator could get this information based on their charts, or answers from the patient on healthcare resource use related to CRSwNP. The HCRUQ collects information on unscheduled healthcare resource encounters related to CRSwNP, including inpatient visits, emergency visits, and physician office visits, and includes the dates of visits and duration of any hospitalizations, together with the reason for the visits.

Loss of smell score (LoS)

The LoS score is a patient-reported assessment that evaluates smell impairment severity on a daily basis. Patients use an e-diary to record smell impairment on a 0–3 categorical scale where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms.

Lund-Mackay computed tomography (LMK-CT)

The LMK-CT system is a widely-validated physician-derived assessment based on evaluation of sinus opacification, with points assigned for degree of opacification (0 = normal, 1 = partial opacification, 2 = total opacification). Points are assigned for the maxillary, anterior ethmoid, posterior ethmoid, sphenoid, and frontal sinus on each side. The is graded as 0 = not occluded or 2 = occluded, deriving a maximum score of 12 per side and a total score range of 0–24. For patients in whom the osteomeatal complex is missing (because of a previous surgery) the CT scan reader should consider the location of the former osteomeatal complex and provide a scoring (as if the OC was there).

Mini Asthma Quality of Life Questionnaire (MiniAQLQ)

The MiniAQLQ has 15 items and was designed to meet the needs of large studies and long-term monitoring. Each item is rated on a 7-point Likert scale (from 1–7). There are 4 domains, with the number of items in each domain as follows:

- Symptoms (5 items)
- Activity limitation (4 items)
- Emotional function (3 items)
- Environmental stimuli (3 items)

A global score is calculated as an average of the domain scores, ranging from 1–7, where higher scores indicate better quality of life. The instrument has been shown to be reliable, valid, and sensitive to change. The MCID is a change in score of ≥0.5.

Nasal congestion/obstruction (NC) score

NC score is assessed by patients on a daily basis throughout the study, using an e-diary to record daily morning ante meridiem (AM) symptom severity. Scoring is assessed using a 0–3 categorical scale where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms and 3 = severe symptoms. The NC score is then calculated from the monthly average of patient-assessed daily scores.

Patient Oriented Eczema Measure (POEM)

The POEM is to be completed by patients with concurrent atopic dermatitis. It is a 7-item, validated questionnaire used in clinical practice and clinical trials to assess disease

symptoms in children and adults. The format is a response to 7 items (dryness, itching, flaking, cracking, sleep loss, bleeding, and weeping) based on the frequency of these disease symptoms during the past week (ie, days, 1 = 1– 2 days, 2 = 3–4 days, 3 = 5–6 days, and 4 = all days) with a scoring system of 0–28; the total score reflects disease-related morbidity.

Peak nasal inspiratory flow (PNIF)

PNIF evaluates a physiologic measure of air flow through both nasal cavities during forced inspiration, expressed in liters of air per minute. It is the best validated technique for the evaluation of nasal flow through the nose. Nasal inspiration correlates with the patient's subjective feeling of nasal obstruction, and is the best validated technique for monitoring nasal flow in clinical trials.

PNIF is recorded through the use of a PNIF meter. Patients are instructed on the use of the device, and PNIF efforts are recording via daily e-diary. Taking the best of 3 effort outcomes with less than 10% variation is considered to be the best means of expression of the result.

Short-Form 12 Version 2.0 (SF-12)

The SF-12 is a generic patient-reported questionnaire measuring general health status during the last 4 weeks. It has 12 items that measure 8 multi-item dimensions of health: physical functioning; social functioning; role limitations due to physical problems; role limitations due to emotional problems; mental health; energy/vitality; pain; and general health perception.

Sino-Nasal Outcome Test (SNOT-22)

The SNOT-22 is to be completed by patients with concurrent chronic (rhino) sinusitis and/or nasal polyposis. It is a validated questionnaire to assess the impact of chronic rhinosinusitis on HRQoL. The SNOT-22 has 22 items, 5 domains, and a global score. The 5 domains include:

- Nasal (range 0 to 30)
- Ear (range 0 to 15)
- Sleep (0 to 20)
- General and practical (0 to 30)
- Emotional (0 to 15)

The range of the global score is 0–110, and the MCID is ≥8.9. Lower scores indicate less impact. The recall period of the assessment is within the past 2 weeks.

Sniffin Stick test

The Sniffin' stick test consists of 12 scented pens, each with an associated test card that provides a multiple-choice question with four alternative words to describe the odour. The odorant is released through removal of the pen cap. The pen is held 2 cm from the nose and patients smell the odour for 2–3 seconds before selecting an answer, to provide a score out of 12 possible correct answers. Outcomes are normalised for patient age and gender to indicate the level of smell impairment.

Spirometry

Spirometry is performed according to the standard-of-care at each study center. The following assessments are suggested: forced expiratory volume in 1 second, peak expiratory flow, forced vital capacity, and forced expiratory flow between 25% to 75% of vital capacity.

Standardized Rhinoconjunctivitis Quality of Life Questionnaire (≥12 Years of Age) (MiniRQLQ(S))

The MiniRQLQ(S) is an instrument with 28 items across 7 domains for patients ≥12 years of age and older: activities (3 items); sleep (3 items); non-hay-fever symptoms (7 items); practical problems (3 items); nasal symptoms (4 items); eye symptoms (4 items); and emotions (4 items). The recall period of the assessment is within the past week. Patients record their score for each item on a 7-point Likert-type response scale from 0 (“not troubled” or “none of the time”) to 6 (“extremely troubled” or “all of the time”). Domain and overall scores range from 0–6 where a lower score indicates better HRQoL.

Total Symptom Score (TSS)

Patients will complete the electronic diary in the morning to report severity of 4 symptoms: 1) nasal congestion; 2) anterior rhinorrhea (runny nose); 3) posterior rhinorrhea (post-nasal drip); and 4) loss of sense of smell, scored using a 0 to 3 categorical scale where 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms. TSS is a composite score (range 0–9) consisting of the sum of the following symptoms assessed daily: nasal congestion/obstruction, decreased/loss of sense of smell, rhinorrhea (average of anterior/posterior nasal discharge).

University of Pennsylvania Smell Identification Test (UPSIT)

The UPSIT is a rapid and easy-to-administer method to quantitatively assess human olfactory function that, when administered in the standardized manner, shows a high degree of uniformity in performance when tested in different laboratories.

The test consists of 4 booklets, each containing 10 odorants with one odorant per page (40 odours in total). The test-time is about 15 min. Stimuli are embedded in 10–50 μm diameter plastic microcapsules on brown strips at the bottom of each page. Above each odorant strip is a multiple-choice question with four alternative words to describe the odour. The odorant is released by rubbing the strip with the tip of a pencil, and the patient indicates which of four words best describes the odour, to provide a score out of 40 possible correct answers. The odorants of the UPSIT test take into account cultural differences.

A particular strength of this test is that it provides an olfactory diagnosis based on comparison of the patient's test score with normative data, providing a percentile score of an individual relative to his or her age-matched normal group. Furthermore, a clinician can distinguish patients with a normal sense of smell from those with different levels of smell impairment or loss.

Work Productivity and Activity Impairment Questionnaire for chronic rhinosinusitis with nasal polyps (WPAI-CRSwNP)

The WPAI-CRSwNP is designed to assess the impact of CRSwNP on patient productivity. It is a 6-item questionnaire that measures impairments in work and activities over a 7-day recall period. Outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity. The WPAI-CRSwNP will only be administered to adult patients who are working, either part time or full time. If patients are not working at baseline, they will not complete the questionnaire. For reference period(s) when

the patient is not working for the entire reference period, the questionnaire does not need to be completed.

DUPILUMAB

Assessing Long-te**R**m **O**utcomes of Dupilu**MA**b (**AROMA**): **Real-world** global registry of **dupilumab** for chronic rhinosinusitis with nasal polyps

AROMA registry (NCT04959448)

Screening

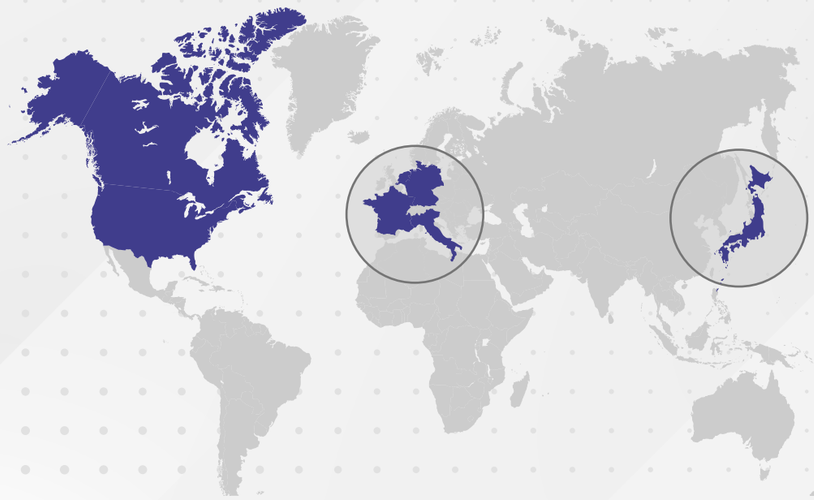
- Recruitment target of 1000 dupilumab-naïve adult patients with severe CRSwNP

Baseline

- Initiation of dupilumab and assessment of real-world demographics, disease characteristics, coexisting conditions, and treatment history

Study period

- Scheduled visits every 3 months to Month 24 then every 6 months to Month 36



120 study sites in 7 countries:
USA, Canada, France, Germany, Italy, Netherlands, Japan

Endpoints

Primary

- Objective disease measures assessed as part of routine clinical care
- Patient-reported outcomes

Secondary

- Concomitant medications
- Adverse events

Exploratory

- Steroid use
- Requirement for surgery
- Controller medication use in patients with coexisting asthma

Conclusion

The AROMA registry will prospectively characterise the effectiveness of dupilumab in a real-world setting