AROMA: real-world global registry of dupilumab for chronic rhinosinusitis with nasal polyps

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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 https://bit.ly/3BEEB8N

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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 European Union, 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 (ClinicalTrials.gov: 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 randomised clinical trials. The registry will also provide evidence on disease progression in patients with CRSwNP, including those with coexisting diseases.

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 USA 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 coexisting type 2 inflammatory diseases such as asthma, nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (NSAID-ERD) 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. Sino-nasal 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 and SINUS-52 (ClinicalTrials.gov: NCT02912468 and NCT02898454, respectively) 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 sino-nasal 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 coexisting 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 the RCTs and those experienced in the real-world setting, the Assessing Long-teRm Outcomes of DupiluMAb (AROMA; ClinicalTrials.gov: 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 USA 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 is 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

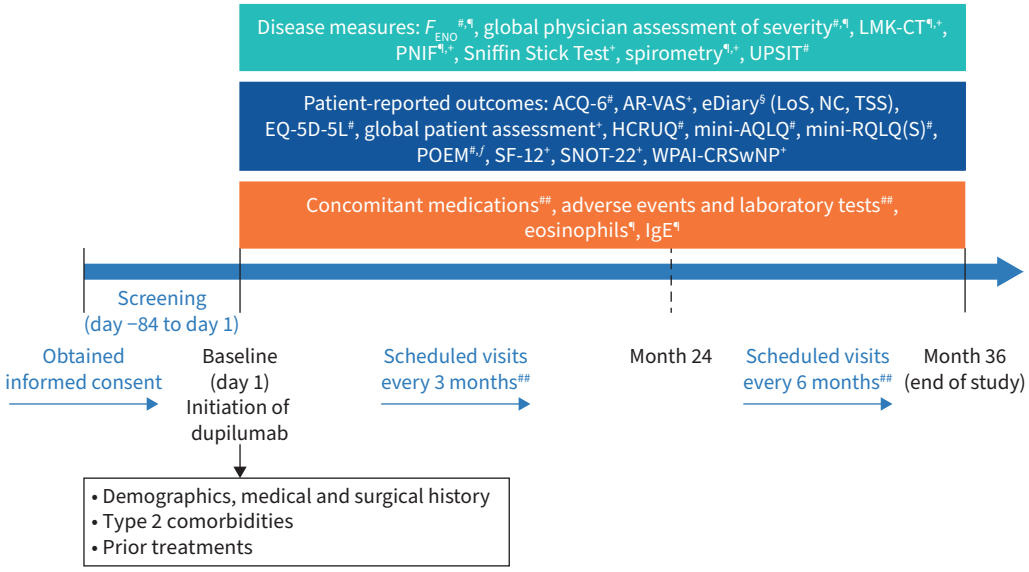

FIGURE 1 AROMA study design. [#]: assessed at baseline and every 6 months of study; [¶]: not required per protocol (data will be collected, if available); [+]: assessed at baseline, every 3 months in the first 2 years and every 6 months in the last year of the study; [§]: electronic diary (eDiary) assessments will be completed daily after an initial 4-week period from the screening/baseline visit, then daily over 2-week time periods commencing at weeks 10, 22, 46, 70, 94, 118 and 142, and at any early termination visit. [ƒ]: to be completed by patients with concurrent atopic dermatitis; [##]: assessed throughout the study. ACQ-6: six-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; F_{ENO}: fractional exhaled nitric oxide; HCRUQ: Healthcare Resource Utilization Questionnaire; LMK-CT: Lund–Mackay computed tomography; LoS: loss of smell score; mini-AQLQ: Mini Asthma Quality of Life Questionnaire; mini-RQLQ(S): Mini Standardised Rhinoconjunctivitis Quality of Life Questionnaire for patients ⩾12 years of age; 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.

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.

TABLE 1 AROMA inclusion and exclusion criteria

Inclusion criteria
Patients aged ⩾18 years at initiation
All patients who are newly initiated on dupilumab for the treatment of chronic rhinosinusitis with nasal polyps according to the country-specific prescribing information (product label or summary of product characteristics)
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

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 1) to characterise the real-world utilisation of dupilumab for patients with CRSwNP, 2) to collect global data on disease severity and patient satisfaction with treatment, and 3) to collect long-term safety data on dupilumab in patients with CRSwNP. Exploratory objectives are listed in table 2.

TABLE 2 AROMA objectives and end-points

Objectives	End-points	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	Descriptive summary of symptoms, HRQoL and change over time	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[¶]
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 patients and disease characteristics with CRSwNP and type 2 comorbidities	Not mandated per protocol; data will be collected if available for: F_{ENO}, 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 during the study, including the most commonly used treatments, dosage, adherence, interruption, place and frequency of administration (home or clinic)	
To collect patient and physician global assessment of disease severity and treatment satisfaction for patients receiving dupilumab for CRSwNP	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)	Global patient assessment[¶], global physician assessment[#]
To collect long-term safety data for patients receiving dupilumab for CRSwNP	Descriptive summary of adverse events[f]	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 and IgE
Exploratory		
To assess INCS/SCS/OCS treatment patterns in patients with CRSwNP	Descriptive summaries of INCS/SCS/OCS use in CRSwNP patients during both pre- and post-use of dupilumab	
To assess the use of controller medications in overlap patients with comorbid asthma	Descriptive summaries of the use of controller medications in patients with comorbid asthma	
To collect information regarding surgery for CRSwNP in patients treated with 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; [+]: electronic diary (eDiary) assessments will be completed daily after an initial 4-week period from the screening/baseline visit, then daily over 2-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; [f]: assessed throughout the study. ACQ-6: six-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; F_{ENO}: fractional exhaled nitric oxide; HCRUQ: Healthcare Resource Utilization Questionnaire; HRQoL: health-related quality of life; INCS: intranasal corticosteroid; LMK-CT: Lund–Mackay computed tomography; LoS: loss of smell score; mini-AQLQ: Mini Asthma Quality of Life Questionnaire; mini-RQLQ(S): Mini Standardised Rhinoconjunctivitis Quality of Life Questionnaire for patients ⩾12 years of age; NC: nasal congestion/obstruction score; 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.

Study end-points

The study end-points were defined to support the study objectives (table 2). Primary end-points 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 end-points 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. End-points 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 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 end-point 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 and 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 end-point will be assessed at baseline and every 6 months, including the Standardised Rhinoconjunctivitis Quality of Life Questionnaire for patients ⩾12 years of age, 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 six-item Asthma Control Questionnaire, and those with coexisting eczema will be requested to complete 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 4-week period from the screening/baseline visit, then daily over 2-week time periods commencing at weeks 10, 22, 46, 70, 94, 118 and 142, and at any early termination visit. Secondary end-points of the Global Impression for Symptom Severity – Treatment Satisfaction (global patient assessment) will be assessed at baseline, every 3 months in the 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 h 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 fetuses 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 3 years of each patient's participation in the study. Descriptive summaries will be provided as part of the exploratory analyses.

Further details of the assessments are provided in the supplementary material.

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 an 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 (*e.g.* 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 sino-nasal 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 allergic rhinitis (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 end-points 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.

Conclusions

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 RCTs, 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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