Ergebnisbericht gemäß § 42b (1) & (2) AMG

SAR231893/REGN668/Dupilumab / EFC14146
EudraCT-Number: 2015-003101-42

Name and address of the company:

Marketing Autorisation Holder
Sanofi-aventis groupe
54, rue La Boétie
75008 Paris
Frankreich

Name and address of the Sponsor:
Sanofi-aventis Recherche & Développement
1 avenue Pierre Brossolette
91380 Chilly Mazarin
Frankreich

Name of finished product: Dupixent®
Name of active substance: Dupilumab

Individual Study Table: Referring to Part of the Dossier (Volume, Page): n.a.

Title of Study: A randomized, 24-week treatment, double-blind, placebo-controlled efficacy and safety study of dupilumab 300 mg every other week, in patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids

Sponsor's protocol code number, version and date: SAR231893/REGN668/Dupilumab/EFC14146

Refers to the final version of the protocol dated 04-Aug-2016:

Protocol amendment 1 dated: 17-MAY-2017,
Summary of changes:
1) Clarify Early Treatment Discontinuation Language
2) Retesting of dynamic laboratory values during screening
3) Analysis changed to Systemic Corticosteroids from Oral Corticosteroids
4) EQ-5D elevated from exploratory endpoint to secondary endpoint
5) Clarified CT Scan Administration to be mandatory unless not approved by local ethics committee or IRB.
6) Intranasal decongestants added to list of prohibited medications except as needed for nasal endoscopy procedure.
7) Study procedures can be performed over 3 days if necessary as long as the visit window is respected.
8) Updated safety language throughout the protocol to be consistent with most current safety information per latest investigators brochure: Male birth control no longer required.
9) Clarified that rescue therapy prescribed by the investigator will not be provided by the sponsor

SYNOPSIS

Title of the study:	A randomized, 24-week treatment, double-blind, placebo-controlled efficacy and safety study of dupilumab 300 mg every other week, in patients with bilateral nasal polyposis on a background therapy with intranasal corticosteroids **– EFC14146**
Investigator(s):	Joseph Han, MD, Eastern Virginia Medical School, United States
Study center(s):	67 centers in 13 countries (Bulgaria, Czechia, France, Germany, Hungary, Italy, Netherlands, Poland, Romania, Ukraine, Russia, United Kingdom, and the United States [US])
Publications (reference):	None
Study period:	
Date first patient enrolled:	05 December 2016
Date last patient completed:	05 July 2018
Phase of development:	3
Primary objective:	To evaluate the efficacy of dupilumab 300 mg q2w compared to placebo on a background of mometasone furoate nasal spray (MFNS) in reducing nasal congestion (NC)/obstruction severity and endoscopic nasal polyps score (NPS) in patients with bilateral nasal polyposis (NP)
Secondary objectives:	• To evaluate the efficacy of dupilumab in improving total symptoms score (TSS). • To evaluate the efficacy of dupilumab in improving sense of smell. • To evaluate the efficacy of dupilumab in reducing computed tomography (CT) scan opacification of the sinuses (for Japan, this is part of the primary objective) • To evaluate the ability of dupilumab to reduce the proportion of patients who require treatment with systemic corticosteroids (SCS) or surgery for NP. • To evaluate the efficacy of dupilumab on patient reported outcomes (PROs) and health related quality of life (HRQoL). • To evaluate the effect of dupilumab in the subgroups of patients with prior surgery and comorbid asthma (including non-steroidal anti-inflammatory drug exacerbated respiratory disease [NSAID-ERD]). • To evaluate the residual effect of dupilumab through the 24-week follow-up period. • To evaluate the safety of dupilumab in patients with bilateral NP. • To evaluate functional dupilumab concentrations (systemic exposure) and incidence of treatment-emergent antidrug antibodies (ADA).
Methodology:	Multinational, multicenter, randomized, double-blind, placebo-controlled, parallel arm study to evaluate dupilumab administered subcutaneously (SC) for 24 weeks in patients with bilateral NP.
Number of patients:	Planned: 240 Randomized: 276 Treated: 275
Evaluated:	Efficacy: 276 Safety: 275 Pharmacokinetics: 142 ADA: 275

Diagnosis and criteria for inclusion:

Patients ≥18 years of age with bilateral sino-nasal polyposis that despite prior treatment with SCS anytime within the past 2 years; and/or who had a medical contraindication/intolerance to SCS; and/or had prior surgery for NP at the screening visit were eligible for inclusion in this study if they met the following criteria:

- An endoscopic bilateral NPS at screening of at least 5 out of a maximum score of 8 (with a minimum score of 2 in each nasal cavity)
- Ongoing symptoms (for at least 8 weeks before screening) of:
  - Nasal congestion/ blockade/obstruction with moderate or severe (symptom severity score 2 or 3) at screening and a weekly average severity of greater than 1 at time of randomization

    AND
  - Another symptom such as loss of smell, rhinorrhea (anterior/posterior)

Randomization was stratified based on asthma status (history of asthma/NSAID-ERD or not), prior NP surgery (yes or no), and country.

Study treatments

Investigational medicinal product(s): dupilumab or placebo

Formulation: Sterile dupilumab was provided as a 150 mg/mL solution in a glass pre-filled syringe to deliver 300 mg in 2 mL. Sterile placebo for dupilumab was provided in identically matched glass pre-filled syringes to deliver 2 mL.

Route of administration: SC

Dose regimen: Arm A: dupilumab 300 mg q2w SC until Week 24;
Arm B: placebo matching dupilumab SC q2w administration until Week 24.

Batch number(s): Dupilumab 300 mg/2 mL: C1062628, C1062032, C1066192, C1067468
Placebo 2 mL: C1061704, C1066098

Noninvestigational medicinal product: Mometasone furoate (MFNS, NASONEX®)

Formulation: MFNS 50 µg/actuation nasal spray was provided by the Sponsor in a bottle with 18 g (140 actuations) of product formulation.

Route(s) of administration: Intranasal

Dose regimen: 2 actuations (50 µg/actuation) of MFNS in each nostril twice daily (BID) (total daily dose of 400 µg)

Duration of treatment: 24 weeks

Duration of observation: The clinical trial consisted of 3 periods with a total duration of 52 weeks for each patient: run-in period (4 weeks ± 3 days), randomized treatment (24 weeks ± 3 days), and post-treatment follow-up (24 weeks ± 3 days).

Criteria for evaluation:

Efficacy: The coprimary efficacy variables were the change from baseline in NPS and NC at Week 24 assessed for dupilumab versus placebo.

Key secondary efficacy endpoints:

- Change from baseline in TSS at Week 24: composite severity score consisting of the patient daily AM assessed NC, decreased/loss of sense of smell, anterior/posterior rhinorrhea.
- Change from baseline in the UPSIT smell test at Week 24.
- Change from baseline in the severity of decreased/loss of smell daily assessed by the patient at Week 24.
- Change from baseline in opacification of sinuses assessed by CT scans using the LMK score at Week 24. (This endpoint will not be assessed as a secondary endpoint for Japan as it is already a coprimary endpoint.)
- Change from baseline in SNOT-22 at Week 24.
- Proportion of patients during study treatment receiving SCS and/or planned to undergo surgery for nasal polyps.

Additional secondary efficacy endpoints:

- Change from baseline at Week 24 in:
  - VAS for overall rhinosinusitis.
  - Nasal peak inspiratory flow (NPIF).
  - Rhinorrhea (anterior/posterior nasal discharge) daily symptom scoreassessed by the patient.
- Efficacy endpoints for the subgroups of patients with prior surgery and patients with comorbid asthma (including NERD history).
- Efficacy endpoints through the 24-week follow up period.
- Safety (incidence of treatment-emergent AEs (TEAE), of treatment-emergent serious AEs (TESAEs), and TEAEs leading to treatment discontinuation), laboratory values, vital signs.
- Dupilumab concentration in serum and ADA.
- Total SCS rescue dose prescribed (in mg) during the treatment period.
- Total SCS rescue intake in days during the treatment period.
- Patient reported outcomes including HRQoL scales (EQ-5D-5L VAS score, self-rated health).

Efficacy analyses in subpopulation of patients with asthma and/or NSAID-ERD:

- Change from baseline in NPS and NC at Week 24 assessed for dupilumab versus placebo and through the follow-up period
- Change from baseline to Week 24 in forced expiratory volume in one second (FEV_1) and Asthma Control Questionnaire-6 (ACQ-6) for dupilumab versus placebo

Efficacy analyses in subpopulation of patients with prior NP surgery:

- Change from baseline in NPS and NC at Week 24 assessed for dupilumab 300 mg versus placebo and through the follow-up period in patients with prior NP surgery

Safety: Treatment-emergent adverse events (TEAEs), vital signs, electrocardiogram (ECG) parameters, standard hematology and clinical chemistry.

Pharmacokinetics: Serum dupilumab concentrations and ADA.

Pharmacodynamics: Biomarkers included plasma eotaxin-3, serum total immunoglobulin E (IgE), allergen-specific IgE for aeroallergens, serum thymus and activation-regulated chemokine (TARC), serum periostin, and leukotriene E4 (LTE4) and a metabolite of prostaglandin D2 (PGDM) from urine.

Pharmacokinetic/Pharmacodynamics sampling times and bioanalytical methods:

Serum dupilumab concentrations: Predose serum dupilumab concentrations were assessed at Day 1; dupilumab trough levels at Weeks 4, 8, 16, and 24; and follow-up serum dupilumab at Week 36 and 48. Serum dupilumab concentrations were determined using a validated enzyme-linked immunosorbent assay (ELISA) method (REGN668-AV-13074-VA-01V1) with a lower limit of quantification (LLOQ) of 0.0780 mg/L, under the responsibility of Bioanalytical Operations, Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA.

Anti-dupilumab antibody: ADA status (negative or titer value) was determined at Day 1, Weeks 8, 16, 24, 36, and 48. Serum ADA was measured using a validated electrochemiluminescence method (REGN668-AV-13089-VA-01V3) under the responsibility of Bioanalytical Operations, Regeneron Pharmaceuticals Inc., Tarrytown, NY, USA.

Biomarkers: Eotaxin-3, periostin, and TARC were assessed at baseline. Spot urine for biomarkers (LTE4, PGDM, and creatinine) and allergen-specific IgE panel for biomarker sampling were collected at Day 1 and Week 24.

Eotaxin-3 was measured in heparinized plasma with a validated enzyme immunoassay (human eotaxin-3 quantikine ELISA kit; R&D Systems). Concentrations of IgE were measured using quantitative ImmunoCAP assays. TARC was assayed with a validated enzyme immunoassay (Human TARC Quantikine ELISA kit; R&D Systems). Periostin was assayed using a validated immunoassay.

Statistical methods:

Analysis of the co-primary efficacy variables: Each of the 2 co-primary efficacy endpoints were analyzed using a hybrid method of worst-observation carried forward (WOCF) and multiple imputation (MI). With this approach, for patients who undergo surgery for NP or receive SCS for any reason, data collected postsurgery or post-SCS were set to missing, and the worst postbaseline value on or before the time of surgery or SCS was used to impute the missing Week 24 values. For patients who discontinued treatment without being rescued by surgery or receiving SCS, an MI approach was used to impute the missing Week 24 values, and this imputation used all patients who were not rescued by surgery or receiving SCS at Week 24, and data collected after treatment discontinuation were included in the analysis. The completed dataset, including imputed values were analyzed by fitting an analysis of covariance (ANCOVA) model with the baseline covariate and factors for treatment, asthma status, prior surgery history, and regions. Statistical inference obtained from all imputed data was combined using Rubin's rule. Descriptive statistics including number of patients, mean, standard error, and least squares (LS) means are provided. In addition, difference in LS means and the corresponding 95% confidence intervals (CI) are provided along with the p-values.

Analyses of key secondary efficacy endpoints: Changes from baseline in LMK, TSS, UPSIT, daily loss of smell, and SNOT-22 score at Week 24 were assessed for dupilumab versus placebo and were analyzed using the hybrid method of the WOCF and the MI in the same fashion as for the co-primary endpoints.

Analysis of proportion of patients requiring rescue medication: The proportion of patients with SCS rescue or surgery (actual or planned) for NP during the 24-week treatment period was derived and analyzed using the Cox proportional hazards model. Dupilumab group was compared to the placebo group.

Analyses in subpopulations of patients with comorbid asthma and patients with prior NP surgery: Changes from baseline in NPS, NC, FEV_1, ACQ-6 at Week 24 for patients with comorbid asthma were assessed for dupilumab versus placebo and were analyzed using the hybrid method of the WOCF and the MI in the same fashion as for the co-primary endpoints. Change from baseline in NPS and NC at Week 24 for patients with prior NP surgery were analyzed in the same fashion as for the patients with asthma.

Multiplicity considerations: A hierarchical testing procedure was applied to control the overall type-I error rate for testing the co-primary and selected secondary endpoints. The overall alpha was 0.05. The comparisons with placebo were tested based on the pre-specified hierarchical order at 2-sided $\alpha = 0.05$.

Summary:

Population characteristics:

Patients' demographics and characteristics at baseline were similar across treatment groups:

- 58.3% of patients had a history of asthma and 30.4% had a history of NSAID-ERD
- 71.7% of patients had prior NP surgery
- In the 2 years prior to randomization 179 (64.9%) patients received SCS at least once
- Baseline characteristics indicated severe disease at baseline, with a mean bilateral NPS of 5.75 and mean NC severity score of 2.35

12 [4.3%] patients discontinued treatment prior to Week 24 (5 [3.5%] in the dupilumab group and 7 [5.3%] in the placebo group). Of the 276 patients randomized 263 (95.3%) completed the 24-week study period and 262 (94.9%) completed the 48-week study period.

Efficacy results:

In patients with severe CRSwNP, dupilumab treatment at a dose of 300 mg q2w on top of intranasal corticosteroids significantly improved endoscopic nasal polyps score, rhinosinusitis symptoms, sinus disease assessed by CT scan, and other clinical outcomes of CRSwNP relative to intranasal corticosteroids alone.

The study met its coprimary endpoints with small p-values, and robust sensitivity analyses showing a high degree of consistency across endpoints, subgroups of patients, and analytic approaches to the data. Dupilumab 300 mg q2w demonstrated a statistically significant and clinically meaningful reduction in polyp size and in nasal congestion. At 24 weeks of treatment the LS mean difference versus placebo for NPS was -2.06 with 95% CI: -2.43 to -1.69; p<0.0001), and for NC symptom score the LS mean difference versus placebo was -0.89 with 95% CI: -1.07 to -0.71; p<0.0001).

Dupilumab added on to intranasal corticosteroid sprays resulted in consistently significant and clinically relevant improvements across all elements of CRSwNP disease. This broad effect was not only due to the reduction in nasal polyps but also direct effects of dupilumab on the underlying chronic type 2 inflammation in the paranasal sinuses as demonstrated by marked improvement of sinus disease bilaterally on radiological examination (as assessed by sinus opacification CT scan score [LMK]) and patient reported clinical outcomes characterizing chronic rhinosinusitis (composite score of total symptoms of the main rhinositusitis symtptoms, sense of smell, and UPSIT), and improvement in quality of life as assessed by SNOT-22. Each of these key secondary endpoints for this study showed a statistically significant and clinically meaningful mean improvement from baseline for the dupilumab group compared with the placebo group at Week 24, with LS mean differences versus placebo and 95% CIs as follows, and each with p<0.0001:

- Sinus opacification CT scan score (LMK): -7.44 with 95% CI: -8.35 to -6.53
    - The significant improvement in the LMK total scores reflected numerical improvement in all sinuses bilaterally.
- TSS score: -2.61 with 95% CI: -3.04 to -2.17
- UPSIT: 10.56 with 95% CI: 8.79 to 12.34
- Loss of smell (patient reported severity) score: -1.12, 95% CI: -1.31 to -0.93
- SNOT-22 score: -21.12 with 95% CI: -25.17 to -17.06.
    - The mean improvement in SNOT-22 in the dupilumab group when compared to placebo group exceeded the MCID threshold of 8.9 for this instrument.

Efficacy was shown across additional secondary and exploratory endpoints, including substantial effects of dupilumab 300 mg q2w on rhinosinusitis severity measured on a VAS, rhinorrhea, loss of taste, NPIF, and quality of life as measured by EQ-5D VAS.

Dupilumab demonstrated a rapid onset of action across many efficacy endpoints. A substantial difference between the dupilumab group and placebo group was seen as early as the first evaluation for each endpoint (Week 2 to Week 4) after initiation of treatment. Early beneficial effect was followed by progressive improvement through 24 weeks without reaching a plateau. Through the 24-week follow-up period, the beneficial treatment effects across all endpoints diminished relatively quickly once dupilumab was discontinued; there was no observed rebound effect during the post-treatment follow-up period up to Week 48.

The current first line of therapy recommended for CRSwNP is the use of daily intranasal corticosteroids (which are only indicated for the NP component of disease), short bursts of SCS when symptoms worsen or become uncontrolled, and surgery for NP if medical management fails. In the 2 years prior to randomization in the current study, 98.2% of patients had prior surgery for nasal

polyposis or received SCS at least once during the past 2 years. In this study, dupilumab reduced the proportion of patients who required rescue treatment with SCS or NP surgery during the 24-week treatment period compared with placebo treatment (7.2% versus 22.3%, with a hazard ratio [95% CI] of 0.268 [0.131, 0.549], nominal p=0.0003). Overall, dupilumab reduced the proportion of patients requiring SCS by 70.3% and NP surgery by 69.1%. The lack of a placebo response despite the use of nasal steroids supports the fact that patients with severe CRSwNP do not respond adequately to this treatment alone.

This study demonstrated that dupilumab treated not only CRSwNP but also the comorbid type 2 disease which was present in many of these patients. In fact, consistent with what has been previously reported about patients with CRSwNP, the majority of patients in this study reported type 2 comorbidities such as asthma, allergic rhinitis, and NSAID-ERD. Comorbid CRSwNP in patients with asthma and/or NSAID-ERD, frequently contribute to poor asthma control. Prespecified subgroup analyses in this study showed that dupilumab therapy in patients with severe CRSwNP and comorbid asthma resulted in significant and meaningful improvement not only of the CRSwNP outcome measures (NPS, NC, sinus opacification CT scan score [LMK]) but also in lung function (FEV_1) and asthma control (ACQ-6). The LS mean difference in the dupilumab group versus placebo at Week 24 was as follows:

- FEV_1 in patients with asthma: 0.21 L with 95% CI: 0.10 to 0.33 (nominal p=0.0004)
- ACQ-6 in patients with asthma: -0.76 with 95% CI: -1.00 to -0.51 (nominal p<0.0001)

These findings demonstrate that dupilumab treatment for CRSwNP has important clinical benefits in concomitant lower airways diseases such as asthma. Similar efficacy in both CRSwNP, lung function, and asthma control was also shown in patients with NSAID-ERD.

In summary, this study demonstrated robust efficacy of dupilumab in reducing NC and sinus inflammation, in restoring olfactory function, in improving the symptoms associated with CRSwNP, in improving quality of life in adults with CRSwNP, and in reducing the need for systemic steroids and surgeries. Across all of these domains the results were both highly statistically significant and robustly clinically meaningful. In patient subgroups that are generally more challenging to treat for CRSwNP, including patients with comorbid asthma, NSAID-ERD, or with prior surgery for NP, dupilumab showed equally meaningful results. Furthermore, in patients with comorbid asthma, treatment with dupilumab improved lung function and asthma control in a clinically meaningful manner.

Safety results:

Data from this study indicate that dupilumab is generally well tolerated and has an acceptable safety profile for the treatment of adults with bilateral CRSwNP on a background therapy with MFNS.

The mean duration of treatment exposure was 164.56 days in the dupilumab group and 163.39 days in the placebo group, and cumulative exposure to treatment for dupilumab was similar to that of placebo.

Overall, TEAEs were reported in 65.0% of patients in the dupilumab group compared with 70.5% of patients in the placebo group. At the SOC level, infections and infestations SOC had the highest proportion of patients with AEs; the incidence was lower in the dupilumab group compared with the placebo group (31.5% versus 37.9%). The respiratory, thoracic and mediastinal disorders SOC had the second highest proportion of patients with AEs, with a lower incidence in the dupilumab group compared to the placebo group (26.6% versus 33.3%). At the PT level, the most frequently occurring TEAEs were nasal polyps and nasopharyngitis, both of which occurred with a lower frequency in the dupilumab group compared with the placebo group. The incidence of individual TEAEs was generally well balanced across all treatment groups, with the exception of epistaxis (7.7% in the dupilumab group versus 3.0% in the placebo group).

One patient in the placebo group died during the posttreatment period of acute myocardial infarction. This event was considered unrelated to the IMP. The proportion of patients with treatment-emergent SAEs was lower in the dupilumab group compared with the placebo group (4.2% of patients in the dupilumab group versus 14.4% in the placebo group). One SAE of EGPA occurred in the dupilumab and placebo arms each. Most individual SAEs were reported by single patients only (with the exception of nasal polyps with 2 patients in the dupilumab group versus 7 patients in the placebo group). There was 1 patient in the dupilumab group and 1 patient in the placebo group with SAEs in the cardiac disorders SOC, and no events in the vascular disorders SOC.

The overall discontinuation rate due to AEs was 3.5% in the dupilumab group versus 2.3% in the placebo group. The most frequently reported TEAE leading to permanent treatment discontinuation was nasal polyps, occurring in 2 (1.4%) patients in the dupilumab group and 1 (0.8%) patient in the placebo group. All other TEAEs that led to discontinuation occurred in only 1 patient each in either treatment group.

Among AESIs and other selected AE groupings, there were no cases of anaphylaxis, pregnancy, symptomatic overdose of IMP or NIMP, or suicidal behavior.

The following AESIs or other select AE groupings occurred with a lower incidence in the dupilumab group compared with the placebo group: Injection site reaction (high-level term) (9.1% versus 12.9%), severe or serious infection (1.4% versus 3.8%); or occurred infrequently with no difference between the dupilumab and placebo groups: parasitic infection (0% versus 0.8%), opportunistic infections (0% versus 0.8%), potentially drug-related hepatic disorder (0.7% versus 0%), and malignancy (0% versus 0.8%). The following AESIs were generally low but occurred with a higher incidence in the dupilumab group compared with the placebo group: Conjunctivitis (2.1% versus 0.8%) and eosinophilia (2.1% versus 1.5%).

Epistaxis occurred with a higher incidence in the dupilumab group compared with the placebo group (7.7% versus 3.0%). None of these events were considered serious and none led to permanent treatment discontinuation.

All cases of eosinophil counts >3 Giga/L on treatment were to be reported as AEs in this study per protocol instructions. Among the 5 reported cases of eosinophilia (3 in the dupilumab group and 2 in the placebo group), most were self-limited and reported as pure laboratory findings without any associated clinical symptoms or TEAEs. Two cases of eosinophilia under the HLT eosinophilic disorders plus the PT eosinophil count increased were reported as SAEs, including one case in the dupilumab group and one case in the placebo group.

An increase in mean blood eosinophil counts was noted from the first assessment at Week 16 in the dupilumab group. Mean eosinophil count decreased by Week 24 in the dupilumab group but did not reach baseline levels. Median percent blood eosinophil count remained relatively unchanged throughout the treatment period, indicating mean elevation in blood eosinophil count was driven by only a subset of patients.

Other than eosinophils, none of the laboratory parameters, vital signs or ECG parameters assessed showed a clinically relevant trend toward increase or decrease over time.

The overall safety results from this study were consistent with the known safety profile of dupilumab.

Pharmacokinetic results:

Following administration of dupilumab at 300 mg, concentrations of dupilumab in serum increased over time to Week 24. Mean dupilumab concentration decreased following discontinuation of study treatment.

Immunogenicity results:

Overall, in this CRSwNP patient population, the observed incidence of treatment-emergent ADA was 15.4% in the dupilumab group. The majority of the ADA responses had low ADA titer.

Dupilumab exposure largely overlapped between patients with treatment-emergent positive ADA response and ADA-negative patients.

There was generally no evidence of altered efficacy in patients developing ADA response as assessed by change from baseline in NPS or NC.

ADA formation did not appear to correlate with any safety findings, with no apparent pattern or increase in TEAE incidence in the few ADA-positive patients compared with the ADA-negative patients, and no temporal relationship between the ADA positive response and the occurrence of SAEs or AEs of interest.

Pharmacodynamic results:

Consistent with its mechanism of action and biology of the disease, dupilumab was associated with decreases in mean concentration of circulating biomarkers of type 2 inflammation in blood (total IgE) and urine LTE. For these endpoints, the decrease was apparent at the only postbaseline measurement at Week 24.

Conclusions:

In patients with severe CRSwNP, dupilumab treatment at a dose of 300 mg q2w on top of intranasal corticosteroids showed significant and clinically meaningful improvement in the coprimary and all key secondary efficacy endpoints. This study demonstrated the robust efficacy of dupilumab in reducing the burden of all facets of CRSwNP disease including NPS, NC, and sinus inflammation, in restoring olfactory function, in improving quality of life, and in reducing the need for systemic steroids and surgeries. Treatment effects were rapid followed by gradual and continued improvement for all efficacy endpoints through 24 weeks. Through the 24-week follow-up off-treatment period, treatment effect diminished across all endpoints indicating a need for continuous treatment in order to sustain treatment effect; there was no observed rebound effect. Dupilumab significantly reduced the need for systemic corticosteroids and surgery for NP in patients with CRSwNP. In the difficult to treat subgroup of patients with co-morbid asthma and NSAID-ERD, dupilumab significantly not only improved outcome measures of upper airway (NPS, NC, sinus opacification CT scan score [LMK]) but also simultaneously improved lung function and asthma control. Broad efficacy across all outcome measures of CRSwNP is consistent with the mechanism of action of dupilumab, which by inhibiting IL-4/IL-13 signaling blocks the underlying type 2 inflammation as evidenced by suppression of systemic (blood and urine) and local (nasal secretions) type 2 biomarkers that drive the CRSwNP disease process. Dupilumab was generally well tolerated with an acceptable safety profile. Thus dupilumab offers the potential to provide significant benefit for patients with severe CRSwNP with improvement in multiple facets of the disease when there is high disease burden despite standard of care therapies.

Dupilumab was generally well tolerated with an acceptable safety profile.

Date of report: 11-Dec-2018

EFC14146 - Number of randomized patients per study site

Study Site No.	Principal Investigator name (last name followed by first name)	Study Site Address	Number of screened patients	Number of randomized patients
1000001		MMA MHAT Sofia AD- Clinic of Oto-rhino-laringology diseases MMA MHAT Sofia AD- Clinic of Oto-rhino-laringology diseases3 Georgi Sofiiyski St. 1606 Sofia NA Bulgaria	14	8
1000002		UMHAT Tsaritsa Yoanna – ISUL UMHAT Tsaritsa Yoanna – ISUL8 Byalo more St. 1527 Sofia NA Bulgaria	3	2
1000003		UMHAT "Sveti Georgi" UMHAT "Sveti Georgi"66 Peshtersko shose Blvd. 4002 Plovdiv NA Bulgaria	2	1
2030001		Fakultni Nemocnice Hradec Kralove Klinika otorinolaryngologie a chirurgie hlavy a krkuSokolska 581 50005 Hradec Kralove NA Czech Republic	3	1
2030002		Nemocnice Pardubickeho kraje, a.s. Klinika otorinolaryngologieKyjevska 44 53203 Pardubice NA Czech Republic	6	5
2030004		Vseobecna Fakultni Nemocnice V Praze Oddeleni otorinolaryngologieU nemocnice 2 128 08 Praha 2 NA Czech Republic	2	2

Study Site No.	Principal Investigator name (last name followed by first name)	Study Site Address	Number of screened patients	Number of randomized patients
2500001		Hopital Gui De Chauliac 80 Rue Augustin Fliche 34000 Montpellier NA France	5	2
2500003		Hopital De La Croix Rousse Pneumologie103, Gde Rue De La Croix Rousse 69317 Lyon NA France	1	1
2500004		CHU de Nancy Service ORL et chirurgie Cervico-Facialerue du Morvan 54511 VANDOEUVRE-LES-NANCY NA France	2	1
2500005		Centre Hospitalier Departemental Vendee Boulevard Stephane Moreau 85925 LA ROCHE SUR YON NA France	6	2
2500006		CHR Hotel Dieu OrlPlace Alexis Ricordeau 44035 Nantes NA France	2	2
2760001	OLZE Heidi	Charite - Campus Virchow-Klinikum Klinik fur Hals-, Nasen-, Ohrenheilkunde (CCM und CVK)ChariteCentrum Audiologie/Phoniatrie, Augen- und HNO-Heilkunde CC 16Augustenburger Platz 1 13353 Berlin NA Germany	19	11

Study Site No.	Principal Investigator name (last name followed by first name)	Study Site Address	Number of screened patients	Number of randomized patients
2760002	RUDACK Claudia	Universitatsklinikum Munster Klinik fur Hals-, Nasen und OhrenheilkundeKardinal-von-Galen-Ring 10 48149 Munster NA Germany	14	2
2760003	GROGER Moritz	Klinikum der Universitat Munchen - Campus GroBhadern Klinik und Poliklinik fur Hals-, Nasen und OhrenheilkundeMarchioninistraBe 15 81377 Munchen NA Germany	4	3
3480001		Szegedi Tudomanyegyetem ÁOK Ful-Orr-Gegeszeti es Fej-Nyaksebeszeti KlinikaTisza Lajos krt. 111. 6725 Szeged NA Hungary	13	5
3480002		Pecsi Tudomanyegyetem, ÁOK Klinikai Kozpont Ful-Orr-Gegeszeti es Fej-nyaksebeszeti KlinikaMunkacsy u. 2. 7621 Pecs NA Hungary	5	5
3480003		Szent Janos Korhaz Eszak-Budai Egyesitett Korhazak Ful-orr-gege, Fej-nyak- es szajsebeszeti Osztaly, Dios arok 1-3. 1125 Budapest NA Hungary	8	6

Study Site No.	Principal Investigator name (last name followed by first name)	Study Site Address	Number of screened patients	Number of randomized patients
3480004		Szent Imre Egyetemi Oktatokorhaz Ful- Orr- Gegeszeti Profil,Tetenyi ut 12-16. 1115 Budapest NA Hungary	9	8
3480005		Debreceni Egyetem Klinikai Kozpont Ful-Orr-Gegeszeti es Fej-Nyaksebeszeti Klinika,Nagyerdei krt. 98. 4032 Debrecen NA Hungary	6	5
3480006		Magyar Honvedseg Egeszsegugyi Kozpont Ful-orr-gegeszet, Fej-Nyaksebeszeti Osztaly Podmaniczky u. 109-111. 1062 Budapest NA Hungary	3	1
3480007		Semmelweis Egyetem Ful-Orr-Gegeszeti es Fej-Nyaksebeszeti KlinikaSzigony u. 36. 1083 Budapest NA Hungary	6	4
3800001		Azienda Ospedaliero-Universitaria Pisana Dipartimento Cardiotoracico SVD Fisiopatologia respiratoriaVia Paradisa, 2 56124 Pisa Pisa Italy	6	5
3800002		AOU Policlinico Vittorio Emanuele via S. Sofia, 78 U.O. di Pneumologia Riabilitativa ed Allergologia 95123 Catania Catania Italy	9	5

Study Site No.	Principal Investigator name (last name followed by first name)	Study Site Address	Number of screened patients	Number of randomized patients
3800003		ASST Settelaghi Varese - Ospedale del Circolo ASST Settelaghi Varese - Ospedale del Circolovia Guicciardini 9 21100 Varese Varese Italy	3	1
3800005		HUMANITAS RESEARCH CENTER ASTHMA & ALLERGY CENTER - RESPIRATORY DISEASE UNIT VIA MANZONI, 56 20089 ROZZANO Milano Italy	9	7
3800006		Azienda Ospedaliera San Paolo Azienda Ospedaliera San PaoloVia A. Di Rudinì, 8 20142 Milano Milano Italy	5	3
3800007		Ospedale Bellaria Ospedale BellariaVia Altura, 3 40139 Bologna Bologna Italy	4	2
5280001		Academisch Medisch Centrum Amsterdam Meibergdreef 9 1105 AZ Amsterdam NA Netherlands	6	3
6160001		SPZOZ Uniwersytecki Szpital Kliniczny nr 1 Wewnetrznych, Astmy i Alergii z Odcinkiem dla Dzieci SPZOZ USK nr 1 im.Norberta Barlickiego ul. Kopcinskiego 22 90-153 Lodz Lódzkie Poland	8	2

Study Site No.	Principal Investigator name (last name followed by first name)	Study Site Address	Number of screened patients	Number of randomized patients
6160002		Centrum Medyczne Angelius Provita ul. Fabryczna 13D 40-611 Katowice Slaskie Poland	8	8
6160003		Wojskowy Instytut Medyczny i Onkologii Laryngologicznej z Klinicznym Oddzialem Chirurgii Czaszkowo-Szczekowo-Twarzowejul. Szaserow 128 04-141 Warszawa Mazowieckie Poland	7	6
6420003		Spitalul Sf. Maria MI Spitalul Sf. Maria MIBlvd. Ion Mihalache nr. 37-39, Sector 1 011172 Bucuresti NA Romania	3	3
6420007		Centrul Medical Diagnostic Tratament Ambulatoriu Neomed SRL Centrul Medical Diagnostic Tratament Ambulatoriu Neomed SRLStr. Crisului Nr. 1, bl.1, sc.C, ap. 2 500283 Brasov NA Romania	15	9
6420008		Spitalul Clinic Judetean de Urgenta Craiova Spitalul Clinic Judetean de Urgenta CraiovaStr. Tabaci Nr.1 200642 Craiova NA Romania	4	3

Study Site No.	Principal Investigator name (last name followed by first name)	Study Site Address	Number of screened patients	Number of randomized patients
6420009		Spitalul Clinic CF Cluj-Napoca Spitalul Clinic CF Cluj-NapocaStr. Republicii Nr. 18 400015 Cluj-Napoca NA Romania	17	13
6420010		SC Adria Med SRL, Punct de lucru Centrul Medical Galenus SC Adria Med SRL, Punct de lucru Centrul Medical GalenusStr. Mihai Viteazul, Nr.31 540098 Targu-Mures NA Romania	1	1
6420013		Centrul Medical Diagnostic Tratament Ambulatoriu Neomed SRL Centrul Medical Diagnostic Tratament Ambulatoriu Neomed SRLStr. Crisului Nr. 1, bl.1, sc.C, ap. 2 500283 Brasov NA Romania	12	10
6430001		City Outpatient clinic 107 36, Kommuny str., 195030 Saint-Petersburg NA Russian Federation	8	5
6430002		Saint-Petersburg Research Institute of ENT and Speech 9, Bronnitskaya str. 190013 St-Petersburg NA Russian Federation	6	6
6430003		Federal State Institution Polyclinic 3 31, Grokholsky per. 129090 Moscow NA Russian Federation	8	3

Study Site No.	Principal Investigator name (last name followed by first name)	Study Site Address	Number of screened patients	Number of randomized patients
6430004		University Clinical Hospital 1 under First MSMU Bolshaya Pirogovskaya St. 6/1 119435 Moscow NA Russian Federation	4	1
6430006		Clinical Emergency Hospital named N.V. Solovyev 11, Zagorodny Sad Str. 150003 Yaroslavl NA Russian Federation	5	3
6430007		1st Saint Petersburg State Medical University n.a.I.P.Pavlov 6/8, Lva Tolstogo str., 197022 Saint-Petersburg NA Russian Federation	3	2
8040001		Clinical Hospital named after M.V. Sklifosovskiy ENT department. 23, Shevchenko str. 36011 Poltava NA Ukraine	7	1
8040002		Central City Clinical Hospital 114, Hetmana Mazepy str. 76000 Ivano-Frankivsk NA Ukraine	17	10
8040004		Regional clinical specialized Center of Radiation protection 85, Novgorodska str. 61166 Kharkiv NA Ukraine	21	13

Study Site No.	Principal Investigator name (last name followed by first name)	Study Site Address	Number of screened patients	Number of randomized patients
8040005		MAIN MILITARY MEDICAL CLINICAL CENTER «MMCH» 18, Hospitalna str., otolaryngology clinic 01133 Kyiv NA Ukraine	2	2
8040006		Institute of otolaryngology n.a. prof. O.S. Kolomyichenko 3, Zoologichna Str. 03680 Kyiv NA Ukraine	8	6
8040008		Ternopil Municipal City Hospital 2 14, Kupchynskogo str. 46000 Ternopil NA Ukraine	20	13
8260001		Bradford Royal Infirmary Duckworth Lane BD9 6RJ Bradford NA United Kingdom	6	5
8260002		Ninewells Hospital & Medical School University of DundeeDundee DD1 9SY Dundee Tayside United Kingdom	9	6
8260004		Stepping Hill Hospital Bp & Heart Research CentrePoplar Grove SK2 7JE Stockport Cheshire United Kingdom	1	1

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8260005		Wrightington, Wigan and Leigh NHS Foundation Trust Wrightington, Wigan and Leigh NHS Foundation TrustRoyal Albert Edward InfirmaryWigan Lane WN1 2NN Wigan Greater Manchester United Kingdom	3	3
8260006		Guys And StThomas Hospital Lambeth Palace Road SE1 7EH London Greater London United Kingdom	6	3
8260007		James Paget Hospital Lowestoft RoadGorleston NR31 6LA Great Yarmouth Norfolk United Kingdom	3	1
8400001		Pharmaceutical Research & Consulting, Inc. 5499 Glen Lakes Dr.Suite 200 75231 Dallas Texas United States of America	10	6
8400005		Mayo Clinic of Rochester 200 1st St. SW 55905 Rochester Minnesota United States of America	2	2
8400008		Piedmont Ear, Nose and Throat Associates 110 Charlois Blvd 27103 Winston Salem North Carolina United States of America	7	4

Study Site No.	Principal Investigator name (last name followed by first name)	Study Site Address	Number of screened patients	Number of randomized patients
8400009		Allergy And Asthma Care Center 3816 Woodruff AvenueSuite 209 90720 Long Beach California United States of America	5	1
8400013		University of South Florida 13801 Bruce B Downs BlvdSuite 505 33613 Tampa Florida United States of America	2	1
8400014		Allergy and Asthma Medical Group and Research Center 5776 Ruffin Rd 92123 San Diego California United States of America	7	4
8400015		Eastern Virginia Medical School (EVMS) Medical Group - Otola 600 Gresham Dr. River PavillionSuite 1100 23507 Norfolk Virginia United States of America	10	5
8400016		Colorado Allergy / Asthma Center 13111 E. Briarwood Road, Suite 340 80112 Centennial Colorado United States of America	11	4
8400018		Medical University of South Carolina MUSC Nose and Sinus 135 Rutledge AvenueMSC 550 29425 Charleston South Carolina United States of America	7	1

Study Site No.	Principal Investigator name (last name followed by first name)	Study Site Address	Number of screened patients	Number of randomized patients
8400019		Vital Prospects Clinical Research Institute, P.C. 7307 S. Yale Ave, Suite 200 74136 Tulsa Oklahoma United States of America	14	2
8400020		Crisor, LLC c/o Clin Res Inst/Southern Oregon, Inc 3860 Crater Lake Ave.Suite B 97504 Medford Oregon United States of America	5	2
8400021		The Clinical Research Center, LLC 1040 N Mason Rd.Suite 112 63141 St Louis Missouri United States of America	12	2