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HEALTH TECHNOLOGY BRIEFING
MAY 2019

Omalizumab for chronic rhinosinusitis with nasal polyps

NIHRIO ID	20394	**NICE ID**	9804
Developer/Company	Novartis Pharmaceuticals UK	**UKPS ID**	647073

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Omalizumab is in clinical development for the treatment of chronic rhinosinusitis with nasal polyps (CRwNP). Chronic rhinosinusitis is a condition in which the lining of the sinuses becomes inflamed. It is characterised by symptoms including nasal congestion, discharge, decreased or loss of sense of smell, facial pain and headache. The condition is referred to as CRSwNP if nasal polyps are also present. Polyps are growths inside the nasal passages and sinuses, which usually only cause problems if they are large or grow in clusters, causing an obstruction. Additional symptoms of nasal polyps include a blocked nose, snoring and disturbed sleep. Corticosteroids are often prescribed for CRSwNP to reduce or eliminate the swelling. Surgery is recommended when the drug treatment fails.

Omalizumab is a monoclonal antibody that targets and blocks the immunoglobulin E (IgE). Human IgE is produced in large quantities in patients with allergies and triggers an allergic reaction in response to an allergen. By attaching to IgE, omalizumab 'mops up' the free IgE circulating in the blood. This means that when the body encounters an allergen, there is less IgE available to trigger an allergic reaction. This helps to reduce the symptoms of CRSwNP. If licensed, omalizumab will offer a treatment option as add-on therapy for patients with CRSwNP who have had an inadequate response to current standard-of-care treatments.

PROPOSED INDICATION

Treatment of nasal polyps in patients who have had an inadequate response to standard-of-care treatments.[a]

TECHNOLOGY

DESCRIPTION

Omalizumab (Xolair) is a recombinant DNA-derived humanised monoclonal antibody that selectively binds to human immunoglobulin E (IgE). The antibody is an IgG1 kappa that contains human framework regions with the complementary-determining regions of a murine parent antibody that binds to IgE.[1] Omalizumab binds to the FcεR1 epitope of human IgE, preventing human IgE from binding to its receptor on mast cells and basophils, thus inhibiting the histamine release response which is normally triggered by exposure to allergens.[2]

Omalizumab is in clinical development for patients with chronic rhinosinusitis with nasal polyps (CRSwNP) who have had an inadequate response to standard-of-care treatments. In the phase III clinical trials (POLYP 1; NCT03280550, POLYP 2; NCT03280537), omalizumab is administered as a subcutaneous (SC) injection once every 2 or 4 weeks for 24 weeks. This is followed by an open-label extension study (NCT03478930) where participants still enrolled will further receive omalizumab for 28 weeks before entering a 24-week off-treatment observation phase of the study. The treatment dosage was not specified.[3-5] Dosage will be determined by total IgE serum level and body weight according to the dosing table.[a]

INNOVATION AND/OR ADVANTAGES

Chronic rhinosinusitis (CRS) usually responds incompletely to medical therapy which may need to be continued long term.[6] Nasal polyps (NP) are known to shrink when steroid-containing nasal sprays or drops are used. Stronger steroids usage are limited to short courses because some is absorbed into the body. Steroids in tablet form can provide good relief of symptoms but the effects are short-lived and they are used sparingly because of concerns about side effects. If medicines are not effective then surgery is needed. In three out of four patients the polyps come back after an average period of four years.[7]
Clinical studies have shown that treatment with omalizumab reduces the size of NP significantly and patients did not require additional surgery during treatment. There was also marked reduction in usage of intranasal corticosteroids for CRS patients.[8,9]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Omalizumab is currently licenced in the EU/UK for IgE mediated asthma and chronic spontaneous urticaria.[1]

The most common side effects with omalizumab (seen in between 1 and 10 patients in 100) in allergic asthma are headache and injection site reactions, including swelling, redness, pain and itching. In patients with chronic spontaneous urticaria, the most common side effects with omalizumab (seen

[a] Information provided by Novartis Pharmaceuticals UK

in between 1 and 10 patients in 100) are sinusitis, headache, arthralgia, injection site reactions and upper respiratory tract infection.[10]

PATIENT GROUP

DISEASE BACKGROUND

Sinusitis implies inflammation of the sinus linings but in practice rarely occurs without concomitant rhinitis; therefore, rhinosinusitis is the preferred term. Depending on the time course, rhinosinusitis is described as acute or chronic, with symptoms lasting under 12 weeks regarded as acute. In any individual, rhinosinusitis may be predominantly allergic, non-allergic, or infective, sometimes resulting from immune deficiency (innate or acquired). Mixed forms also occur.[6]

CRS is an umbrella term for a group of heterogeneous diseases featuring inflammation of the nose and sinuses. It can be further sub-classified into those with or without nasal polyps (CRSwNP and CRSsNP) respectively.[11] CRSwNP is characterised by the presence of fleshy swellings (nasal polyps) that develop in the lining of the nose and paranasal sinuses. Nasal polyps are believed to arise in the nasal mucosa because of chronic inflammation.[12] CRSwNP is also characterised by different phenotypes depending on: comorbidity, endoscopic findings, radiological features and cytology. [13]

Symptoms of CRSwNP include anterior or posterior rhinorrhoea, nasal congestion, hyposmia and/or facial pressure or pain that last for greater than 12 weeks duration.[14] Males are more likely to be affected than females but no specific genetic or environmental factors have been strongly linked to the development of this disorder. Defects in the sinonasal epithelial cell barrier, increased exposure to pathogenic and colonised bacteria, and dysregulation of the host immune system are all thought to play prominent roles in disease pathogenesis. CRSwNP is a disease of middle age with the average age of onset being 42 years and the typical age of diagnosis ranging from 40–60 years.[14]

CRSwNP is estimated to occur in 7% of all asthmatics while asthma is reported in 26–48% of patients with CRSwNP. Increased asthma severity has also been shown to be associated with enhanced sinonasal inflammation. It is estimated that approximately 10% of patients with nasal polyps have Aspirin Exacerbated Respiratory Disease (AERD).[14]

Sleep disruption prevalence is significantly higher in CRS patients, and is linked with worse Quality of Life (QoL), impaired cognitive function and mood disturbances.[15]

CLINICAL NEED AND BURDEN OF DISEASE

CRS is a highly prevalent condition affecting 10% of the UK adult population. Among all people with CRS, around 25% to 30% have CRSwNP.[16,17] Applying the 2017 mid-year adult population estimates of England and Wales, the number of people with CRS would be 4,624,935 while 1,156,234 to 1,387,481 would have CRSwNP.[b]

Hospital admissions data for England in 2017-2018 for nasal polyps (ICD 10: J33) were recorded as 10,160 finished consultant episodes (FCE), 10,067 hospital admissions and 7,265 day cases and polyp of nasal cavity (ICD 10: J33.0) had 3,205 FCE, 3,172 hospital admissions and 2,244 day cases.[18]

[b] Information provided by Novartis Pharmaceuticals UK

There is over 8-fold variation in procedure rates for sinus surgery per 100,000 population by clinical commissioning groups across England. In patients with CRSwNP nearly 50% of patients undergoing surgery report having received more than one operation, with a mean number of 3.3 procedures per patient (range 2–30).[16]

Primary procedure carried out in England on polypectomy of internal nose carried out (OPCS Classification of Interventions and Procedures (OPCS-4): E08.1) recorded 5,692 FCE, 5,666 admissions and 4,042 day cases.[18]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Treatment should be based on severity of symptoms. Severity is determined using severity of visual analogue scale, Nasal Polyps Score (NPS) and endoscope.[19]

Medical management of CRSwNP focuses on controlling tissue inflammation and, depending on severity, includes use of intranasal corticosteroids, nasal saline irrigation, antibiotics, or short-course oral steroids. In patients in whom polyps and symptoms persist despite medical treatment, surgical excision is considered. Surgery is recommended as the next treatment option for patients who experience medical therapy failure; however, a substantial proportion of patients experience postsurgical recurrence and require additional surgery.[20]

Patients undergoing surgery within 12 months of onset of symptoms that fail to respond to maximum medical therapy, achieve significantly better measured outcomes in terms of improvements in Sinonasal Outcome Test (SNOT-22) than those undergoing surgery at a later stage; therefore once medical therapy has been deemed to have failed there should be no further delay in referral.[16]

CURRENT TREATMENT OPTIONS

According to the Royal College of Surgeons Commission Guide on Chronic Rhinosinusitis (2016), treatment recommendation (in secondary care) for patients with CRSwNP with moderate/severe symptoms are:[16]

- Continue nasal saline irrigation
- Short course oral steroids
- Consider topical drops (fluticasone propionate or beclamethasone) or continue intranasal corticosteroid spray
- Consider antibiotics (doxycycline)
- Review after 3 months for moderate disease, 1 month for severe disease.
- Consider endoscopic sinus surgery after failure of maximum medical therapy above and persistent moderate/severe symptoms

PLACE OF TECHNOLOGY

If licensed, omalizumab will offer a treatment option as an add-on therapy for patients with CRSwNP who have had an inadequate response to standard-of-care treatments.

CLINICAL TRIAL INFORMATION

Trial	**POLYP 1, NCT03280550**, EudraCT-2017-001724-22, GA39688; aged 18-75 years; omalizumab vs placebo; phase III	NCT03478930, EudraCT-2017-003450-16, aged 18-75 years; omalizumab vs placebo; phase III extension
Sponsor	Hoffmann-La Roche	Hoffmann-La Roche
Status	Completed	Ongoing
Source of Information	Trial registry[4]	Trial registry[3]
Location	5 EU countries (incl UK), USA, Canada, Ukraine, Mexico and Russia	10 EU countries (incl UK), USA, Canada, Ukraine, Mexico and Russia
Design	Randomised, placebo-controlled, parallel assignment, double-blinded	Non-randomised, open-label, parallel assignment
Participants	n=138; aged 18-75 years; nasal polyp score (NPS) >= 5, with a unilateral score of >= 2 for each nostril, at screening (day -35), and on day -7; Sino-Nasal Outcome Test-22 (SNOT-22) score >=20 at screening (day -35) and at randomisation (day 1)	n=240; aged 18-75 years; participation in study GA39688 or GA39855, including completion of endoscopy and other assessments at week 24, without discontinuation of study drug; completion of eDiary daily assessments for at least 4 out of 7 days in the week prior to the week 24 visit of study GA39688 or GA39855
Schedule	Participants are randomised to: • Omalizumab administered as a SC injection every 2 or 4 weeks • Matching placebo administered as a SC injection every 2 or 4 weeks	Participants are allocated based on previous studies into; Experimental cohort A (Study GA39688): Participants who received omalizumab once every 2 weeks (Q2W) or once every 4 weeks (Q4W) in study GA39688 will continue to receive omalizumab at week 24 at the same dosing schedule Participants who received placebo Q2W or Q4W in study GA39688 will start receiving omalizumab Q2W or Q4W at week 24 at the same dosing schedule Experimental cohort B (Study GA39855): Participants who received omalizumab Q2W or Q4W in study GA39855 will continue to receive omalizumab at week 24 at the same dosing schedule

		Participants who received placebo Q2W or Q4W in study GA39855 will start receiving omalizumab Q2W or Q4W at week 24 at the same dosing schedule
Follow-up	28 weeks	Up to 76 weeks
Primary Outcomes	• Change from baseline at week 24 in average daily Nasal Congestion Score (NCS) • Change from baseline at week 24 in nasal polyps score Nasal Polyp Score (NPS)	• Change from baseline in NPS [Time frame: baseline, weeks 4, 8, 16, 24, 36, 52, 64, and 76] • Change from baseline in average daily NCS [Time frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, and 76] • Percentage of participants with adverse events [Time frame: from start to end (weeks 24 to 76) of open label extension (OLE) study] • Percentage of participants with adverse events leading to discontinuation of omalizumab [Time frame: from start to end (weeks 24 to 76) of OLE study]
Secondary Outcomes	• Change from baseline at week 24 in the average daily total nasal symptom score (TNSS) • Change from baseline at week 24 in the average daily sense of smell score • Change from baseline at week 24 in the average daily posterior rhinorrhea score • Change from baseline at week 24 in the average daily anterior rhinorrhea score • Change from baseline at week 24 in patient reported health-related quality of life (HRQoL) as assessed by the total SNOT-22 • Change from baseline at week 24 in sense of smell, as assessed by the University of Pennsylvania Smell Identification Test (UPSIT) • Change from baseline at week 24 in Asthma Quality of Life Questionnaire (AQLQ) of >= 0.5 (in patients with comorbid asthma only) • Change from baseline at week 16 in the average daily NCS	• Change from baseline in average daily total nasal symptom score (TNSS) [Time frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, and 76] • Change from baseline in loss of smell score [Time frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, and 76] • Change from baseline in average daily posterior rhinorrhea score [Time frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, and 76] • Change from baseline in average daily anterior rhinorrhea score [Time frame: baseline, weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60, 64, 68, 72, and 76] • Change from baseline in health-related quality of life (HRQoL) as assessed by the total sino-nasal outcome test (SNOT)-22 score

	• Change from baseline at week 16 in NPS • Percentage of participants with reduction in the need for surgery by week 24, as defined by an NPS of <= 4 (unilateral score of <= 2 on each side) and improvement in SNOT-22 score of >= 8.9 • Percentage of participants with requirement of rescue treatment (systemic CS for >= 3 consecutive days) or having had surgery for nasal polyps through week 24 • Percentage of participants with requirement of rescue treatment (systemic CS for >=3 consecutive days) through week 24 • Percentage of participants having had surgery for nasal polyps through week 24 • Percentage of participants with incidence of adverse events (up to week 28) • Percentage of participants with incidence of serious adverse events • Percentage of participants with incidence of adverse events leading to omalizumab/placebo discontinuation • Percentage of participants with clinically significant change in laboratory values • Serum concentration of omalizumab at specified timepoints [Time frame: day 1, day 112, day 168, day 196] • Serum concentration of total and free IgE at specified timepoints [Time frame: screening (day -35)day 1, day 112, day 168, day 196]	[Time frame: baseline, weeks 4, 8, 16, 24, 36, 52, 64, and 76] • Change from baseline in European quality of life 5-dimension 5-level questionnaire (EQ-5D-5L) score [Time frame: baseline, weeks 16, 24, 36, 52, 64, and 76] • Change from baseline in asthma quality of life questionnaire (AQLQ) score (in participants with comorbid asthma only) [Time frame: baseline, weeks 4, 8, 16, 24, 36, 52, 64, and 76] • Change from baseline in sense of smell, as assessed by the university of pennsylvania smell identification test (UPSIT) score [Time frame: baseline, weeks 8, 16, 24, 36, 52, 64, and 76] • Percentage of participants with a clinically significant change from baseline in laboratory values [Time frame: baseline, weeks 36, 52, 64, and 76] • Minimum serum concentration (cmin) of omalizumab [Time frame: predose at weeks 36, 52, 64, and 76] • Serum concentration of total immunoglobulin e (ige) [Time frame: predose at weeks 36, 52, 64, and 76] • Serum concentration of free ige [Time frame: predose at weeks 36, 52, 64, and 76]
Key Results	Not reported	-
Adverse effects (AEs)	Not reported	-
Expected reporting date	Primary completion date reported as March 2019	Estimated primary completion date reported as March 2020

Trial	**POLYP 2, NCT03280537**, EudraCT-2017-001718-28, GA39855; aged 18-75 years; omalizumab vs placebo; phase III
Sponsor	Hoffmann-La Roche
Status	Completed
Source of Information	Trial registry[5]
Location	6 EU countries (not incl UK), USA, Ukraine, Mexico and Russia
Design	Randomised, placebo-controlled, parallel assignment, double-blinded
Participants	n=127; aged 18-75 years; nasal polyp score (NPS) >= 5, with a unilateral score of >= 2 for each nostril, at screening (Day -35), and on Day -7; Sino-Nasal Outcome Test-22 (SNOT-22) score >=20 at screening (day -35) and at randomisation (day 1)
Schedule	Participants are randomised to: • Omalizumab administered as a SC injection every 2 or 4 weeks • Matching placebo administered as a SC injection every 2 or 4 weeks.
Follow-up	28 weeks
Primary Outcomes	• Change from baseline at week 24 in average NCS • Change from baseline at week 24 in NPS
Secondary Outcomes	• Change from baseline at week 24 in the average daily TNSS • Change from baseline at week 24 in the average daily sense of smell score • Change from baseline at week 24 in the average daily posterior rhinorrhea score • Change from baseline at week 24 in the average daily anterior rhinorrhea score • Change from baseline at week 24 in patient reported health-related quality of life (HRQoL) as assessed by the total SNOT-22 • Change from baseline at week 24 in sense of smell, as assessed by the University of Pennsylvania Smell Identification Test (UPSIT) • Change from baseline at week 24 in Asthma Quality of Life Questionnaire (AQLQ) of >= 0.5 (in patients with comorbid asthma only) • Change from baseline at week 16 in the average daily NCS • Change from baseline at week 16 in NPS • Percentage of participants with reduction in the need for surgery by Week 24, as defined by an NPS of <= 4 (unilateral score of <= 2 on each side) and improvement in SNOT-22 score of >= 8.9 • Percentage of participants with requirement of rescue treatment (systemic CS for >= 3 consecutive days) or having had surgery for nasal polyps through week 24 • Percentage of participants with requirement of rescue treatment (systemic CS for >=3 consecutive days) through week 24

	• Percentage of participants having had surgery for nasal polyps through week 24 • Percentage of participants with incidence of adverse events (up to week 28) • Percentage of participants with incidence of serious adverse events • Percentage of participants with incidence of adverse events leading to omalizumab/placebo discontinuation • Percentage of participants with clinically significant change in laboratory values • Serum concentration of omalizumab at specified timepoints [Time frame: day 1, day 112, day 168, day 196] • Serum concentration of total and free IgE at specified timepoints [Time frame: day 1, day 112, day 168, day 196]
Key Results	Not reported
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as March 2019

ESTIMATED COST

Omalizumab is already marketed in the UK; a 150mg/1ml solution for injection costs £256.15 while a 75mg/0.5ml solution for injection costs £128.07.[21]
There is a confidential patient access scheme (PAS) currently in place for the existing indications.[c]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Dupilumab for treating chronic rhinosinusitis with nasal polyps (ID1179). Expected publication date, TBC
- NICE medical technology guidance. XprESS multi sinus dilation system for treating chronic sinusitis (MTG 30). December 2016.
- NICE interventional procedures guidance. Corticosteroid-eluting bioabsorbable stent or spacer insertion during endoscopic sinus surgery to treat chronic rhinosinusitis (IPG551). March 2016.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Manual for prescribed specialist services 2018/19. Highly specialist allergy services (adults and children). September 2018.

OTHER GUIDANCE

[c] Information provided by Novartis Pharmaceuticals UK

- Royal College of Surgeons. Commissioning guide: Chronic Rhinosinusitis. 2016.[16]
- British Society for Allergy and Clinical Immunology (BSACI). BSACI guidelines for the management of rhinosinusitis and nasal polyposis. 2007.[6]

ADDITIONAL INFORMATION

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