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HEALTH TECHNOLOGY BRIEFING
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Ligelizumab for chronic spontaneous urticaria

NIHRIO ID	13245	**NICE ID**	10319
Developer/Company	Novartis Pharmaceuticals Ltd	**UKPS ID**	652161

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

SUMMARY

Ligelizumab is in clinical development for the treatment of chronic spontaneous urticaria (CSU) in adult and adolescent patients. CSU is a skin condition characterised by raised and itchy rash (wheals) and/or angioedema that has lasted for more than six weeks, in the absence of an identified external cause (spontaneous) and in some cases up to 5 or more years. Patients with CSU are twice as likely to have mental disorders such as anxiety and depression when compared with the general population, with negative effects on sleep, daily activities, school or work life, and social interactions.

Ligelizumab is developed as a subcutaneous injection to block the inflammatory processes involved in CSU. If licensed, ligelizumab would offer an alternative treatment option for adult and adolescent patients with inadequate response to antihistamine treatment.

PROPOSED INDICATION

Treatment of chronic spontaneous urticaria (CSU) in adolescents and adults inadequately controlled with H1-antihistamines.[1,2]

TECHNOLOGY

DESCRIPTION

Ligelizumab (QGE031) is a humanised anti-IgE monoclonal antibody, that belongs to the IgG1/κ isotype subclass.[3] Immunoglobulin E (IgE) plays a key role in the pathogenesis of many allergic diseases. Thus, IgE-mediated immunologic pathways are an attractive target for intervention in allergic diseases and mast cell-driven disease.[4,5] Monoclonal antibodies are a type of targeted drug therapy that mimic natural antibodies but are made in a laboratory.[6] Ligelizumab blocks the IgE/FcεRI pathway activation responsible for histamine release from mast cells which is a key driver of the inflammatory process in CSU.[7-9]

Ligelizumab is in clinical development for the treatment of chronic spontaneous urticaria. In the phase III clinical trials (NCT03580369, NCT03580356), ligelizumab will be administered as subcutaneous injection at a dose of 72mg or 120mg every 4 weeks (Q4W).[1,2,10]

INNOVATION AND/OR ADVANTAGES

Currently there are limited approved therapies for patients with CSU.[7] Data show ligelizumab binds to IgE, a key driver of CSU, with significantly higher affinity than the current standard of care (omalizumab). Earlier phase IIb study results also show more patients are completely symptom-free from CSU with ligelizumab, thus suggesting ligelizumab to be potentially more effective.[8,11,12]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Ligelizumab does not currently have Marketing Authorisation in the EU/UK for any indication.

Ligelizumab has received breakthrough therapy designation by the US FDA for chronic spontaneous or idiopathic urticaria in January 2021.[3,7]

PATIENT GROUP

DISEASE BACKGROUND

CSU, also called chronic idiopathic urticaria, is a skin condition characterised by spontaneous episodes of hives and/or angioedema which occur without specific triggers, and are present for at least or greater than 6 weeks and for most days of the week.[13-15] CSU is a self-limited disease, yet most patients will suffer with symptoms for several years (beyond 5 years) despite treatment.[16] There is no cure for chronic urticaria.[15]

Patients with CSU can experience urticaria independent of any external stimulus, even though they can define circumstances that may worsen symptoms.[17] Chronic urticaria is more frequent in women, up to 70%.[13] Symptoms of CSU include; raised or swollen welts on the skin (hives or wheals) that appear and reappear over the course of 6 weeks or more; itching that is sometimes severe; swelling of the lips, eyelids, or throat (angioedema).[18]

Patients with CSU often have a severely impaired quality of life, with negative effects on sleep, daily activities, school or work life, and social interactions.[19] When compared with the general population, patients with chronic urticaria (CU) are twice as likely to have mental disorders such as anxiety and depression.[20]

CLINICAL NEED AND BURDEN OF DISEASE

In the UK, approximately 15% of people experience urticaria at some time in their lives and the lifetime prevalence of chronic urticaria is 0.5–1% (between 500 and 1,000 per 100,000). For around 40–50% of people with urticaria, the cause of their condition is unknown. In approximately 50% of people, symptoms may persist for 3–5 years, or for more than 10 years in 20% of people.[21] Nearly 60% of patients with CSU continue to have the disease despite treatment with antihistamines at the licensed dose.[22]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Therapy of CSU is often difficult however the initial approach should employ high-dose non-sedating antihistamines. Over half of the patients are refractory to antihistamines and as such other agents should be tried, such as short-term oral corticosteroids, sedating antihistamines, immune suppressants and monoclonal antibodies.[18,23] Diets low in salicylates and benzoates have been anecdotally adopted in the management of urticaria.[24]

CURRENT TREATMENT OPTIONS

Treatment options for CU include:[24]

- Use of H1-antihistamines
- Tranexamic acid, which appears to benefit patients with angioedema particularly those without wheals
- Leukotriene receptor antagonists
- Anti-IgE therapy, for example Omalizumab is effective in patients with spontaneous and autoimmune CU who have persistent symptoms despite high-dose antihistamines
- Ciclosporin. Low-dose ciclosporin may also be considered in patients with severe unremitting disease uncontrolled by antihistamines
- Mycophenolate mofetil
- H2-antihistamines
- Corticosteroids
- Intramuscular adrenaline

- Icatibant and CI inhibitor
- Topical preparations—Cooling antipruritic lotions such as 2% menthol in aqueous cream can be soothing

PLACE OF TECHNOLOGY

If licensed, ligelizumab will offer an additional treatment option for CSU in adolescents and adults inadequately controlled with H1-antihistamines.

CLINICAL TRIAL INFORMATION

Trial	**NCT03437278, 2017-004207-52;** A Multicenter, Randomized, Double-blind, Placebo-controlled Phase 2b Dose-finding Study to Investigate the Efficacy and Safety of Ligelizumab (QGE031) in Adolescent Patients With Chronic Spontaneous Urticaria (CSU) **Phase II** – completed **Location(s)** – 4 EU countries, Canada and other countries **Study completion date -** Feb 2021
Trial design	Randomised, parallel assignment, quadruple-blinded, placebo-controlled
Population	N=49; Subjects with a diagnosis of CSU refractory to approved doses of H1-antihistamines; all sexes; aged 12 to 18 years
Intervention(s)	Ligelizumab injection (high or low dose)
Comparator(s)	Matched placebo
Outcome(s)	Primary Outcome Measures : Change in the Urticaria Activity Score (UAS7) between baseline and Week 24 [Time Frame: 24 weeks] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**NCT02477332; 2014-005559-16;** A Multi-center, Randomized, Double-blind, Placebo, and Active-controlled Phase 2b Dose-finding Study of QGE031 as add-on Therapy to Investigate the Efficacy and Safety in Patients With Chronic Spontaneous Urticaria (CSU) **Phase II** - completed	**NCT02649218;** 2015-003636-13**;** An Open Label, Multicenter, Extension Study to Evaluate the Long-term Safety of QGE031 240 mg s.c. Given Every 4 Weeks for 52 Weeks in Chronic Spontaneous Urticaria Patients Who Completed Study CQGE031C2201 **Phase II –** completed

	Location(s): 3 EU countries, UK, USA, Canada and other countries **Study completion date -** Jun 2017	**Location(s):** 3 EU countries, UK, USA, Canada and other countries **Study completion date –** May 2019
Trial design	Randomised, parallel assignment, triple-blinded, placebo-controlled, active-controlled	Open label
Population	N=382; Subjects with a diagnosis of CSU for at least 6 months; all sexes; aged 18 to 75 years	N=226; Patients who completed the treatment epoch in study CQGE031C2201 and completed at least Visit 203 (Week 32 of the follow-up epoch, ⩾16 weeks after last injection) and present with active disease as defined by UAS7≥12; all sexes; aged 18 to 75 years
Intervention(s)	Ligelizumab SC every 4 weeks See trial record for full details	Ligelizumab 240mg SC every 4 weeks
Comparator(s)	• Matched placebo • Omalizumab 300 mg SC every 4 weeks	No comparator
Outcome(s)	Primary Outcome Measures: Percentage of Participants With Complete Hives Response (HSS7=0) [Time Frame: Week 12] See trial record for full list of other outcomes	Primary Outcome Measures: Number of Participants With at Least One Treatment Emergent Adverse Event (AE) [Time Frame: Within 16 weeks after Week 48] See trial record for full list of other outcomes
Results (efficacy)	See trial record	See trial record
Results (safety)	See trial record	See trial record

Trial	**NCT03580369**; 2018-000839-28; A Multi-center, Randomized, Double-blind, Active and Placebo-controlled Study to Investigate the Efficacy and Safety of Ligelizumab (QGE031) in the Treatment of Chronic Spontaneous Urticaria (CSU) in Adolescents and Adults Inadequately Controlled With H1-antihistamines **Phase III** - ongoing **Location(s):** 12 EU countries, USA, Canada and other countries **Primary completion date:** Jul 2021
Trial design	Randomised, parallel assignment, triple-blinded; active- and placebo-controlled

Population	N=1072; Subjects with CSU diagnosis for ⩾ 6 months and refractory to H1-AH at approved doses; all sexes; aged 12 years and older
Intervention(s)	Ligelizumab injection every 4 weeks
Comparator(s)	• Omalizumab 300 mg injection every 4 weeks • Matched placebo
Outcome(s)	Primary Outcome Measures : Absolute change from baseline in UAS7 at Week 12 [Time Frame: Week 12] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**NCT03580356**; A Multi-center, Randomized, Double-blind, Active and Placebo-controlled Study to Investigate the Efficacy and Safety of Ligelizumab (QGE031) in the Treatment of Chronic Spontaneous Urticaria (CSU) in Adolescents and Adults Inadequately Controlled With H1-antihistamines **Phase III** - ongoing **Location(s):** 11 EU countries, UK, USA and other countries **Primary completion date –** Jun 2021
Trial design	Randomised, parallel assignment, triple-blinded, active- and placebo-controlled
Population	N=1079; Subjects with CSU diagnosis for ⩾ 6 months and refractory to H1-AH at approved doses; all sexes; aged 12 years and older
Intervention(s)	Ligelizumab injection every 4 weeks
Comparator(s)	• Omalizumab 300 mg injection every 4 weeks • Matched placebo
Outcome(s)	Primary Outcome Measures: Absolute change from baseline in UAS7 at Week 12 [Time Frame: Week 12] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**NCT04210843;** 2019-001792-37**;** A Multi-center, Double-blinded and Open-label Extension Study to Evaluate the Efficacy and Safety of Ligelizumab as Retreatment, Self-administered Therapy and Monotherapy in Chronic Spontaneous Urticaria Patients Who Completed Studies CQGE031C2302, CQGE031C2303, CQGE031C2202 or CQGE031C1301 **Phase III –** ongoing

	Location(s): 16 EU countries, USA, Canada and other countries **Primary completion date –** October 2022
Trial design	Non-randomised, parallel assignment, triple-blinded, open label
Population	N=1713; Subjects who successfully completed all of the treatment period and the follow-up period in any of the following studies: CQGE031C2302, CQGE031C2303, CQGE031C2202 or CQGE031C1301; all sexes; aged 12 years and older
Intervention(s)	Ligelizumab injection See trial record for full details
Comparator(s)	No comparator
Outcome(s)	Primary Outcome Measures: The proportion of subjects with well-controlled disease (UAS7 ⩽ 6) at Week 12 [Time Frame: Week 12] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of ligelizumab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Omalizumab for previously treated chronic spontaneous urticaria (TA339). June 2015.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- No relevant guidance

OTHER GUIDANCE

- BSACI guideline for the management of chronic urticaria and angioedema. Clinical & Experimental Allergy. 2015.[24]

ADDITIONAL INFORMATION

REFERENCES

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