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Galcanezumab for the prophylaxis of episodic and chronic migraine

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LAY SUMMARY

Migraine is a complex condition that impacts the nervous system (the network of nerve cells and fibres that send signals between parts of the body). It is the third most common condition in the world and affects women three times as much as men. Typical symptoms of migraine attacks are moderate to severe one-sided throbbing headaches, often accompanied by nausea, vomiting, increased sensitivity to light and sound. Two particular subtypes are migraine without aura and migraine with aura (including visual disturbances). Migraine can be further classified as episodic migraine (headache occurs on fewer than 15 days per month on average) and chronic migraine (headache is experienced on 15 or more days per month for more than 3 months, having the features of migraine headache on at least 8 days per month). Migraine has been associated with an increased risk of developing other mental and physical health conditions such as depression, anxiety and heart disease.

Galcanezumab is being developed as one of a class of specific anti-migraine preventative drugs. By stopping a very specific protein in the brain and nervous system, galcanezumab reduces migraine attacks. Additionally as it is given once-a-month as treatment, it avoids the need to take numerous pills per day. If marketed, galcanezumab may be more preferable to current treatment options for episodic migraine and chronic migraine prevention.

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TARGET GROUP CIC

Migraine (episodic and chronic) – prophylaxis

TECHNOLOGY

DESCRIPTION

Galcanezumab (LY2951742) is a new molecular entity under development for the prevention of episodic migraine (EM), chronic migraine (CM) and cluster headache.[1]

It is a humanized monoclonal antibody that selectively inhibits the calcitonin gene related peptide (CGRP). CGRP is a vasodilator, particularly in the cerebral circulation and is involved in neurogenic inflammation. Elevated blood concentrations of CGRP have been associated with migraine. Galcanezumab neutralizes CGRP and blocks it from binding to its receptor. By inhibiting CGRP's effects on nearby tissue, galcanezumab reduces the average number of monthly migraine headache days migraine attacks as well as potentially decrease the severity of patient symptoms.[1]

Galcanezumab is in phase III clinical trials as a self-administered once-monthly injection, taken for three,[2] six[3,4] and twelve months[5] for the prevention of EM and CM. In these studies, it has been administered at a prescription dose of 120 mg following an initial loading dose of 240 mg.

Galcanezumab is also in phase III clinical trials for the prevention of chronic cluster headache.[6]

Galcanezumab does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

In the preventative market there are several drugs that have been approved for the management of migraine prevention, but the majority of these drugs have been approved for other indications and subsequently approved for migraine prevention on a label extension. Many of these drugs have a poor efficacy profile and are associated with adverse events, which led to an unmet need for a specific, effective, and safe prophylactic treatment.[7,8]

Key opinion leaders state that CGRP monoclonal antibodies are set to be the first specific anti-migraine preventative drugs, where there is currently a great unmet need. Additionally these have a high rate of efficacy, limited side effects and only need to be administered once a month due to a longer half-life,[7] which reduces the burden of taking pills every day. Also as migraine is often treated with repurposed medications from other indications such as epilepsy or depression, and can be a stigmatising condition, the availability of a target medication for migraine specifically, could provide a sense of legitimacy for people living with migraine.[8]

Therefore, galcanezumab is advantageous to the current treatment options offered for the prophylaxis of EM and CM.

DEVELOPER

Eli Lilly & Company Ltd

PATIENT GROUP

BACKGROUND

Migraine is a complex disabling neurological disorder, characterised by repeated bouts of headache.[9] Typical symptoms of migraine are throbbing, unilateral moderate to severe headaches that increase with activity, often accompanied by nausea, vomiting, increased sensitivity to light and sound. There are two subtypes, migraine with aura (including include visual disturbances (flashing lights, blind spots, zig-zag patterns) and migraine without aura, being the most common and experienced in an estimated 70-90% of all cases.[10,11]

Whilst migraines can have a broad impact on a person's emotional and physical well-being, they additionally disrupt social and academic functioning and place a vast strain on employers and the healthcare system.[12] Migraines can be further classified into episodic migraine (EM) or chronic migraine (CM), based on the prevalence of headache days. EM refers to a diagnosis of migraine with headache frequency occurring on fewer than 15 days per month on average,[13] whereas CM has been defined by the International Headache Society as occurring when a headache is experienced on 15 or more days per month for more than 3 months, having the features of migraine headache on at least 8 days per month.[14]

Of the two sub-types, CM is regarded as the more debilitating disorder following the findings from various population and clinical studies. For example, CM compared to EM patients are more likely to be unemployed, overweight and tend to experience more depression and anxiety.[15] Greater migraine-related disability[16] and impairment in headache quality of life[17] were also found in CM compared to EM. Comorbid conditions of EM include psychiatric disorders such as anxiety and depression,[18] asthma[19] and heart disease,[20] however when comparing the frequency of common comorbidities in a large population-based sample, it was reported that psychiatric, respiratory, cardiovascular and chronic pain measures were all more commonly associated with CM.[13]

Despite there being a lack of understanding surrounding the exact mechanism at play when a migraine attack is initiated, brain dysfunction involving peripheral and central components of the trigemino-vascular system is thought to lead to the release of inflammatory mediators that ultimately result in propagation and perpetuation of pain.[21] Furthermore elevated levels of CGRP, but not of other neuropeptides, were found in the external jugular vein during the headache phase of migraine whereas these levels normalised when headache improved.[22] The importance of CGRP is further highlighted as infusion of human CGRP was found to trigger a migraine attack in susceptible individuals, while CGRP levels returned to normal after migraine treatment with triptans.[23] These findings provide insight into a putative role of CGRP in the pathophysiology of migraine, opening newer pathways for therapeutic intervention.[24]

CLINICAL NEED and BURDEN OF DISEASE

Migraine is the third most common condition in the world[9] and affects 15% of the UK adult population.[25] Prevalence has been reported to be 5–25% in women and 2–10% in men. The prevalence of CM in the UK is not known, although some clinicians consider the rate could be 1 in 1000 people. Of those diagnosed with CM, an estimated 34.6% have not responded to at least 3 prior pharmacological prophylactic therapies. This equates to approximately 51,000 adult patients in England.[26]

Every year, between 3 to 5% of people with EM go on to experience CM.[26] People with CM are 3 times more likely to consult their GP compared to those with EM. In the UK, 43% of patients with CM visit a neurologist compared to 18% of people with EM. The World Health Organisation (WHO) has recognised the impact of migraine worldwide and categorised it as the same level of disability as dementia, quadriplegia and acute psychosis. Furthermore WHO classified CM as more disabling than blindness, paraplegia angina or rheumatoid arthritis. Some estimates put the cost of migraine, just in terms of medications at £150 million annually in the UK, but it is thought that overall costs are well in excess of this figure. An estimated 25 million working days are lost due to migraine, and at average gross weekly pay of £450, this costs the UK £2.25 billion per annum.[27]

In 2015-16, there were 25,360 hospital admissions for migraine (ICD 10 G43), resulting in 27,698 bed days and 31,279 finished consultant episodes.[28]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal. Botulinum toxin type A for the prevention of headaches in adults with chronic migraine (TA260). June 2012.
- NICE guidelines. Headaches in over 12s: diagnosis and management (CG150). September 2012. (Updated November 2015).
- NICE quality standard. Headaches in over 12s (QS42). August 2013.
- NICE interventional procedure guidance in development. Transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine (GID-IP1293). May 2016.
- NICE interventional procedure guidance. Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine (IPG552). March 2016.
- NICE interventional procedure guidance Implantation of a sphenopalatine ganglion stimulation device for chronic cluster headache (IPG527). June 2015.
- NICE interventional procedure guidance. Transcranial magnetic stimulation for treating and preventing migraine (IPG477). January 2014.
- NICE interventional procedure guidance. Occipital nerve stimulation for intractable chronic migraine (IPG452). April 2013.
- NICE interventional procedure guidance. Percutaneous closure of patent foramen ovale for recurrent migraine (IPG370). December 2010.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. NHS standard contract. Occipital nerve stimulation for intractable headaches and migraine D08/P/c.
- NHS England. NHS standard contract for specialised pain. Specialised services for pain management (Adult). D08/S/a.

OTHER GUIDANCE

- Pringsheim, T., Davenport, W. J., Marmura, M. J., Schwedt, T. J. and Silberstein, S. (2016), How to Apply the AHS Evidence Assessment of the Acute Treatment of Migraine in Adults to your Patient with Migraine. *Headache*, 56: 1194–1200. doi:10.1111/head.12870
- Beran, R. Management of chronic headache. *Australian family physician*. March 2014.
- Headache Classification Committee of the International Headache Society (IHS. The international classification of headache disorders, (beta version). *Cephalalgia*. 2013.
- British Association for the Study of Headache Treatment Guidelines. December 2010.
- Scottish Intercollegiate Guidelines Network. Diagnosis and management of headaches in adults (SIGN 107). November 2008.

CURRENT TREATMENT OPTIONS

In the preventative market there are several drugs that have been approved for the treatment of migraine, but the majority of these drugs have been approved in another indication and subsequently approved for migraine on a label extension.[7]

For the acute treatment of migraine, the following treatment options are recommended by NICE: [29]

- Combination therapy with an oral triptan and a nonsteroidal anti-inflammatory drug (NSAID), or an oral triptan and paracetamol, accounting for person's preference, comorbidities and risk of adverse events. For people aged 12–17 years consider a nasal triptan in preference to an oral triptan
- For people who prefer to take only one drug, consider monotherapy with an oral triptan, NSAID, aspirin (900 mg) or paracetamol accounting for the person's preference, comorbidities and risk of adverse events
- Consider an anti-emetic in addition to other acute treatment for migraine even in the absence of nausea and vomiting

For people in whom oral preparations (or nasal preparations in young people aged 12–17 years) for the acute treatment of migraine are ineffective or not tolerated:[29]

- Offer a non-oral preparation of metoclopramide or prochlorperazine and
- Consider adding a non-oral NSAID or triptan if these have not been tried

Additional procedures used in the treatment for acute migraine have been recommended by NICE:[29]

- Transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine
- Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine
- Transcranial magnetic stimulation for treating and preventing migraine

For the prophylactic treatment of migraine:[29]

- Offer topiramate or propranolol according to the person's preference, comorbidities and risk of adverse events. Advise women and girls of childbearing potential that topiramate is associated with a risk of foetal malformations and can impair the effectiveness of hormonal contraceptives. Ensure they are offered suitable contraception if needed

- Consider amitriptyline according to the person's preference, comorbidities and risk of adverse events
- If both topiramate and propranolol are unsuitable or ineffective, consider a course of up to 10 sessions of acupuncture over 5–8 weeks according to the person's preference, comorbidities and risk of adverse events
- Advise people with migraine that riboflavin (400 mg once a day) may be effective in reducing migraine frequency and intensity for some people
- Flunarizine despite unlicensed is recommended in the treatment pathway because of the potential clinical impact of long-term prescribing in primary care

Botulinum toxin type A is recommended as an option for the prophylaxis of headaches in adults with CM (defined as headaches on at least 15 days per month of which at least 8 days are with migraine) in those:[26]

- That have not responded to at least three prior pharmacological prophylaxis therapies and
- Whose condition is appropriately managed for medication overuse

Additional procedures used in the prevention of migraine have been recommended by NICE: [29]

- Transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine
- Transcutaneous stimulation of the cervical branch of the vagus nerve for cluster headache and migraine
- Transcranial magnetic stimulation for treating and preventing migraine
- Occipital nerve stimulation for intractable CM
- Percutaneous closure of patent foramen ovale for recurrent migraine

It has been reported that up to 73% of patients with CM overuse headache medication. Daily use of acute medication may result in further complications, therefore help from a GP or neurologist should be sought if medication use is this regular.[27]

EFFICACY and SAFETY	
Trial	REGAIN, NCT02614261; adults aged 18 – 65 years; galcanezumab (experimental dose 1) vs galcanezumab (experimental dose 2) vs placebo; phase III
Sponsor	Eli Lilly and Company
Status	Ongoing
Source of Information	GlobalData,[1] trial registry,[2] publication[30] and press release[31]
Location	EU (incl UK), USA, Canada and other countries.
Design	Randomised, placebo-controlled, double-blind, open-label, prevention study
Participants	n=1113; aged 18-65 years; chronic migraine (15 headache days per month)
Schedule	Randomised to dose 1 and received galcanezumab at dose of 120 mg/ml subcutaneous (SC) injection once a month up to 3 months following a 240 mg loading dose; or dose 2 and received galcanezumab at dose of 120 mg/ml SC injection once a month for 3 months following a 240 mg loading dose; or placebo as a SC injection once a month for 3 months.
Follow-up	Subjects may be eligible for optional open label extension for additional nine months at the end of the double blind period with dose level 1 or dose level 2.
Primary Outcomes	Number of monthly migraine headache days
Secondary Outcomes	• Proportion of participants with reduction from baseline ≥50%, ≥75% and 100% in monthly migraine headache days • Mean change from baseline on the migraine-specific quality of life questionnaire • Mean change from baseline in the number of monthly migraine headache days requiring medication for the acute treatment of migraine or headache • Mean change from baseline in the patient global Impression of Severity (PGI-S) score • Mean change from baseline in headache hours • Mean change from baseline on the Migraine Disability Assessment Test (MIDAS) total score • Percentage of participants developing anti-drug antibodies to galcanezumab • Pharmacokinetics (PK): area under the concentration time curve (AUC) of galcanezumab • Plasma concentration of CGRP
Key Results	Both doses of galcanezumab were superior to placebo in the reduction in monthly migraine headache days, with significantly higher percentages of patients reducing their monthly migraine headache days by ≥50%. The 240 mg dose was also superior to placebo on most key secondary measures. Both galcanezumab doses appear to be efficacious, safe, and well-tolerated for the preventive treatment of CM.[31]
Adverse effects (AEs)	The most commonly reported adverse events were injection site reactions.[31]
Expected reporting date	Study completion date reported as July 2019.

Trial	EVOLVE-1, NCT02614183; adults aged 18 – 65 years; galcanezumab (experimental dose 1) vs galcanezumab (experimental dose 2) vs placebo; phase III
Sponsor	Eli Lilly and Company
Status	Ongoing
Source of Information	GlobalData,[1] trial registry,[3] and press release[31]
Location	USA and Canada
Design	Randomised, placebo-controlled, double-blind, prevention study
Participants	n=858; aged 18-65 years; episodic migraine (4-14 migraine headache days per month)
Schedule	Randomised to dose 1 and received galcanezumab at dose of 120 mg/ml subcutaneous (SC) injection once a month for 6 months following a 240 mg loading dose; or dose 2 and received galcanezumab at dose of 240 mg/ml SC injection once a month for 6 months following a 240 mg loading dose; or placebo as a SC injection once a month for 6 months.
Follow-up	-
Primary Outcomes	Number of monthly migraine headache days
Secondary Outcomes	• Proportion of participants with reduction from baseline ≥50%, ≥75% and 100% in monthly migraine headache days • Mean change from baseline on the migraine-specific quality of life questionnaire • Mean change from baseline in the number of monthly migraine headache days requiring medication for the acute treatment of migraine or headache • Mean change from baseline in the patient global Impression of Severity (PGI-S) score • Mean change from baseline in headache hours • Mean change from baseline on the Migraine Disability Assessment Test (MIDAS) total score • Percentage of participants developing anti-drug antibodies to galcanezumab • Pharmacokinetics (PK): area under the concentration time curve (AUC) of galcanezumab • Plasma concentration of CGRP
Key Results	Over the six-month treatment period, patients with episodic migraine treated with galcanezumab 120 mg and 240 mg doses experienced a statistically significantly greater decrease in the average number of monthly migraine headache days compared to patients treated with placebo, with statistically significant improvements observed at each month starting at one month of treatment.[31] A statistically significantly greater percentage of patients treated with both doses of galcanezumab achieved at least a 50 percent, 75 percent and 100 percent reduction in the number of migraine headache days compared to placebo over the six-month treatment period, in both studies after multiplicity adjustment.[31]

Adverse effects (AEs)	The most commonly reported adverse events were injection site reactions. [31]
Expected reporting date	Study completion date reported as October 2018.

Trial	EVOLVE-2, NCT02614196; adults aged 18 – 65 years; galcanezumab (experimental dose 1) vs galcanezumab (experimental dose 2) vs placebo; phase III
Sponsor	Eli Lilly and Company
Status	Ongoing
Source of Information	GlobalData,[1] trial registry,[4] and press release[31]
Location	EU (incl UK), USA and other countries
Design	Randomised, placebo-controlled, double-blind, prevention study
Participants	n=915; aged 18-65 years; episodic migraine (4-14 migraine headache days per month)
Schedule	Randomised to dose 1 and received galcanezumab at dose of 120 mg/ml SC injection once a month for 6 months following a 240 mg loading dose; or dose 2 and received galcanezumab at dose of 240 mg/ml SC injection once a month for 6 months following a 240 mg loading dose; or placebo as a SC injection once a month for 6 months.
Follow-up	-
Primary Outcomes	Number of monthly migraine headache days
Secondary Outcomes	• Proportion of participants with reduction from baseline ≥50%, ≥75% and 100% in monthly migraine headache days • Mean change from baseline on the migraine-specific quality of life questionnaire • Mean change from baseline in the number of monthly migraine headache days requiring medication for the acute treatment of migraine or headache • Mean change from baseline in the patient global Impression of Severity (PGI-S) score • Mean change from baseline in headache hours • Mean change from baseline on the Migraine Disability Assessment Test (MIDAS) total score • Percentage of participants developing anti-drug antibodies to galcanezumab • Pharmacokinetics (PK): area under the concentration time curve (AUC) of galcanezumab • Plasma concentration of CGRP
Key Results	Over the six-month treatment period, patients with episodic migraine treated with galcanezumab 120 mg and 240 mg doses experienced a statistically significantly greater decrease in the average number of monthly migraine headache days compared to patients treated with placebo, with statistically significant improvements observed at each month starting at one month of treatment.[31]

	A statistically significantly greater percentage of patients treated with both doses of galcanezumab achieved at least a 50 percent, 75 percent and 100 percent reduction in the number of migraine headache days compared to placebo over the six-month treatment period, in both studies after multiplicity adjustment.[31]
Adverse effects (AEs)	The most commonly reported adverse events were injection site reactions. [31]
Expected reporting date	Study completion date reported as April 2019.

Trial	NCT02614287; adults aged 18 – 65 years; galcanezumab (experimental dose 1) vs galcanezumab (experimental dose 2)
Sponsor	Eli Lilly and Company
Status	Ongoing
Source of Information	GlobalData,[1] trial registry[4] and press release[32]
Location	EU (not incl UK), USA and Canada
Design	Randomised, uncontrolled, open-label study
Participants	n=270; aged 18-65 years; episodic migraine and chronic migraine
Schedule	Randomised to dose 1 and received galcanezumab at dose of 120 mg/ml SC injection once a month for up to 12 months; or dose 2 and received galcanezumab at dose of 240 mg/ml SC injection once a month for up to 12 months.
Follow-up	-
Primary Outcomes	Percentage of participants who discontinue
Secondary Outcomes	• Pharmacokinetics (PK): area under the concentration time curve (AUC) of galcanezumab • Plasma concentration of CGPR • Percentage of participants developing anti-drug antibodies to galcanezumab • Mean change from baseline in the number of migraine headache days • Mean change from baseline in the number of headache days • Proportion of participants with reduction from baseline ≥50% in monthly migraine headache days • Mean change from baseline in the frequency of medication use for the acute treatment of migraines or headaches • Mean Patient Global Impression-Improvement (PGI-I) Score • Mean change from baseline on the Migraine Disability Assessment Test (MIDAS) total score • Mean change from baseline on the migraine-specific quality of life questionnaire • Participant Satisfaction with Medication Questionnaire-Modified (PSMQ-M) score • Subcutaneous Administration Assessment Questionnaire (SQAAQ) score

Key Results	Over the 12-month treatment period, galcanezumab was also associated with a statistically significant reduction in the number of monthly migraine headache days with both doses (5.6 days for 120 mg and 6.5 days for 240 mg, p<0.001 for both dosing groups). Notably, there was no clinically meaningful difference in the rate of adverse events between galcanezumab 120 mg and 240 mg dosing groups.[32]
Adverse effects (AEs)	The most commonly reported adverse events (≥10%) in both dosing groups included injection site pain, nasopharyngitis and upper respiratory tract infection. Serious adverse events were reported by three patients in the 120 mg dosing group and seven patients in the 240 mg group.[32]
Expected reporting date	Study completion date reported as December 2018.

ESTIMATED COST and IMPACT

COST

The cost of galcanezumab is not yet known

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: *improved quality of life for carers, improved patient convenience, wider societal benefits as in earlier return to normal activities, including employment*

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs

☒ Other reduction in costs: *reduced use of secondary care/specialist services, reduced need for interventional procedures*

☐ Other

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified

☒ None identified

INFORMATION FROM

Information was received by Eli Lilly and Company

UK PharmaScan ID number 646369

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