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Lanadelumab for prevention of attacks in adults and adolescents with Type I and Type II hereditary angioedema

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LAY SUMMARY

Angioedema is a rare blood disorder characterised by rapid swelling below the skin. Most often affect are hands, feet, eyes, lips or genitals. The swelling is caused by a collection of fluid in the deep layers of the skin. Hereditary Angioedema (HAE) is a rare condition caused by mutations that reduce the production or expression of the C1 inhibitor protein – a regulator of inflammatory pathways.

Individuals usually start suffering from HAE in the first or second decade of life. Most attacks are associated with trauma, medical procedures, emotional stress, menstruation, oral contraceptive use, infections or the use of medications. These attacks most often last approximately 2 to 5 days before resolving spontaneously. Some attacks can be life threatening.

Treatment of HAE consists of management of acute attacks as well as long-term prophylaxis. Concentrates of C1 inhibitors are usually given to raise the level of C1 inhibitor in the blood and halts the progress of acute attacks.

TARGET GROUP

- For the prophylactic prevention of attacks in adults and adolescents with Type I and Type II hereditary angioedema

TECHNOLOGY

DESCRIPTION

Lanadelumab [DX 2930; DX-2930; DX2930; kallikrein inhibitor, Dyax; lanadelumab; SHP-643; SHP643] is a sc fully recombinant human IgG MAb inhibiting plasma kallikrein (pKal), under development by Shire (Dyax before the acquisition) for the prophylactic treatment of bradykinin-mediated angioedema.

Lanadelumab has been granted orphan drug status for the treatment of hereditary angioedema.

In Phase III clinical trials lanadelumab is administered 300mg every 2 or 4 weeks by subcutaneous injection and 150mg every 4 weeks.

INNOVATION and/or ADVANTAGES

If licensed, Lanadelumab could offer an additional treatment option for the treatment of acute attacks in adults and adolescents with Type I and Type II hereditary angioedema.

Lanadelumab (DX-2930) is a new kallikrein inhibitor with the potential for prophylactic treatment of hereditary angioedema with C1 inhibitor deficiency.[1]

DEVELOPER

Shire Pharmaceutical Contract Ltd.

AVAILABILITY, LAUNCH or MARKETING

Lanadelumab is currently in phase III clinical trials.

PATIENT GROUP

BACKGROUND

Angioedema is the rapid swelling of the dermis. Symptoms include swelling caused by a collection of fluid in the deep layers of the skin, which most often affects the hands, feet, eyes, lips, or genitals. In severe cases, the inside lining of the throat, bowel, urethra bladder and stomach.[2]

Hereditary angioedema (HAE) is a rare condition, arising from a genetic deficiency of C1- inhibitor, which is a regulator of inflammatory pathways.[2] Normally, this protein controls enzyme cascade reactions so that uncontrolled swelling of the subcutaneous and submucosal tissues do not occur.[3] In HAE patients, at times of physiological or psychological stress, the function of the C1-inhibitor is

insufficient, resulting in the accumulation of excessive fluid (oedema) and localised oedematous swellings.[2] These usually occur as:[3]

- Swelling in the airway – this is particularly dangerous and can lead to death by if the patient is not able to breathe properly
- Swelling in the gut – this can cause severe pain in the stomach area, feeling sick (nausea) and being sick (vomiting)
- Swellings in the deep tissues of the skin – this can cause significant disability for example if the hands, feet or genitals are affected.

There are 3 types of HAE, whereby Type I is defined by low plasma levels of a normal C1-INH protein reflecting an abnormality of one of the gene alleles of the protein. In Type two, normal or elevated levels of a dysfunctional C1-INH are present, with one of the two gene alleles being abnormal. Here, the allele leads to the release of a non-functional protein.[4] In Type III the deficiency of INHC does not occur, however, it is known that oestrogen has a role not yet fully understood in the crisis of HAE Type III.[5] Type I (85%) and II (15%) account to almost all cases of Hereditary angioedema.[6]

HAE usually occurs during the second or first decade of life. Although some attacks lack an identifiable trigger, most are associated with trauma, medical procedures, emotional stress, menstruation, oral contraceptive use, infections, or the use of medications such as ACE inhibitors. Attacks usually last approximately 2 to 5 days before resolving spontaneously.[7]

CLINICAL NEED and BURDEN OF DISEASE

Although urtcaria and angioedema are common problems, affecting almost 20% of the population, HAE is a rare disorder. It accounts for approximately 2% of clinical angioedema cases and occurs in 1 per 50,000-150,000 population. Persons of any race can be affected, with no reported bias in different ethnic groups. It was initially thought that HAE occurs only in women, however, recent studies described as well males with HAE.[4]

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

No guidance is currently available.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. Clinical Commissioning Policy: Treatment of Acute Attacks in Hereditary Angiodema (Adult). NHSCB/B09/P/b. April 2013.
- NHS England. Clinical Commissioning Policy: Plasma derived C1-esterase inhibitor for prophylactic treatment of hereditary angioedema (HAE) types I and II. 16045/P. July 2016.
- NHS England. 2013/14 NHS Standard Contract for Specialised Immunology (all ages). B09/S/a.
- NHS England. 2013/14 NHS Standard Contract for Specialised Allergy Services (all ages). B09/S/b.
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OTHER GUIDANCE

- Craig T, et al. 2012. WAO Guideline for Management of Hereditary Angiodema. World Allergy Organ J 2012. 5(12):182-99.
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- Cicardi M et al. Evidence-based recommendations for the therapeutic management of angioedema owing to C1 inhibitor deficiency; consensus report of an international working group. Allergy 2012;67:147-157

CURRENT TREATMENT OPTIONS

Treatment of HAE consists of management of acute attacks as well as long-term prophylaxis and transient prophylaxis.

The main cause of death in HAE is laryngeoedema. In acute attacks, intubation and emergency tracheostomy are used in case the airway is compromised. Intravenous fluid replacement is important, as some patients develop hypotension.

Abdominal attacks make pain management crucial. Prior therapy with fresh frozen plasma is controversial due to its side effects.

Current treatments of acute attacks include the use of kallikrein inhibitor or injection of a bradykinin receptor antagonist, icatibant or C1 inhibitor.

As long-term prophylaxis daily use of 17 alpha-alkylated androgens is suggested. The two widely used drugs are stanazolol and danazol, both synthetic androgens.

C1-INH concentrate (Cinryze) is approved for prophylaxis to prevent attacks of angioedema. It is given IV every 3-4 days. Due to the high cost of this new drug, it is not widely used.

Prophylaxis for surgical procedures, most commonly dental work, daily high dose androgen therapy is recommended for at least 4 days prior to surgery and 2-4 days afterwards.[6] WAO Guidelines (Craig et al.) recommend C1 inhibitors as first line treatment for pre procedural prophylaxis. Berinert is another concentrate of C1 Inhibitor, which raises the level of C1 inhibitor in the blood and halts the progress of an acute attack of oedema. Further, Ruconest, which is derived from milk of female rabbits that have been genetically altered to produce the human C1 inhibitor protein, is used and licenced for acute treatment.[8]

EFFICACY and SAFETY

Trial	2015-003943-20 DX-2930-03 NCT02586805
Sponsor	Dyax Corp., Shire
Status	Closed.
Source of Information	Trialtrove

Location	Canada, Germany, Italy, Jordan, Puerto Rico, UK, US
Design	Randomized, multicentre, double-blind, placebo-controlled, parallel assignment
Participants	Planned N= 120. > Or = 12 years. Documented diagnosis of HAE, Type I or II. Baseline rate of at least 1 investigator-confirmed HAE attack per 4 weeks.
Schedule	Arm 1: Experimental: DX-2930 300 mg every 2 weeks 300 mg DX-2930 administered every 2 weeks by subcutaneous injection. Drug: DX-2930 - 300mg/2wk 300 mg DX-2930 administered every 2 weeks by subcutaneous injection. Arm 2: Experimental: DX-2930 300 mg every 4 weeks 300 mg DX-2930 administered every 4 weeks by subcutaneous injection. Drug: DX-2930 - 300mg/4wk 300 mg DX-2930 administered every 4 weeks by subcutaneous injection. To maintain the study blind, subjects will be given placebo injections every other 2 weeks when they are not receiving drug. Arm 3: Experimental: DX-2930 150 mg every 4 weeks 150 mg DX-2930 administered every 4 weeks by subcutaneous injection. Drug: DX-2930 - 150mg/4wk 150 mg DX-2930 administered every 4 weeks by subcutaneous injection. To maintain the study blind, subjects will be given placebo injections every other 2 weeks when they are not receiving drug. Arm 4: Placebo Comparator: Placebo Placebo administered every 2 weeks by subcutaneous injection. Drug: Placebo Placebo administered every 2 weeks by subcutaneous injection.
Follow-up	Not reported.
Primary Outcomes	Efficacy and safety of DX-2930 in preventing acute angioedema attacks in patients with Type I and Type II HAE.
Secondary Outcomes	Number per week of HAE attacks requiring acute attack therapy use for each DX-2930 treatment arm versus placebo arm. Number per week of moderate or severe HAE attacks for each DX-2930 treatment arm versus placebo arm. Number of Investigator confirmed HAE attacks for each DX-2930 treatment arm versus placebo arm occurring on Day 14 through Day 182.
Key Results	Not reported.
Adverse effects (AEs)	Not reported.
Expected reporting date	Not reported.

Trial	DX-2930-04 NCT02741596
Sponsor	Shire
Status	Closed.
Source of Information	Trialtrove, clinicaltrials.gov
Location	Canada, Germany, Israel, Italy, Puerto Rico, UK, US
Design	Open-label, safety, efficacy, non-randomized, single group assignment
Participants	Planned N=220. ≥12 years. Documented diagnosis of HAE Type I or II. A historical baseline HAE attack rate of at least 1 attack per 12 weeks.
Schedule	Arm 1: Experimental: Rollover

	Subjects who rollover from the DX-2930-03 study. Drug: DX-2930 Rollover subjects: 300 mg DX-2930 administered by subcutaneous injection at Day 0. No additional DX-2930 doses until their first reported HAE attack. Following this attack subjects will receive open label doses of 300 mg DX-2930 every 2 weeks by subcutaneous injection throughout the duration of the treatment period. Arm 2: Experimental: Non-rollover Subjects who were not participants in DX-2930-03. Drug: DX-2930 Non-rollover subjects: 300 mg DX-2930 administered every 2 weeks by subcutaneous injection throughout the duration of the treatment period.
Follow-up	Not reported.
Primary Outcomes	Long-term safety and efficacy of DX-2930 for prevention against acute attacks of hereditary angioedema.
Secondary Outcomes	Evaluate the long-term safety of repeated subcutaneous (SC) administrations of DX-2930 through analyses based on treatment-emergent Adverse Events (AEs). The number and percentage of subjects with any AE, any related AE, any SAE, any related SAE, any severe AE, and any related severe AE as well as the total number of events for each category will be summarized. Evaluate the long-term efficacy of DX-2930 in preventing HAE attacks in accordance with the HAE Attack Assessment and Reporting Procedures (HAARP). Characterize the outer bounds of dosing frequency for DX-2930 by assessing the duration of time between a rollover subject's first and second open-label dose.
Key Results	Not reported.
Adverse effects (AEs)	Not reported.
Expected reporting date	Not reported.

ESTIMATED COST and IMPACT

COST

The cost of Lanadelumab is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS and CARERS

☒ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: improved patient convenience

☐ 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

☐ Other ☒ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified ☒ None identified

REFERENCES

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2 NHS England. NHS Commissioning Board Clinical Commissioning Policy: Treatment of Acute Attacks in Hereditary Angiodema (Adult) NHSCB/B09/P/b. Allergy and Immunology. 2013.

3 NHS England. Clinical Commissioning Policy: Plasma-derived C1-esterase inhibitor for prophylactic treatment of hereditary angioedema (HAE) types I and II, 16045/P. Immunology and Allergy. 2016.

4 Michael M Frank. Hereditary Angioedema. 2016 [cited 2017 06.04.]; Available from: http://emedicine.medscape.com/article/135604-overview#a2

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