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Newcastle University

Health Technology Briefing
June 2022

Dersimelagon for previously untreated erythropoietic protoporphyria and X-linked protoporphyria

Company/Developer	Mitsubishi Tanabe Pharma Europe Ltd

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 26730	NICE ID: 10392	UKPS ID: 655041

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Dersimelagon is being developed for the treatment of erythropoietic protoporphyria (EPP) or X-linked protoporphyria (XLP). EPP and XLP are rare diseases that cause intolerance to light. In patients with EPP or XLP, exposure to light can lead to symptoms such as pain and swelling of the skin, which prevent patients from being able to spend time outdoors or in places with bright light. EPP and XLP are inherited diseases which are caused by genetic changes. The most common form of preventing a reaction is to avoid exposure to sunlight.

Dersimelagon is an orally administered drug which binds to a protein called melanocortin-1 receptor (MC1R). Binding to MC1R causes a pigment called eumelanin to be produced which is protective against sunlight as it blocks the penetration of light into cells. If licensed, dersimelagon will provide a treatment option for adults and adolescents with EPP or XLP that has a convenient route of administration and high selectivity for MC1R binding.

Proposed Indication

Erythropoietic protoporphyria or X-linked protoporphyria.[1]

Technology

Description

Dersimelagon (MT-7117) is a novel synthetic, orally-administered, non-peptide small molecule, which acts as a selective agonist of melanocortin-1 receptor (MC1R).[2] Functional MC1R is crucial in eumelanin synthesis. The major biological functions of eumelanin are absorption of sunlight (photoprotection) and scavenging of free radicals (chemoprotection). Thus, MC1R plays a critical role in the ability of melanocytes to provide an anti-oxidative defence mechanism against cell damage from harmful solar irradiation. Dersimelagon has shown high selectivity for MC1R and is effective in inducing eumelanin production in cells.[3]

Dersimelagon is currently in phase III clinical development for the treatment of adult and adolescent patients with EPP or XLP (NCT04402489). In this trial, low dose or high dose dersimelagon is administered orally once daily.[1] A phase III extension study is also ongoing (NCT05005975), in this trial 100mg dersimelagon is administered orally.[4]

Key Innovation

Dersimelagon is innovative as a treatment for EPP and XLP due to its novel route of administration. As a non-peptide small molecule it can be orally administered.[3,5] If licensed, dersimelagon will offer a novel, highly selective oral treatment option for adult and adolescent patients with EPP or XLP who currently have limited therapies available.

Regulatory & Development Status

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

Dersimelagon has been awarded the following regulatory designations:[6,7]

- An orphan drug designation by the EMA in March 2022 for the treatment of EPP
- An orphan drug designation by the FDA in June 2020 for the treatment of cutaneous variants of porphyria

Dersimelagon is also currently in phase II development for the treatment of diffuse cutaneous systemic sclerosis.[8]

Patient Group

Disease Area and Clinical Need

EPP is a rare inherited metabolic disorder caused by a deficiency of the enzyme ferrochelatase (FECH), which results from mutations in the FECH gene. Due to abnormally low levels of this enzyme, excessive amounts of protoporphyrin accumulate in the bone marrow, blood plasma, and red blood cells. Some patients with symptoms of EPP have a genetic change in a different gene called ALAS2. When a patient has a genetic change in this gene, the condition is referred to as XLP.[9] Mutations of the ALAS2 gene lead to the overproduction of a protein known as 5-aminolevulinate synthase 2, which, in turn, results in elevated levels of protoporphyrin. The symptoms of XLP develop because of this abnormal accumulation

of protoporphyrin.[10] EPP is inherited in an autosomal recessive manner. In most cases, affected individuals have one severe mutation that is inherited from one parent, and another weak mutation that is inherited from the other parent. In a small number of cases, an affected individual has two loss-of-function mutations.[11] The major symptoms of EPP and XLP are severe pain on exposure to sunlight and some types of artificial light, such as fluorescent lights (phototoxicity). On sun exposure, patients may first experience tingling, itching, burning of the skin. After continued exposure to light, the skin may become red and swollen.[9]

In Europe, the prevalence of EPP is estimated to be 1 per 50,000 to 75,000.[12] In England (2020/21), there were 3 hospital admissions with primary diagnosis of hereditary erythropoietic porphyria (ICD-10 code: E80.0), and 3 finished consultant episodes (FCEs), resulting in 2 day cases.[13]

Recommended Treatment Options

There are currently no pharmaceutical treatment options recommended by the National Institute for Health and Care Excellence (NICE) for the treatment of EPP or XLP.

Betacarotene may be administered under specialist use only for the management of photosensitivity reactions in erythropoietic protoporphyria in children aged 1 to 17 years old.[14]

An assessment of afamelanotide (which has a UK marketing authorisation under exceptional circumstances for prevention of phototoxicity in adult patients with EPP) is ongoing.[15]

Clinical Trial Information

Trial	NCT04402489, 2019-004226-16; A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy, Safety, and Tolerability of MT-7117 in Adults and Adolescents With Erythropoietic Protoporphyria or X-Linked Protoporphyria **Phase III** – Active, not recruiting **Location(s):** 4 EU countries, UK, USA, Canada and other countries **Primary completion date:** December 2021	NCT05005975; A Phase 3, Multicenter, Open-label, Long-term, Extension Study to Evaluate Safety and Tolerability of Oral Dersimelagon (MT-7117) in Subjects With Erythropoietic Protoporphyria (EPP) or X-Linked Protoporphyria (XLP) **Phase III** – Recruiting **Location(s):** 4 EU countries, UK, USA, Canada and other countries **Primary completion date:** September 2023
Trial Design	Randomised, parallel assignment, triple-blind	Single group assignment, open label
Population	N=184; Subjects with a confirmed diagnosis of EPP or XLP based on medical history; Aged 12 to 75 years	N=175; Subjects who complete NCT04402489 (complete through Week 58 [Visit 12])
Intervention(s)	Dersimelagon oral tablet once daily	Dersimelagon 100mg orally
Comparator(s)	Matched placebo	No comparator
Outcome(s)	**Primary outcome:**	**Primary outcomes:**

	Change from baseline in average daily sunlight exposure time (minutes) to first prodromal symptom (burning, tingling, itching, or stinging) associated with sunlight exposure between 1 hour post sunrise and 1 hour pre-sunset at Week 26. [Time frame: baseline (week 0) and 26 weeks] See trial record for full list of other outcomes	- Number of patients with treatment emergent adverse events (TEAEs) (including serious adverse events [SAEs] and adverse events of special interest [AESIs]). [Time frame: up to a maximum 24 months] - Number of patients with abnormal physical examination data [Time frame: up to a maximum 24 months] - Number of patients with Nevi appearance [Time Frame: up to a maximum 24 months]
Results (efficacy)	-	-
Results (safety)	-	-

Trial	NCT03520036; A Phase II, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Efficacy, Safety, and Tolerability of MT-7117 in Subjects With Erythropoietic Protoporphyria **Phase II** – Completed **Location(s):** USA **Study completion date:** September 2019
Trial Design	Randomised, parallel assignment, quadruple-blind
Population	N=102; Subjects with a confirmed diagnosis of EPP based on medical history; Aged 18 to 75 years
Intervention(s)	Dersimelagon oral low or high dose
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcome:** Change from baseline in average daily duration of sunlight exposure without symptoms [Time frame: baseline (week 0) and week 16] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of dersimelagon was confidential at the time of producing this briefing.

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Afamelanotide for treating erythropoietic protoporphyria (ID927). Expected date of issue to be confirmed.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2018 Implementation Plan for the UK Strategy for Rare Diseases.
- NHS England. 2013/14 NHS Standard Contract for Metabolic Disorders (Adult). E06/S/a.

Other Guidance

- British Association of Dermatologists (BAD). Erythropoietic protoporphyria and X-linked dominant protoporphyria. 2021.[16]

Additional Information

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NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.