NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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STS101 for the acute treatment of migraine

Company/Developer	Satsuma Pharmaceuticals, Inc.

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 27186	NICE ID: 11782	UKPS ID: Not Available

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

STS101 is in development for the acute treatment of migraine, with or without aura. Migraine without aura is a recurrent headache disorder manifesting in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or sensitivity to bright lights and noises. Migraine with aura consists of recurrent attacks, lasting minutes, of visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms. There remains an unmet need for improved acute migraine treatment options that provide rapid relief from pain, are easy to administer, and have long lasting anti-migraine effects.

STS101 is a novel drug-device combination product that consists of a nasal powder formulation of dihydroergotamine (DHE) that can be easily self-administered by patients. It is designed to facilitate rapid absorption of DHE, and achievement of DHE plasma concentrations that maximise efficacy and minimise side effects. DHE interacts with serotonin and adrenergic receptors (targets) in the body to provide anti-migraine effects. Interaction with these receptors results in narrowing of the blood vessels in the brain, anti-inflammatory effects and reduction of pain signalling. If licenced, STS101 will provide an additional treatment option for the acute treatment of migraine with or without aura.

Proposed Indication

The acute treatment of migraine, with or without aura.[1]

Technology

Description

STS101 is a nasal powder formulation of dihydroergotamine (DHE) that incorporates advanced drug particle engineering technologies and a quick and easy-to-use nasal delivery device.[2] DHE is an agonist of 5-HT_{1B} and 5-HT_{1D} serotonin receptors. As a result of its 5-HT_{1B} agonist activity, DHE causes vasoconstriction. The effect of its 5-HT_{1D} agonist activity is a reduction in vasodilation mediated by inhibition of calcitonin gene-related peptide (CGRP) release, a pro-inflammatory, vasoactive peptide with a well-established causative role in migraine. DHE's effects via 5-HT_{1D} receptors also result in inhibition of pain signal transmission within the trigeminovascular system, the activation and sensitization of which plays a key role in migraine pathophysiology. Following binding to 5-$HT_{1B/1D}$ receptors, DHE slowly dissociates, potentially contributing to its long-lived anti-migraine effects. DHE also interacts with adrenergic receptors to modulate nociception pathways. DHE reverses central sensitization of central trigeminovascular neurons and produces anti-inflammatory effects via modulation of the MAP kinase/phosphatase system.[3]

STS101 is in clinical development for the acute treatment of migraines, with or without aura (NCT04940390, NCT04406649). In these phase III trials, STS101 is administered as a nasal powder.[1]

Key Innovation

STS101 is a novel drug-device combination product containing a powder formulation of DHE that is self-administered into a single nostril by an air-driven, single-use, disposable nasal delivery device that does not require assembly or priming. Advantages of the STS101 delivery device include ease and speed of preparation, and quick and simple intranasal administration. STS101 administration results in rapid and sustained drug absorption via the nasal mucosa to achieve DHE plasma concentrations that have been demonstrated to be effective. There continues to be a significant unmet clinical need for a non-injected DHE dosage form that can be quickly and easily self-administered by migraine patients and results in rapid, consistent, and robust efficacy without significant adverse events.[2]

If licenced, STS101 will provide an additional treatment option for the acute treatment of migraines.

Regulatory & Development Status

STS101 does not currently have Marketing Authorisation in the EU/UK for any indication.

STS101 is not in phase II/III clinical development for any other indications.

Patient Group

Disease Area and Clinical Need

A migraine is usually a moderate or severe headache felt as a throbbing pain on one side of the head. Many people also have symptoms such as feeling nausea, vomiting, and increased sensitivity to light or sound. Migraines without aura are the most common type, where the migraine happens without warning signs such as seeing flashing lights.[4] This type of migraine manifests in attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and

phonophobia. Migraines with aura consist of recurrent attacks, lasting minutes, of unilateral fully-reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.[5] The exact cause of migraines is unknown, but they are thought to be the result of abnormal brain activity temporarily affecting nerve signals, chemicals and blood vessels in the brain. It is not clear what causes this change in brain activity, but it is possible that a patient's genes make them more likely to experience migraines as a result of a specific trigger. There are many possible migraine triggers including: hormonal changes; emotional triggers such as stress or anxiety; physical triggers such as tiredness and shoulder tension; dietary triggers; and environmental triggers such as bright lights and certain medicines.[6]

It is estimated that there are 190,000 migraine attacks experienced every day in England. Prevalence has been reported to be 5-25% in women and 2-10% in men.[7] In England (2020/21), there were 27,290 hospital admissions with primary diagnosis of migraine (ICD-10 code G43), and 34,814 finished consultant episodes (FCEs), resulting in 25,807 FCE bed days and 4,867 day cases.[8]

Recommended Treatment Options

Monotherapy, with either aspirin, ibuprofen, or a 5HT1-receptor agonist ('triptan') is recommended as first-line treatment and should be taken as soon as the patient knows that they are developing a migraine. Sumatriptan is the 5HT1-receptor agonist of choice. Alternative 5HT1-receptor agonists include almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, and zolmitriptan. In patients who do not respond to one 5HT1-receptor agonist, a different 5HT1-receptor agonist should be tried as response can be variable between patients. Other NSAIDs that may be used for the treatment of acute migraine include, naproxen (unlicensed indication), tolfenamic acid, and diclofenac potassium. Treatment with paracetamol can be considered in patients who are unable to take other acute treatment options. In patients who fail to respond to monotherapy, combination therapy with sumatriptan and naproxen can be given.[9]

Clinical Trial Information

Trial	**SUMMIT,** NCT04940390; A Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of STS101 (Dihydroergotamine Nasal Powder) in the Acute Treatment of Migraine **Phase III** – Recruiting **Location(s):** US **Primary completion date:** September 2022
Trial Design	Randomised, parallel assignment, double-blinded, placebo-controlled
Population	N=1400 (planned); Subjects with at least 1-year history of migraines (with or without aura); Aged 18 to 65 years
Intervention(s)	STS101 nasal powder
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcomes:** • Pain freedom at 2 hours [Time frame: 2 hours post-dose] • Freedom from most bothersome symptom at 2 hours [Time frame: 2 hours post-dose]
Results (efficacy)	-

Results (safety)	-

Trial	**ASCEND,** NCT04406649; An Open-Label, 12-Month Study to Evaluate the Safety and Tolerability of STS101 (Dihydroergotamine Nasal Powder) in the Acute Treatment of Migraine **Phase III** – Active, not recruiting **Location(s):** US **Primary completion date:** December 2022
Trial Design	Single group assignment, open-label
Population	N=482 (actual); Subjects with at least 1-year history of migraines (with or without aura); Aged 18 to 65 years
Intervention(s)	STS101 nasal powder
Comparator(s)	No comparator
Outcome(s)	**Primary outcome:** • Incidence of treatment-emergent adverse events [safety and tolerability] [Time frame: up to 12 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**EMERGE,** NCT03901482; A Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of Single Doses of STS101 (Dihydroergotamine Nasal Powder) in the Acute Treatment of Migraine **Phase III** – Completed **Location(s):** US **Study completion date:** August 2020
Trial Design	Randomised, parallel assignment, double-blinded, placebo-controlled
Population	N=1201 (actual); Subjects with at least 1-year history of migraines (with or without aura); Aged 18 to 65 years
Intervention(s)	STS101 nasal powder low dose or high dose
Comparator(s)	Matched placebo
Outcome(s)	**Primary outcomes:** • Pain freedom at 2 hours [Time frame: 2 hours post-dose] • Freedom from most bothersome symptom at 2 hours [Time frame: 2 hours post-dose] See trial record for full list of other outcomes

Results (efficacy)	Both dosage strengths of STS101 demonstrated statistically significant effects on both freedom from pain and most bothersome symptom by three hours post-dose and later time points. The high dose demonstrated numerical superiority to placebo at all time points (15 minutes to 48 hours post-dose).[10]
Results (safety)	Both STS101 dosage strengths were well-tolerated in the EMERGE trial, with low adverse event rates and no serious adverse events reported.[10]

Estimated Cost

The cost of STS101 is not yet known.

Relevant Guidance

NICE Guidance

- NICE technology appraisal. Lasmiditan for treating acute migraine (GID-TA10807). Expected March 2023.
- NICE technology appraisal. Rimegepant for treating or preventing migraine (GID-TA10839). Expected March 2023.
- NICE clinical guideline. Headaches in over 12s: diagnosis and management (CG150). September 2012.
- NICE interventional procedure guidance. Transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine (IPG559). 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. Transcranial magnetic stimulation for treating and preventing migraine (IPG477). January 2014.
- NICE interventional procedure guidance. Percutaneous closure of patent foramen ovale for recurrent migraine (IPG370). December 2010.

NHS England (Policy/Commissioning) Guidance

- NHS England. NHS Standard Contract for Specialised Pain. D08/S/a.
- NHS England. NHS Standard Contract for Neurosurgery. D03/S/a.
- NHS England. Clinical Commissioning Policy: Occipital Nerve Stimulation for Adults with Intractable Chronic Migraines and Medically Refractory Chronic Cluster Headaches. D08/P/c. July 2015.

Other Guidance

- Scottish Intercollegiate Guidelines Network. Pharmacological management of migraine. 2018.[11]
- Berkshire West Integrated Care System. Migraine: Acute Therapy Guidelines. 2015.[12]
- British Association for the Study of Headache. Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type Headache, Cluster Headache, Medication-Overuse Headache. 2010.[13]

Additional Information

Satsuma Pharmaceuticals did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in

development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

References

1 Clinicaltrials.gov. *A Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study to Assess STS101 in the Acute Treatment of Migraine (SUMMIT). Trial ID: NCT04940390*. 2021. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04940390 [Accessed 16 June 2022].

2 Albrecht D, Iwashima M, Dillon D, Harris S, Levy J. A Phase 1, Randomized, Open-Label, Safety, Tolerability, and Comparative Bioavailability Study of Intranasal Dihydroergotamine Powder (STS101), Intramuscular Dihydroergotamine Mesylate, and Intranasal DHE Mesylate Spray in Healthy Adult Subjects. *Headache: The Journal of Head and Face Pain*. 2020;60(4):701-12. Available from: https://doi.org/10.1111/head.13737.

3 Satsuma Pharmaceuticals. *What is Dihydroergotamine (DHE)?* Available from: https://www.satsumarx.com/areas-of-focus/dihydroergotamine/ [Accessed 16 June 2022].

4 National Health Service. *Overview: Migraine.* 2019. Available from: https://www.nhs.uk/conditions/migraine/ [Accessed 10 January 2022].

5 The International Headache Society. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211. Available from: https://doi.org/10.1177/0333102417738202.

6 National Health Service. *Causes: Migraine.* 2019. Available from: https://www.nhs.uk/conditions/migraine/causes/ [Accessed 10 January 2022].

7 National Institute for Health and Care Excellence. *Lasmiditan for treating acute migraine: Draft scope.* 2021. Available from: https://www.nice.org.uk/guidance/gid-ta10807/documents/draft-scope-post-referral [Accessed 20 July 2022].

8 NHS Digital. *Hospital Admitted Patient Care Activity 2020-21.* 2021. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2020-21 [Accessed 7 June 2022].

9 National Institute for Health and Care Excellence. *Migraine.* Available from: https://bnf.nice.org.uk/treatment-summaries/migraine/ [Accessed 10 June 2022].

10 Satsuma Pharmaceuticals. *Satsuma Pharmaceuticals Announces Topline Results from EMERGE Phase 3 Trial of STS101 for the Acute Treatment of Migraine.* 2020. Available from: https://investors.satsumarx.com/2020-09-10-Satsuma-Pharmaceuticals-Announces-Topline-Results-from-EMERGE-Phase-3-Trial-of-STS101-for-the-Acute-Treatment-of-Migraine [Accessed 16 June 2022].

11 Scottish Intercollegiate Guidelines Network. *Pharmacological management of migraine.* 2018. Available from: https://www.sign.ac.uk/sign-155-migraine [Accessed 12 January 2022].

12 Berkshire West Integrated Care System. *Migraine: Acute Therapy Guidelines.* 2015. Available from: https://www.berkshirewestccg.nhs.uk/media/2317/apc-clindoc-012-migraine-acute-therapy-guidelines.pdf [Accessed 16 June 2022].

13 British Association for the Study of Headache. *Guidelines for All Healthcare Professionals in the Diagnosis and Management of Migraine, Tension-Type, Cluster and Medication-Overuse Headache.* 2010. Available from: https://bash.org.uk/wp-content/uploads/2012/07/10102-BASH-Guidelines-update-2_v5-1-indd.pdf [Accessed 12 January 2022].

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