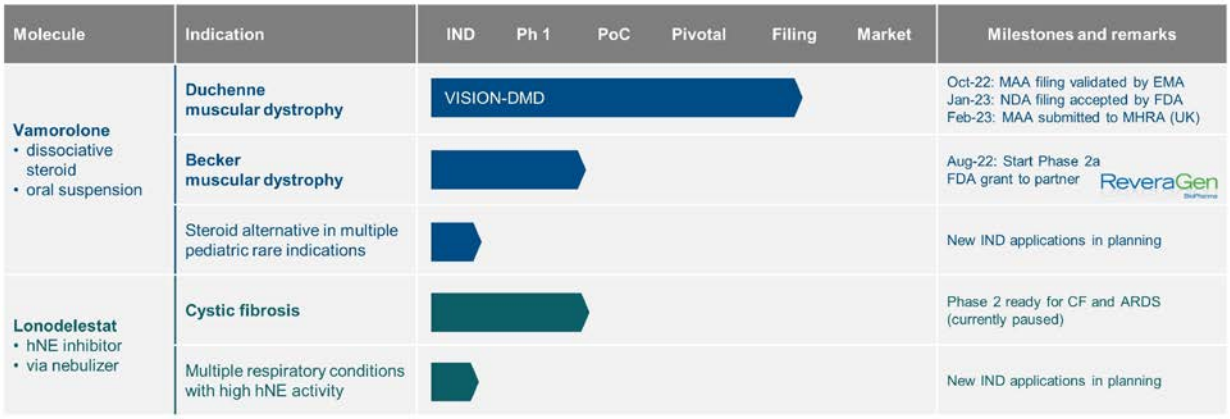
RARE DISEASE FOCUS

Our Pipeline

Passionate about providing treatment options for rare diseases, Santhera focuses its efforts on promising therapeutic options for rare **neuromuscular** and **pulmonary** diseases with high unmet medical need.



Vamorolone worldwide license from ReveraGen in Sep 2020; Lonodelestat worldwide license from now Spexis in Feb 2018; Lonodelestat formerly POL6014
PoC: proof of concept; EMA: European Medicines Agency; MHRA: Medicines and Healthcare products Regulatory Agency

Vamorolone, our lead pipeline candidate, is under regulatory review for the treatment for Duchenne muscular dystrophy (**DMD**) in the U.S. and Europe. In January 2023, the U.S. Food and Drug Administration (**FDA**) accepted the filing of a new drug application (**NDA**) and Santhera expects an approval decision by October 26, 2023, the PDUFA target decision date. In the EU and the United Kingdom, corresponding marketing authorization applications (**MAA**) were submitted in September 2022 and February 2023, respectively, and approval decisions are expected in both regions in late 2023.

Lonodelestat, in early clinical stage, is an innovative new investigational drug for which Phase 2a studies are ready in the prime indication acute respiratory distress syndrome (**ARDS**) and in cystic fibrosis (**CF**). Owing to financial and human resource constraints, further work is currently paused.

Both vamorolone and lonodelestat represent **platform-type pipeline molecules**, each with potential for outlicensing or development in a range of additional indications beyond DMD, ARDS and CF, respectively, in collaboration with partners. For vamorolone, an FDA-funded Phase 2 clinical trial is ongoing in Becker muscular dystrophy (**BMD**), a progressive muscle wasting disease similar to DMD but usually milder. In addition, the product is being evaluated as a steroid alternative for multiple pediatric rare diseases in the planning phase. Beyond neuromuscular diseases like DMD and BMD, Santhera believes vamorolone to have the potential to treat certain other inflammatory diseases with high unmet medical need. For lonodelestat, based on its mode of action as an inhibitor of human neutrophil elastase (**hNE**), multiple respiratory conditions which are characterized by high hNE activity are under evaluation.

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Vamorolone Highlights

Vamorolone, proposed as a dissociative steroid, has been developed for patients with Duchenne muscular dystrophy (DMD) who require an anti-inflammatory, muscle preserving treatment with a potentially differentiated safety and tolerability profile, starting at an early stage. The successfully completed clinical program aims at offering an alternative to the standard of care in DMD and culminated in the filing of a new drug application (NDA) to the U.S. FDA and marketing authorization applications (MAA) to health authorities in the EU and the UK. Subject to regulatory approvals, which are expected in late 2023, Santhera plans to launch vamorolone in the U.S. and first markets in Europe shortly thereafter. Vamorolone is an investigational medicine and is currently not approved for use by any health authority.

Duchenne muscular dystrophy

DMD is one of the most common and devastating types of muscular degeneration affecting 30,000 - 35,000 patients in U.S. and EU combined. It is an inherited condition, caused by mutations in specific regions (so-called exons) of the gene that encodes dystrophin in the cell nucleus, and primarily affects boys starting at an age between three and five years on average. DMD is characterized by a loss of a protein called dystrophin, which links the muscle cytoskeleton and extracellular matrix to maintain muscle integrity, acting as a shock absorber preventing muscle cell damage when muscle fibers contract and relax with use. This results in progressive muscle weakness, loss of muscle tissue and early illness and death due to cardio-respiratory failure. Patients are commonly unable to walk by their teenage years. Progressive respiratory muscle weakness leads to a need for mechanical ventilation to prolong the life of the patient beyond the late teenage years.

Current and emerging treatment options for DMD

Numerous potential treatments using different therapeutic approaches are in clinical development. Physicians can expect new options to treat DMD to emerge, allowing them to tailor therapies to individual needs including combining treatments to create the 'best mix' for each patient.

Glucocorticoids are effective anti-inflammatory agents and current standard of care in DMD. They are prescribed in order to slow the decline in muscle strength and function caused by DMD regardless of the genetic mutation underlying DMD. There is currently growing evidence to suggest that continued use of glucocorticoids may be beneficial beyond the time of loss of ambulation and in later stages of disease. However, their long-term use is hindered by their well-known side effects (e.g. weight gain, cushingoid features, behavioral problems, stunted growth and increased rate of fractures) that often result in down-titration to subtherapeutic doses to manage tolerability issues and eventually premature discontinuation of treatment. There is a high medical need for a treatment providing steroidal efficacy with a more benign tolerability and safety profile.

Non-steroid therapies include several approaches targeting the genetic defect or treating symptoms. Exon skippers (available to patients) aim to restore functional dystrophin. They work by 'skipping' over the mutated exon, thereby enabling the production of a truncated partially functional dystrophin protein. As exon skippers are specific for certain mutations, they typically only work in subpopulations of DMD-patients. Gene therapy approaches

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aim to deliver functional copies of a shortened dystrophin ('mini- or micro-dystrophin') gene to the affected muscles. In clinical development programs, gene therapy is commonly evaluated in addition to a base therapy with glucocorticoids. While gene therapy holds promise for treating DMD, no such treatment has as of today gained marketing authorization. A range of developmental therapies address DMD disease symptoms with treatments focusing on muscle development and protection being most advanced.

All approaches share one objective: slow the progression of muscle weakness, improve quality of life and prolong life expectancy for individuals with this devastating disease. It is the combination of these different mechanistic approaches that may lead to improved and/or synergistic treatment strategies, possibly also altering the current standard of care. Glucocorticoids have long been a staple in the treatment of DMD and are expected to continue playing a vital role in combination therapies.

Novel mode of action of vamorolone drives its potentially differentiated clinical profile

Vamorolone is proposed as a first-in-class, dissociative steroidal anti-inflammatory drug candidate with a novel mechanism of action and pharmacological profile, i.e. it aims at having the structural properties required for its desired clinical action, but structural properties which are believed to limit side effects or safety concerns. Preclinical studies have shown that like other glucocorticoids vamorolone induces transrepression, thus retaining steroid-like anti-inflammatory properties. However, unlike glucocorticoids, vamorolone minimizes transactivation, the main cause of undesirable side effects of glucocorticoid drugs, through subtle modification to the steroidal backbone.

Collectively, this potentially novel molecule retains steroid like anti-inflammatory efficacy but uniquely may be growth- and bone-sparing with a dose dependent profile for other common side effects typically associated with chronic glucocorticoids use. In addition, preclinical studies have also shown that vamorolone is a mineralocorticoid antagonist which, unlike other glucocorticoids, may translate into additional benefits that require further investigation.

Vamorolone was well tolerated in clinical studies, and its potentially differentiated safety profile may allow treating physicians to initiate and maintain treatment with vamorolone for longer than current standard of care. Based on its distinct structure, as well as its pharmacologic and clinical differences, vamorolone has been proposed as a new pharmacological class.

Positive pivotal VISION-DMD study establishing efficacy with statistical significance

VISION-DMD was a Phase 2b study comprising a (1) pivotal double-blind 24-week period to demonstrate efficacy and safety of vamorolone (2 and 6 mg/kg/day) versus placebo and prednisone (0.75 mg/kg/day, internal control arm), followed by a (2) 24-week period to evaluate the maintenance of efficacy and collect additional longer-term safety and tolerability data. 121 ambulant boys aged 4 to <7 years with DMD were included in the study. The trial met its primary endpoint of superiority in change of time to stand from supine position (**TTSTAND**) velocity with vamorolone 6 mg/kg/day versus placebo (p=0.002) at 24 weeks (period 1).

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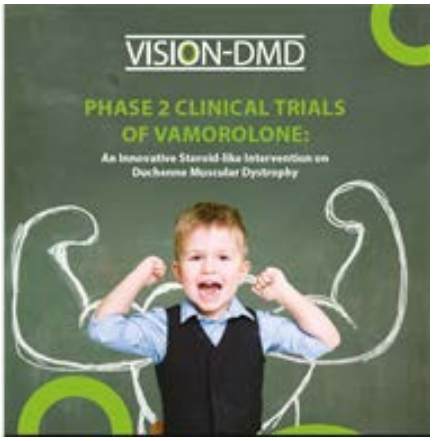

Vamorolone 6 mg/kg/day also met its secondary efficacy endpoints – including six-minute walk test (**6MWT**), time to run/walk 10 meters (**TTRW**) – and no statistically significant differences were observed between vamorolone and prednisone.

During the second 24 weeks of this 48-week study (period 2), all participants received vamorolone. Participants from the placebo and prednisone arms were randomized to either the 2 or 6 mg/kg/day dose of vamorolone and the vamorolone arms continued on their existing dose. Efficacy observed at 24 weeks for vamorolone 6 mg/kg/day was maintained across multiple endpoints over 48 weeks. In study participants starting on prednisone 0.75 mg/kg/day and switching to vamorolone 6 mg/kg/day after 24 weeks, efficacy was maintained across all functional endpoints.

Clinical data indicate a potentially favorable and differentiated safety and tolerability profile of vamorolone

Based on the available clinical data, vamorolone is believed to offer the efficacy of glucocorticoids with a favorable safety and tolerability profile, which would allow physicians to maintain chronic treatment for longer and could therefore represent an alternative to current standard of care.

Treatment with vamorolone 6 mg/kg/day was well tolerated with an incidence of clinically relevant adverse events similar to placebo. Whilst the safety profile of vamorolone shares some risks with those described with glucocorticoids, such as adrenal suppression, cushingoid features or weight gain in a dose dependent manner, the available clinical data shows clinically important differences indicating an improved safety profile:

- *Absence of deleterious effects on bone metabolism with the potential to reduce vertebral fractures.* Vamorolone has shown that it does not depress bone biomarkers, allows for bone biomarkers that were depressed because of prednisone treatment to recover after switching to vamorolone, and results also indicate fewer and less severe spinal fractures after long-term treatment with vamorolone compared to an external control study.
- *No stunting of growth.*
  No growth stunting has been observed in the pivotal VISION- DMD study and over the 30 months duration of extension treatment with vamorolone.
- *Reduced incidence, frequency and severity of behavior-related events.*
  Results showed a lower risk for developing clinically relevant behavior problems affecting the psychosocial adjustment of children with DMD compared with the current standard of care.
- *Lower frequency and severity of overall treatment emergent adverse events compared to prednisone.* While vamorolone and prednisone show comparable powerful anti-inflammatory properties, findings from clinical studies to date indicate a more benign tolerability and safety profile of vamorolone.

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Potential benefits of vamorolone in broader age groups of DMD patients studied in Phase 2 trial

An ongoing open-label, multiple dose Phase 2 study (VBP-006, ClinicalTrials.gov ID: NCT05185622) is evaluating the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of vamorolone 2 or 6 mg/kg/day over a treatment period of 12 weeks in steroid-naïve boys aged 2 to <4 years as well as boys aged 7 to <18 years who are currently untreated but may have taken glucocorticoids before. The study, which aims to enroll 54 participants and is part of the pediatric investigation plan (PIP) to support the authorization of a medicine for children, started in March 2022 and completion is expected by year-end 2024. Defeat *Duchenne Canada*, a patient advocacy group providing leadership in research, advocacy and support in the fight to defeat DMD, is supporting the study.

Vamorolone in regulatory review – first U.S. and EU launches anticipated in late 2023

In the U.S., the Food and Drug Administration (**FDA**) has set October 26, 2023, as the Prescription Drug User Fee Act (**PDUFA**) target action date upon which approval of the new drug application (**NDA**) for vamorolone in DMD is expected. In the EU, a corresponding MAA has been validated and is under review by the European Medicines Agency (**EMA**) with an expected approval in late 2023. Subject to approvals, Santhera plans to launch vamorolone in both the U.S. and the EU in late 2023. In February 2023, post balance sheet date, Santhera submitted an MAA for vamorolone in DMD to the UK Medicines and Healthcare products Regulatory Agency (**MHRA**).

Vamorolone has been granted Orphan Drug status in the U.S. and in Europe for DMD and has received Fast Track and Rare Pediatric Disease designations by the U.S. FDA and Promising Innovative Medicine (**PIM**) status from the UK MHRA for DMD.

Vamorolone in Becker muscular dystrophy – additional indications under evaluation

In August 2022, the first patient was dosed in a Phase 2a clinical trial of vamorolone in Becker muscular dystrophy (**BMD**). The trial is a randomized, double-blind, placebo-controlled study that intends to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory clinical efficacy on motor function out-comes of daily vamorolone compared to placebo over a treatment period of 24 weeks in 39 males with BMD between 18 and under 65 years of age (ClinicalTrials.gov ID: NCT05166109). Two thirds of participants will receive vamorolone and one third will receive placebo. Partner ReveraGen received a USD 1.2 million grant from the FDA to fund this Phase 2a clinical trial.

BMD is an inherited condition that is caused by partial loss of function of the dystrophin protein in muscle tissues and some non-muscle cells, with progressive dysfunction of skeletal muscles and/or heart muscle (cardiomyopathy). In contrast to DMD, where a complete loss of dystrophin is present, BMD has high clinical variability with patients of various ages. Some BMD patients lose the ability to walk as the disease progresses, while others do not. The severity of BMD ranges from nearly as severe as DMD to asymptomatic.

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With regards to additional indications, Santhera will focus its development plan on rare pediatric conditions where a product profile such as displayed by vamorolone is expected to represent clear clinical benefit over current standards of care. In parallel, Santhera is evaluating vamorolone's potential in treating certain other inflammatory and non-inflammatory diseases with high unmet medical need beyond DMD and BMD, to be pursued with partners.

Achievements

- Feb 27, 2023: Submission of MAA to the UK MHRA for vamorolone in DMD.
- Jan 9, 2023: U.S. FDA accepted the NDA filing for vamorolone in DMD with October 26, 2023, PDUFA date.
- Oct 31, 2022: EMA validated the MAA for vamorolone in DMD.
- Oct 27, 2022: Completion of NDA submission to the U.S. FDA for vamorolone in DMD.
- Oct 3, 2022: Submission of a MAA to the EMA for vamorolone in DMD.
- Aug 22, 2022: First patient dosed in a Phase 2 pilot study to assess vamorolone in BMD.
- Mar 29, 2022: Start of rolling submission of NDA with the FDA for vamorolone in DMD.
- Jan 4, 2022: Exclusive license agreement for vamorolone in rare diseases in Greater China with Sperogenix Therapeutics

Near-term milestones

- Q3-2023: CHMP opinion on the vamorolone MAA to the EMA
- Oct 26, 2023: PDUFA target action date; U.S. FDA approval of the NDA for vamorolone in DMD expected.
- Late 2023: EU approval subject to a positive CHMP opinion.
- Late 2023: Subject to approvals, Santhera plans to launch vamorolone in both the U.S. and in Europe.