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An open-label study to collect long-term safety and efficacy data from boys with DMD who have completed prior studies with vamorolone (GUARDIAN Study)

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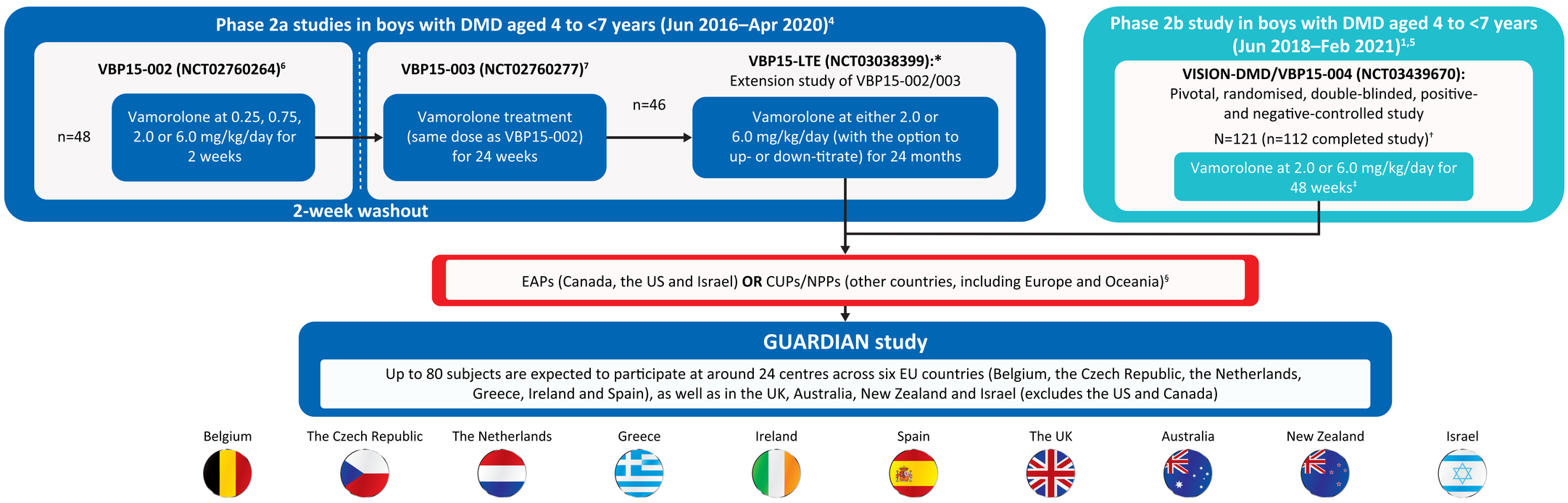
Background

- Vamorolone, a novel dissociative corticosteroid with a chemical structure distinct from classic corticosteroids, was recently approved for the treatment of patients with Duchenne muscular dystrophy (DMD) in the US (in patients aged ≥2 years) and the European Union (EU) (in patients aged ≥4 years).[1–3]
- The efficacy and safety of vamorolone in boys with DMD (aged 4 to <7 years) was previously investigated in randomised Phase 2a studies (VBP15-002/003/LTE) and a Phase 2b study (VBP15-004 [VISION-DMD]) (**Figure 1**).[1,4,5]
  - After 30 months in VBP15-LTE, and 48 weeks in VBP15-004, treatment with vamorolone was associated with similar efficacy to prednisone in timed function tests, and improved linear growth,[1,4,5] favourable bone biomarker profile,[1,4,5] and fewer behavioural problems.[1,5]
- Boys who completed studies VBP15-002/003/LTE and VBP15-004 were offered access to continued treatment with vamorolone 2.0 to 6.0 mg/kg/day if they enrolled in one of several country-specific programmes (compassionate use programmes [CUPs], expanded access programmes [EAPs] or named patient programmes [NPPs]) (**Figure 1**).
- Here we describe the design and initiation of GUARDIAN, an open-label, multicentre study that will collect long-term safety and efficacy data from boys with DMD who participated in the clinical development programme and are staying on continuous treatment with vamorolone for up to 8 years.

Objectives of the GUARDIAN study

- The primary objective is to evaluate vertebral fractures upon long-term treatment with vamorolone.
- Secondary objectives/endpoints include evaluating non-vertebral fractures, cataracts, puberty delay, weight/height/body mass, changes in muscle function and overall safety.
- Exploratory objectives/endpoints include evaluating cardiomyopathy and bone-age delay as well as long-term compliance with treatment, impact of treatment on quality of life and pharmacoeconomics.

Figure 1. Overview of the previous vamorolone treatment programmes



CUP, compassionate use programme; DMD, Duchenne muscular dystrophy; EAP, expanded access programme; EU, European Union; NPP, named patient programme; UK, United Kingdom; US, United States.
**A total of 41 subjects completed the VBP15-LTE study. Reasons for discontinuation: withdrawal by parent or guardian in the VBP15-003 (n=2) and VBP15-LTE study (n=5). †Reasons for discontinuation: withdrawal by parent or guardian (n=3), adverse events (n=2), physician decision (n=1), other reasons (n=3). ‡In the first part of the study, participants were randomised to receive daily doses of vamorolone 2.0 or 6.0 mg/kg/day, prednisone 0.75 mg/kg/day or placebo for 24 weeks. Participants then went through a transition period of 4 weeks where the placebo and prednisone were tapered to zero. In the second part of the study, participants received vamorolone at a dose of 2.0 or 6.0 mg/kg/day for 20 weeks and were not able to up- or down-titrate. §Adjusted to the regulations of their respective countries.*

GUARDIAN study design

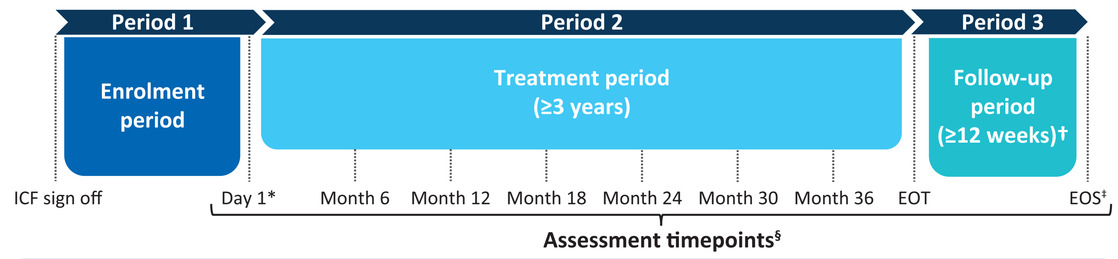
- The Phase 4, open-label, multicentre GUARDIAN study is expected to collect long-term safety and efficacy data on vamorolone in up to 80 boys with DMD who participated in the clinical development programme and are staying on continuous treatment with vamorolone for up to 8 years.
- Key inclusion and exclusion criteria are presented in **Table 1**.
- The study is divided into three periods: the enrolment period, treatment period and follow-up period (**Figure 2**).
  - Subjects will be assessed every 6 months after the first dose of vamorolone, alternating between a "Standard visit" (at Months 6, 18, 30, etc) and a "Full visit" (at Months 12, 24, 36, etc), which includes additional testing such as blood sampling and quality of life.
- All subjects weighing <40 kg will continue to receive the same dose of vamorolone as in the previous CUP, NPP or EAP at the time they are enrolled (between 2.0 to 6.0 mg/kg/day).
  - For subjects weighing ≥40 kg, the dose will be capped at a range of 80–240 mg once daily.
  - The Investigator may adjust doses within the dose range based on tolerability.
- In addition to vamorolone treatment and study-specific assessments, subjects will receive standard-of-care treatments and procedures for the management of their DMD.
- The study is expected to start in the third quarter of 2024, with the first subject expected to be enrolled in the fourth quarter of 2024. The study will conclude when the last subject enrolled has been treated with vamorolone for ≥3 years.

Table 1. Key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Subject and/or subject's parent(s) or legal guardian has provided written informed consent.	Any medical condition which, in the opinion of the Investigator, would affect study participation, performance or interpretation of study assessments.
Subject has previously completed either the VBP15-LTE or VBP15-004 study, and transitioned through the CUP, NPP or EAP.	Vamorolone treatment discontinued for ≥6 months within the year prior to enrolment for a non-safety reason.
Subject is on vamorolone on the day of enrolment.	Vamorolone treatment previously discontinued at any time for a safety reason.
Subject and parent/legal guardian are willing and able to comply with the protocol schedule, assessments and requirements.	Severe hepatic impairment.

CUP, compassionate use programme; EAP, expanded access programme; NPP, named patient programme.

Figure 2. GUARDIAN study design



Safety assessments:
- Central reading of lateral thoracolumbar spine and hand X-rays at baseline and every 2 years
- Evaluations: fractures, cardiology, vital signs, ophthalmology, Tanner stage and physical examination (including height and weight)
- Central laboratory analysis: haematology, biochemistry, LH, FSH, testosterone, HbA1c and cortisol
- Recording AEs, concomitant medications and vamorolone exposure

Efficacy assessments:
- TTSTAND
- NSAA
- 6MWT
- Ambulatory and non-ambulatory milestones

AE, adverse event; EOS, end of study; EOT, end of treatment; FSH, follicle-stimulating hormone; HbA1c, haemoglobin A1c; ICF, informed consent form; LH, luteinising hormone; NSAA, NorthStar ambulatory assessment; TTSTAND, time-to-stand test; 6MWT, 6-minute walk test.
**First dose of study treatment; †In cases where a subject discontinues study medication but switches to Agamree® (commercially available vamorolone), there is no follow-up period (EOT and EOS are combined); ‡The EOS visit should take place at least 3 months after study medication discontinuation; §Some assessment procedures (eg TTSTAND, NSAA and 6MWT) will only take place every 12 months.*

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Conflicts of interest

Ana de Vera, **Kerry Nip**, **Shabir Hasham** and **Pascal Charef**: employees of Santhera. **Sze Choong Wong**: consultancy at Santhera, Roche and Novartis

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