The GuardOne clinical trial: a first in-human, open-label, multinational phase 1/2 study of AVR-RD-02 ex vivo lentiviral vector, autologous gene therapy for Gaucher disease

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Guard1: Phase 1/2 study in Gaucher disease type 1
2 patient dosed to date

Guard1: Study design

**OBJECTIVES**
- Safety and tolerability
- Efficacy
- Engraftment

**PATIENTS**
- Enrollment goal: 8-16 patients
- 18-45-year-old males and females
- Confirmed diagnosis of GD1 considers:
  - Genotype
  - Deficient glucocerebrosidase enzyme activity
  - Clinical features consistent with GD1

GD1 patients (gated sequence)
- First 2 patients: ERT switch stable (ERT stable for ≥24 months; ERT cessation ≥2 weeks prior to transplant)
- Additional patients: ERT switch stable or treatment-naïve (no ERT or SRT in the last 12 months)

AVR-RD-02 has not been approved by FDA or by any other regulatory body and its safety and efficacy has not been established.
GD1, Gaucher disease type 1; ERT, enzyme replacement therapy; SRT, substrate reduction therapy; TH, first half

<table>
<thead>
<tr>
<th>&gt;8 weeks</th>
<th>6-8 weeks</th>
<th>Day 0</th>
<th>52-week follow-up</th>
<th>Additional 14 year follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Q-CGRI (baseline)</td>
<td>AVR-RD-02 infusion</td>
<td>Patient follow up (wks 1, 2, 4, 8, 13, 26, 39, 52)</td>
<td>Scheduled safety and efficacy assessments</td>
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<tr>
<td>Q-CGRI (cell viability)</td>
<td>Adherence (Q-CGRI cell condition)</td>
<td>Baseline assessments</td>
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<tr>
<td>Baseline assessment</td>
<td>Enzyme activity post lentiviral vector infusion</td>
<td>Controlling transgene expression</td>
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ERT cessation ≥2 weeks prior to infusion*

*Resumed post-infusion only if a patient meets pre-specified clinical criteria that suggest a need for additional treatment.

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### Guard1: Primary and secondary outcome measures

<table>
<thead>
<tr>
<th>Primary safety endpoints</th>
<th>Incidence and severity of AEs and SAEs</th>
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<tbody>
<tr>
<td></td>
<td>Changes in clinical laboratory values, vital signs, and ECG findings at Weeks 26 and 52</td>
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<tr>
<td>Primary engraftment endpoints</td>
<td>Changes in VCN in:</td>
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<tr>
<td></td>
<td>• PBL at Weeks 13, 26, 39, and 52</td>
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<td></td>
<td>• Bone marrow and progenitor cells at Weeks 26 and 52</td>
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<tr>
<td>Primary efficacy endpoints</td>
<td>Changes in spleen volume and liver volume at Weeks 26, 39, and 52</td>
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<tr>
<td></td>
<td>Changes in hemoglobin concentration, platelet counts and lyso-Gb1 levels at Weeks 13, 26, 39, and 52</td>
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<td>Secondary endpoints</td>
<td>Changes in GCase activity in peripheral blood leukocytes at Weeks 13, 26, 39, and 52</td>
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<td>ERT frequency and dosing between Weeks 26 through 52, inclusive</td>
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<td></td>
<td>Changes in anti-GCase antibodies at Weeks 5, 13, 26, 39, and 52</td>
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<td>Changes in bone mineral density at Week 52</td>
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<td>Changes in clinical and biomarker indices of Gaucher disease type 1 (e.g., chitotriosidase activity at Weeks 13, 26, 39, and 52 and BMB score at Weeks 26, 39, and 52)</td>
</tr>
</tbody>
</table>

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AE, adverse event; SAE, serious adverse event; ECG, electrocardiogram; VCN, vector copy number; Lyso-Gb1, Glucosylphosphoinositol; GCase, β-Glucosidase; BMD, bone mineral density; BMB, bone marrow burden.

### Baseline characteristics for Patient 1

<table>
<thead>
<tr>
<th>Age at diagnosis/symptom onset</th>
<th>3 months/20 months</th>
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<tbody>
<tr>
<td>Gender</td>
<td>Female</td>
</tr>
<tr>
<td>Mutation</td>
<td>Allele 1: 1448 T&gt;C [L444P]</td>
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<td></td>
<td>Allele 2: 1448 T&gt;C [L444P]</td>
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<tr>
<td>Medical history</td>
<td>Imiglucerase 40 U/kg q2weeks, age 8-31 years</td>
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<tr>
<td></td>
<td>Velaglucerase 2400 U (40 U/kg) q2weeks, age 31 years</td>
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<tr>
<td></td>
<td>Splenectomy, 22 months</td>
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<td></td>
<td>Bilateral hip replacement, 28 years</td>
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<td></td>
<td>H/o bilateral vitreectomy and intermittent migraine</td>
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<td></td>
<td>No CNS manifestations</td>
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<tr>
<td>Age at dosing</td>
<td>31 years</td>
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</table>

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CNS, central nervous system.
**ICIEM 2021**

14TH INTERNATIONAL CONGRESS OF INBORN ERRORS OF METABOLISM

21-23 NOVEMBER 2021, SYDNEY, AUSTRALIA

**GUARDI: PATIENT 1**

Lyso-Gb1 and chitotriosidase reduced below ERT baseline at 6 months

- **Lyso-Gb1** is a sensitive and specific marker of metabolite accumulation in Gaucher disease
  - Baseline (ON ERT): 32 ng/mL
  - 3 months (OFF ERT): 25 ng/mL
  - 6 months (OFF ERT): 18 ng/mL
  - 44% reduction

- **Chitotriosidase** is a marker of activated macrophages (Gaucher cells)
  - Baseline (ON ERT): 151 μU/mL
  - 3 months (OFF ERT): 125 μU/mL
  - 6 months (OFF ERT): 77 μU/mL
  - 49% reduction

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Lyso-Gb1 (plasma normal range: 0.5 - 1.2 ng/mL)
Chitotriosidase plasma activity normal range: 0.5 - 4.4 μU/mL
ERT, enzyme replacement therapy; Lyso-Gb1, glucosylceramidase

**GUARDI: PATIENT 1**

VCN trending as expected and platelet counts and hemoglobin in normal range at 6 months, despite being off ERT

- **Drug Product VCN/kg**
  - Patient 1: 3.7

- **Platelet Count**
  - Normal range

- **Hemoglobin**
  - Normal range

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Platelet count reference value adult: 130-400 x 10^9/L, hemoglobin reference value: males: 13.5-17.5 g/dL, females: 11.5-15.0 g/dL, grey line: local (quality) lab values; pink dots: central (efficiency) lab values; ERT, enzyme replacement therapy; VCN, vector copy number; PSL, peripheral blood leukocytes
No unexpected safety events 12+ months post dosing

No SAEs or AE related to drug product

AEs are consistent with myeloablative conditioning, drugs mandated by protocol or study procedures, underlying disease and pre-existing conditions

No SAEs reported

<table>
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<tr>
<th>Number of Patients Enrolled, n=2</th>
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<tr>
<td>AE reported, n=37</td>
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</table>

Event severity assessment

- 26 AEs were Grade 1 or Grade 2
- 11 AEs were Grade 3 or 4
  - Anemia, leukopenia, neutropenia, thrombocytopenia, eye pain, decreased appetite, dehydration, headache, hypophosphatemia, anemia, tachycardia

Event causality assessment

- 21 AEs definitely, probably or possibly related to busulfan (N= 1 patient dosed)
- 8 AEs definitely, probably or possibly related to G-CSF (N= 2 patients enrolled)
- 1 AE definitely, probably or possibly related to Plerixafor (N= 2 patients enrolled)

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Note: Safety database cut as of August 31, 2021
AE, adverse event; SAE, serious adverse event; G-CSF, granulocyte colony stimulating factor
*Two of the AEs, dehydration and decreased appetite, are noted as related to both G-CSF and busulfan administrations

Summary and conclusions

- Lentiviral gene therapy using AVR-RD-02 was completed in a patient with Gaucher disease type 1 in the Phase 1/2 Guard1 study
- No unexpected trends or safety concerns were identified 12+ months post dosing
- Six-month data from patient 1 show that a single IV infusion of AVR-RD-02 produces:
  - Engraftment of genetically modified cells in bone marrow
  - Reductions in lyso-Gb1 and chitotriosidase below ERT baseline
  - Platelet counts and hemoglobin levels within the normal range, despite being off ERT
- Initial results support the continued development of AVR-RD-02 as a single-dose therapy for adults with Gaucher disease type 1

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IV, intravenous; ERT, enzyme replacement therapy