LAVA-051 is well tolerated early in dose escalation with on-mechanism pharmacodynamics consistent with Vy9V82-T cell engagement

**Introduction**

- LAVA-051: 27kD humanized bispecific single domain antibody (VHH) that directly engages CD1d and the Vγ9Vδ2 TCR chain of Vy9V82-T cells to mediate potent killing of CD1d-expressing tumor cells.
- Engages 2 innate-like T cell populations with inherent antitumor activity: type 1 NKT cells (Nature Cancer 2020;1:1054-1065) and Vy9V82-T cells.
- CD1d: expressed by tumor cells in the majority of patients with CLL (chronic lymphocytic leukemia) and MM (multiple myeloma), while expression in AML (acute myeloid leukemia) is most pronounced on (myelo)monocytic subtypes.
- LAVA-051 has high potency with low potential for cytokine release. LAVA-051 has high potency with low potential for cytokine release.

**Patient Characteristics**

- Male/Female: 5/2
- Median age (range): 66 (60-75)
- Prior therapies, median (range): MM/CLL 5 (4-6) MM/CLL 4/3
- CD1d MF index* on tumor cells, median (range): 3 (1.5-7.8)

**Potential Signs of Activity**

- **CLL:**
  - Patient with R/R CLL (15 µg) experienced enlargement and tenderness of several CLL-affected lymph nodes (LN) accompanied by grade 2 fever early during Cycle 1, followed by a regression of the size of the LNs; this resembled a tumor-flare reaction.
  - Other causes of painful LN enlargement were ruled out.
  - Patient was assessed as having stable disease per CT scan and iwCLL criteria (2018).
  - Percent of clonal B cells in peripheral blood for this patient decreased from 41.8% at baseline to 8.9% at the start of Cycle 4.
  - Patient stopped after Cycle 5 due to COVID-19.

**Pharmacokinetics**

- **Dose vs AUC for Cycle 1 – Cohorts 1-4**

**Summary and Conclusions**

- LAVA-051 is first of a novel class of bispecific γδ T cell engagers with expected broad therapeutic window.
  - Bispecific single domain antibody engaging CD1d and Vγ9Vδ2-TCR chain of Vy9V82-T cells to mediate potent killing.
  - Low potential for CRS observed in preclinical models and clinical setting when Vy9V82-T cells are activated.
  - LAVA-051 has reached 100x the starting dose in CLL and MM. To date:
    - No CRS and no ICANS (ASTCT).
    - Significant increase in the CRS-related cytokine IL-6.
    - Most observed AEs have not been suspected to be related. No DLTs.
    - No ADA's detected to date.
    - Predictable and linear pharmacokinetics.
    - PD parameters reflect changes as expected per MoA:
      - Vy9V82-T cell activation markers (CD25 and CD69) were consistently upregulated following dosing, in each dose cohort.
      - Maximum measured Vy9V82-T cell receptor occupancy increased with higher dose cohorts.
      - NK cell activation was assessable and observed in one patient (cohort 3).
  - First signs of clinical activity in a CLL patient and a MM patient.
  - Trial continuing to enroll and escalate without step-dosing or premedication.
  - Clearance of IND will allow US sites to participate.
  - Plan to evaluate s.c. dosing and impact on PD parameters.

**Selected PD Parameters - Vy9V82 T Cell Frequency, Activation and Receptor Occupancy**

**Time on Treatment and Adverse Events**

- Cycle 1 Worst grade per patient TEAE Grade 22
- Time since first study treatment (days)

**Trial Design and Objectives**

- Open label, accelerated titration design, phase 1/2a study in patients with relapsed/refractory CLL, MM, and AML.
- LAVA-051 administered via a 2 hr intravenous infusion, or subcutaneous injection (day 1, 8 and twice a week thereafter).
- Primary objectives: investigate safety and tolerability of LAVA-051 and determine the recommended Phase 2 dose (RP2D) of LAVA-051.
- Secondary objectives include evaluation of PK, PD, immunogenicity and preliminary antitumor activity.
- Data cut-off date of presented data was 30 May 2022.

**LAVA-051: 27kD humanized bispecific single domain antibody (VHH) that directly engages CD1d and the Vγ9Vδ2-TCR chain of Vy9V82-T cells to mediate potent killing of CD1d-expressing tumor cells.**

**Data cut-off date of presented data was 30 May 2022.**

**CD1d: expressed by tumor cells in the majority of patients with CLL (chronic lymphocytic leukemia) and MM (multiple myeloma), while expression in AML (acute myeloid leukemia) is most pronounced on (myelo)monocytic subtypes.**