LAVA-051, a novel bispecific gamma-delta T-cell engager (Gammabody™), in relapsed/refractory MM and CLL: pharmacodynamic and early clinical data

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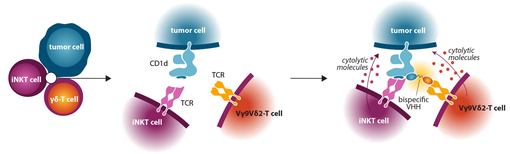
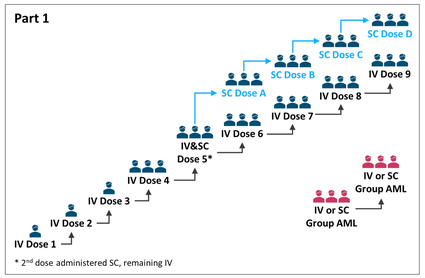
Introduction

- LAVA-051: 27kD humanized bispecific single domain antibody (VHH) that directly engages CD1d and the Vδ2-TCR chain of Vγ9Vδ2-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 Vγ9Vδ2-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 syndrome (CRS) affording an anticipated wide therapeutic window.

Trial Design and Objectives

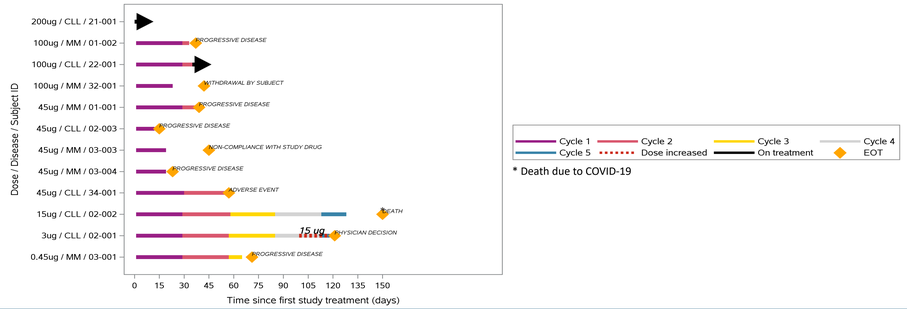


- Open label, accelerated titration design, phase 1/2a study in patients with relapsed/ refractory CLL, MM, and AML (NCT04887259).
- LAVA-051 administered via a 2 hr intravenous infusion, or subcutaneous injection (day 1, 8 and twice a week thereafter).
- Primary objectives: investigate safety and tolerability 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 11 NOV 2022.

Patient Characteristics

MM/CLL	6 / 6
Male/Female	8 / 4
Median age (range)	69 (59-76)
Prior therapies, median (range) – MM/CLL	4 (3-5) 5.5 (4-13)
ECOG (0/1)	6 / 6

Time on Treatment and Adverse Events



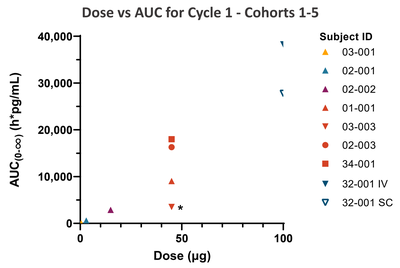
* Death due to COVID-19

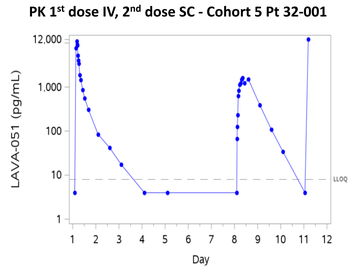
Cycle 1 Worst grade per patient TEAE Grade ≥2

	0.45 µg (N=1)		3 µg (N=1)		15 µg (N=1)		45 µg (N=3)		100 µg (N=3)		Total (N=6)
AE \ Relatedness	NS	S	NS	S	NS	S	NS	S	NS	S	
Anemia									1		1
Bone pain							1				1
Cancer pain	1								1		2
Contrast media allergy							1				1
Decreased appetite							1				1
Diarrhea							1				1
Drug hypersensitivity					1[A]						1
Dyspnea exertional							1				1
Fatigue							1				1
Hypercalcemia							1[C]				1
Hypoalbuminemia							1				1
Hypokalemia							1[C]				1
Hypomagnesemia							1[C]				1
Hypophosphatemia							1[C]				1
Infusion related reaction								1			1
Lumbar vertebral fracture							1				1
Motor dysfunction							1				1
Neutropenia							1	1			2
Pain in extremity							1				1
Pyrexia						1[B]					1
Rhinitis							1				1
Syncope							1				1
Upper limb fracture									1		1
White blood cell count decreased									1		1

NS = not suspected; S = suspected
A: Drug hypersensitivity Gr3 reported for CLL patient to allopurinol administered as TLS prophylaxis; allergy to allopurinol confirmed through repeat occurrence to single agent prophylaxis.
B: Fever Gr2 reported for CLL patient in conjunction with 'tumor flare'.
C: Diverse electrolyte imbalances reported for one MM patient.

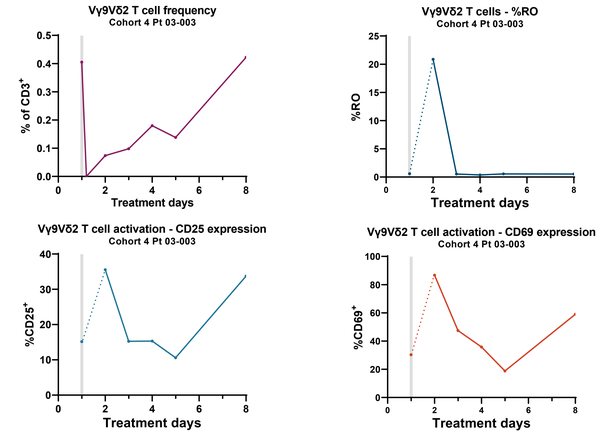
Pharmacokinetics

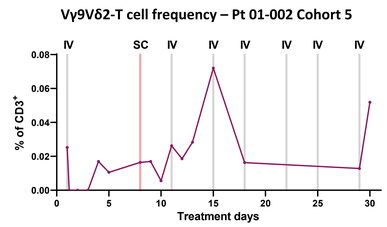




- Pharmacokinetics of LAVA-051 is linear.
- Bioavailability of SC: 74% compared to IV (based on data from Pt 32-001).

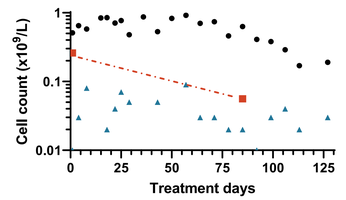
Selected PD Parameters - Vγ9Vδ2 T Cell Frequency, Activation and Receptor Occupancy





- PD reflect changes expected as per MoA for both IV and SC dosing.
  - Pronounced drop in Vγ9Vδ2-T cell frequency after dosing, likely reflective of Vγ9Vδ2-T cell re-distribution with subsequent recovery.
  - Observed drop after SC dosing is slightly delayed as compared to IV dosing, in line with delay in Cmax/peak by several hours after SC dose.
  - Vγ9Vδ2-T cell activation markers (CD25 and CD69) upregulated following dosing.

Pharmacodynamic Analysis Appears to Confirm Tumor Selectivity of LAVA-051



- Percent of PB clonal B cells of R/R CLL patient (15 µg) decreased from 41.8% at baseline to 8.9% at start of Cycle 4, with stable disease by CT scan.
- Numbers of normal CD1d expressing monocytes remained stable over time.

Summary and Conclusions

- LAVA-051 is the first of a novel class of bispecific γδ T cell engagers with expected broad therapeutic window.
- LAVA-051 has safely reached a dose of 200 µg (~400x the starting dose) in MM and CLL patients.
  - Most observed AEs have not been suspected to be related.
  - Frequency and severity of AEs have not correlated with increasing dose levels.
  - No CRS and no ICANS (ASTCT) and no clinically relevant increase in the CRS-related cytokine IL-6.
  - No DLTs.
- Linear pharmacokinetics and satisfactory bioavailability with subcutaneous dosing.
- PD parameters reflect changes as expected per MoA.
- Dose escalation in EU and US is actively continuing based on safety, PK, PD, and initial clinical activity.

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