**Clinical AML Study Design (ASLAN003-003)**

**Study Scheme**

- **Primary objectives:**
  - To determine the optimum dose of ASLAN003 monotherapy based on the efficacy, safety, and tolerability profile in AML patients who are ineligible for standard therapy.
  - To provide preliminary estimates of the efficacy of ASLAN003 at the optimum dose selected from Part 1.

- **Secondary objectives:**
  - To evaluate the pharmacokinetics of ASLAN003 in its metabolite LB186558 in patients with AML.
  - To further assess the safety and tolerability data of ASLAN003 at the optimum dose selected from Part 1.

- **Exploratory objectives:**
  - To examine the myeloid differentiation effects of ASLAN003 using assays including but not limited to in vitro flow cytometry assay.
  - To explore the relationships between molecular abnormalities and measures of clinical response in AML-related AML patients.

**Background**

- AML is a heterogeneous hematological malignancy.
- Limited treatment options exist for relapsed and refractory patients and patients ineligible for intensive therapy and these are associated with poor clinical outcomes.

- DHODH (DHODH) catalyzes the last step of de novo purine biosynthesis in the de novo purine synthesis pathway and is so important in cell division.

- A recent study (Sakakura et al., 2016) has identified DHODH as a critical enzyme in myeloid differentiation using an LB186558 (SDQ) that inhibits ASLAN003, a potent small molecule inhibitor of human DHODH with a good safety profile in Phase 1.

- ASLAN003 induced differentiation of AML blast cells in vitro and in vivo in mouse xenograft models. In addition, ASLAN003 induced differentiation in primary AML blast cells. ASLAN003 reduced tumor burden and proliferative survival in an AML FMS-Val, see (Poster FE).

**Clinical Summary**

**Cohort**

- ASLAN003 treatment after multiple prior treatments and ASLAN003: 18 treatment days
- ASLAN003 refractory disease after multiple prior treatments and ASLAN003: 6 treatment days
- ASLAN003 suspected differentiation syndrome with myeloid differentiation observed
- ASLAN003 stable disease with ASLAN003 treatment for at least 2 months; leucocytes, early recovery by investigator
- ASLAN003 Presentation of relapse at event enrolment rapidly progressed; 4 treatment days
- ASLAN003 Leukocytosis, early termination by investigator

**Safety and Tolerability Profile (Related Adverse Events)**

- **Adverse events:**
  - *grade 1:* less than 5% of patients;
  - *grade 2:* between 5% and 25% of patients;
  - *grade 3:* between 25% and 50% of patients;
  - *grade 4:* over 50% of patients

**Clinical Signs of Efficacy**

- *AML:* the patient is considered as having achieved clinical remission.
- *CR:* complete remission with or without incomplete recovery of peripheral hematopoietic precursors.
- *CRh:* complete remission with granulocyte recovery.
- *MRD:* minimal residual disease.
- *MRD 1:* MRD less than 0.01%
- *MRD 2:* MRD less than 0.1%
- *MRD 3:* MRD less than 1%
- *MRD 4:* MRD less than 10%
- *MRD 5:* MRD less than 100%

- *AML:* acute myeloid leukemia.
- *CR:* complete remission.
- *CRh:* complete remission with granulocyte recovery.
- *AML-MR D:* minimal residual disease.
- *MRD 1:* MRD less than 0.01%
- *MRD 2:* MRD less than 0.1%
- *MRD 3:* MRD less than 1%
- *MRD 4:* MRD less than 10%
- *MRD 5:* MRD less than 100%

**Clinical Study**

**Patient 0003**

- Suspected Differentiation Syndrome.

- After nearly 3 months on the study, the peripheral blasts of patient 0003 decreased in number gradually increased to 66%. There was also concurrent leukocytosis managed by hydroxyurea.

- The patient showed marked differentiation on peripheral blood films and differential counts. The bone marrow was not accessible because of medical reasons.

- The patient had underlying chronic lung infection, but also showed spontaneous symptoms of differentiation syndrome (hyperlipidemia, hypercalcemia). After 12 days from initiation of ASLAN003 treatment, the patient expired due to AML-related clinical deterioration.

**Patient 0007**

- Myeloid differentiation observed.

- Stable disease for more than 4 months.

- After 4 weeks on the trial, the peripheral blast percentage of patient 0007 decreased to 25%. Leucocyte percentage gradually increased to 50%.

- The patient showed early myeloid differentiation with peripheral lymphopenia and bone marrow stability. The blast and neutrophil percentages fluctuated.

**Patient 0011**

- Stable disease for more than 4 months.

- No treatment related SAP reported and the patient was on the trial for more than four months.

**Conclusion**

- This is the first report of clinical activity of a DHODH inhibitor in AML patients. Monotherapy with ASLAN003 was very well tolerated and showed encouraging signs of clinical activity in AML patients. This study is on-going and the optimal dose for AML is currently being determined.

- Of 14 evaluable patients, 4 patients showed clinical signs of efficacy (one had suspected differentiation syndrome with myeloid differentiation and 3 had long term stable disease including one showed early myeloid differentiation syndrome).

- Additional studies of ASLAN003 in combination with hypomethylating agent and chemotherapy will start in 2016.