Successful Emulation of IV Decitabine Pharmacokinetics with an Oral Fixed-Dose Combination of the Oral Cytidine Deaminase Inhibitor (CDAi) E7727 with Oral Decitabine, in Subjects with Myelodysplastic Syndromes (MDS): Final Data of Phase 1 Study

On Behalf of the ASTX727 Investigative Team

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Background and Clinical Hypothesis

- Intravenous (IV) Decitabine (DAC) is an approved therapy for MDS
- Oral bioavailability of DAC is low due to degradation in the gut by cytidine deaminase (CDA)
- MDS treatment requires continued treatment for long periods.
- An oral decitabine would provide significant benefit
- Development of a potent safe CDA inhibitor should enable decitabine oral bioavailability
E7727 – a Potent, Orally Active CDA inhibitor

- E7727, a novel potent CDA inhibitor ($IC_{50}$ is 0.28±0.06 µM)
- Pharmaceutically stable unlike other known CDA inhibitors such as tetrahydourouridine (THU)
- Safe and well tolerated in animals with no observed adverse events up to 1000 mg/kg (mice) and 200 mg/kg (monkey)
- Administering decitabine orally with low dose E7727 (1 mg/Kg) increases decitabine exposure 14-fold in animals (monkey)

Decitabine \[\text{E7727 inhibitor}\]
ASTX727: A New Oral HMA – Phase 1 Study

- **ASTX727** is a new oral combination drug of both *decitabine (DAC)* and the new CDA inhibitor *E7727*
- We designed a Phase 1 dose escalation study of ASTX727
- Primary Objective: To emulate DAC IV (20 mg/m$^2$) PK (AUC exposure) with a safe dose of oral ASTX727
- Secondary Objectives: Clinical Response, and PD (LINE-1 demethylation) of oral ASTX727
Adult patients with MDS Int-1; Int-2; or High Risk IPSS score, or CMML

All prior treatments (including HSCT) allowed except more than one cycle of DAC IV

Adequate hepatic and renal function
- Bilirubin ≤2 ULN; AST/ALT ≤ 2.5 ULN
- Serum creatinine ≤ 1.5 ULN or Cr CL >50 ml/min

Patients with AML (≥ 20% blasts in BM or PB) were excluded
MDS Int-1, Int-2, HR or CMML

DAC IV on Day 1 and Oral ASTX727 (E7727 40 mg + DAC 20 mg) Days 2-5
Review PK of Cohort N=6
↑↓ one drug per cohort until AUC goal is met

Patients continued on ASTX727 until Progression or Toxicity

Target Range
Oral DAC PK AUC ≥ 90% of IV DAC
ASTX727 Phase 1 Study Design
Dosing and PK Schedule

Dosing and PK Schedule:

- **Cycle ≥2 Oral ASTX727 (DAC+E7727) Days 1-5 Q 28 days**

**Day**

-3

**Serial PK**

**Cycle 1**

- **1**
- **2**
- **3**
- **4**
- **5**

**Serial PK**

**Pre-Dose**

**DAC Oral Alone**

**DAC IV Infusion**

1-h

20mg/m²

**DAC + E7727 Oral Combination**
• Goal: Oral ASTX727 combination with DAC AUC ≥90% of DAC IV AUC
• Maximum Tolerated Dose (MTD) not a goal

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
<th>Cohort 4</th>
<th>Cohort 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 mg DAC</td>
<td>20 mg DAC</td>
<td>20 mg DAC</td>
<td>40 mg DAC</td>
<td>30 mg DAC</td>
</tr>
<tr>
<td>40 mg E7727</td>
<td>60 mg E7727</td>
<td>100 mg E7727</td>
<td>100 mg E7727</td>
<td>100 mg E7727</td>
</tr>
<tr>
<td>N=6</td>
<td>N=6</td>
<td>N=6</td>
<td>N=6</td>
<td>N=19</td>
</tr>
</tbody>
</table>

- No DLT
- AUC < 90% IV
- Escalate E7727

20 mg /m² IV DAC Day 1 Cycle 1 used as the intra-patient comparator N=43
## ASTX727 Phase 1 Results

### Patient Characteristics

<table>
<thead>
<tr>
<th>Cohort Number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>19*</td>
<td>43</td>
</tr>
</tbody>
</table>

### Age
- **Median (range):**
  - 68 (59-81)
  - 71 (63-79)
  - 72 (70-83)
  - 76 (66-85)
  - 73 (59-86)
  - 71 (59-86)

### Sex
- **M n (%):**
  - 3 (50)
  - 5 (83)
  - 3 (50)
  - 4 (67)
  - 15 (79)
  - 30 (70)

- **F n (%):**
  - 3 (50)
  - 1 (17)
  - 3 (50)
  - 2 (33)
  - 4 (21)
  - 13 (30)

### ECOG PS n (%)
- **0-1:**
  - 6 (100)
  - 5 (83)
  - 5 (83)
  - 5 (83)
  - 16 (84)
  - 37 (86)

- **2:**
  - 0
  - 1 (17)
  - 1 (17)
  - 1 (17)
  - 3 (16)
  - 6 (14)

### IPSS** n (%)
- **MDS INT-1:**
  - 4 (67)
  - 2 (33)
  - 2 (33)
  - 2 (33)
  - 10 (53)
  - 20 (47)

- **MDS INT-2:**
  - 2 (33)
  - 1 (17)
  - 3 (50)
  - 2 (33)
  - 3 (27)
  - 7 (16)

- **MDS High Risk:**
  - 1 (17)
  - 2 (33)
  - 1 (17)
  - 4 (7)
  - 10 (23)

- **CMML:**
  - 2 (33)
  - 1 (17)
  - 1 (17)
  - 2 (7)
  - 6 (14)

### Prior Treatment n (%)
- **Prior HMA:**
  - 1 (17)
  - 2 (33)
  - 1 (17)
  - 6 (100)
  - 13 (68)
  - 23 (53)

- **Prior HMA:**
  - 0
  - 1 (17)
  - 0
  - 4 (67)
  - 10 (53)
  - 15 (35)

---

*Includes 13 from dose expansion

**International Prognostic Scoring System for MDS (Cheson et al, 2000)
ASTX727: Co-administration of E7727 with DAC enhances oral DAC bioavailability

Dose-dependent increase in DAC exposure with escalation of either drug

At fixed ASTX727 dose of 100 mg E7727 and DAC 40 mg the oral DAC exposure exceeded that of IV DAC.
### ASTX727 Phase 1 Results
5 Days total DAC AUC: Oral/IV

<table>
<thead>
<tr>
<th>Cohort</th>
<th>ASTX727 Oral Dose (mg)</th>
<th>5-Days Total (AUC \text{last})</th>
<th>% of AUC (Oral/IV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DAC\textsuperscript{1}</td>
<td>E7727</td>
<td>N</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
<td>40</td>
<td>5\textsuperscript{2}</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>60</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>40</td>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>100</td>
<td>19\textsuperscript{3}</td>
</tr>
</tbody>
</table>

\textsuperscript{1} DAC oral dose not adjusted by Weight or BSA
\textsuperscript{2} One significant outlier excluded from the PK analysis
\textsuperscript{3} Includes 13 patient dose expansion

- Cohort 4 Oral DAC (at 40 mg) exposure achieved primary objective and exceeded that of IV DAC at 20 mg/m² (Oral/IV 144%)
- Cohort 5 Oral DAC (at 30 mg) exposure was 85% of IV DAC at 20 mg/m²
- Oral DAC dose of 35 mg in ASTX727 (Ongoing Phase 2) should achieve AUC of ~ 85-140% of IV DAC
• ASTX727 cohorts 4 and 5 achieved LINE-1 demethylation from baseline of > 10% (comparable to historical data of DAC IV)
Responses were observed in all cohorts and in patients previously treated with HMAs (56% of patients in Cohort 4-5 were previously treated with azacitidine).

Five patients went on to Hematopoietic Stem Cell Transplant (HSCT).

Median of 5 cycles was administered (Range 1-26).

### ASTX727 Phase 1 Results

#### Clinical Activity

<table>
<thead>
<tr>
<th>Clinical Response</th>
<th>N = 43 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Complete Response (CR)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>Marrow Complete Response (mCR)</td>
<td>2 (5%)</td>
</tr>
<tr>
<td>Hematologic Improvement (HI)</td>
<td>6 (14%)</td>
</tr>
<tr>
<td>Transfusion Independence Response</td>
<td>7/23 (31%)</td>
</tr>
<tr>
<td>Still On Treatment</td>
<td>10 (23%)</td>
</tr>
</tbody>
</table>

1 Assessed by IWG criteria (Cheson et al, 2006)
2 All treated patients included in the analyses
# ASTX 727 Phase 1 Results

## Safety (AEs)

### Most Common Grade ≥ 3 AEs regardless of relationship to ASTX727

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Cohort</th>
<th>1 n=6 N</th>
<th>2 n=6 N</th>
<th>3 n=6 N</th>
<th>4 n=6 N</th>
<th>5 n=19 N</th>
<th>Total n=43 N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td>4</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>6</td>
<td>16 (37)</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>13 (30)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td></td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>12 (28)</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td></td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>9 (21)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td></td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>3</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td></td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>2</td>
<td>6 (14)</td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
<td>4 (9)</td>
</tr>
</tbody>
</table>

- No reported Grade ≥ 3 GI AEs
### ASTX727 Phase 1 Results

#### Safety (Related AEs)

Most Common Grade ≥ 3 AEs reported as related to ASTX727

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Total N=43</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombocytopenia</strong></td>
<td>8 (18)</td>
</tr>
<tr>
<td><strong>Neutropenia</strong></td>
<td>4 (9)</td>
</tr>
<tr>
<td><strong>Anemia</strong></td>
<td>3 (7)</td>
</tr>
<tr>
<td><strong>Bacteremia</strong></td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>C. Difficile colitis</strong></td>
<td>1(2)</td>
</tr>
<tr>
<td><strong>Pneumonia</strong></td>
<td>1 (2)</td>
</tr>
</tbody>
</table>
ASTX727 Phase 1
Conclusions

- **ASTX727**, an oral combination of a novel CDA inhibitor *E7727* with low doses of *decitabine* can emulate the PK and PD of IV decitabine
- **ASTX727** Safety is consistent with IV decitabine with no GI toxicity
- Clinical responses and DNA demethylation observed at all doses
- **ASTX727** Phase 2 trial is ongoing with the recommended doses of *100 mg E7727+35 mg decitabine*:
  - Randomized Cross over Design comparing 5 days of *oral ASTX727* to 5 days of IV decitabine