Abstract
P411-0866

Nonclinical Development of Cedazuridine, a Novel Cytidine Deaminase Inhibitor for use in Combination with Decitabine to Enable Oral Administration to Patients with Myelodysplastic Syndromes (MDS)

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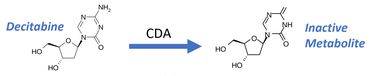
BACKGROUND

Cedazuridine (E7727) is a synthetic nucleoside analog derived from tetrahydrouridine (THU) and designed as a potent inhibitor (IC50 is 0.28±0.06 µM) of cytidine deaminase (CDA) with improved stability over THU. It is currently being developed in combination with hypomethylating agent decitabine (ASTX727) as an oral option for treatment of MDS and CMML

- Cedazuridine is pharmaceutically stable unlike other known CDA inhibitors such as tetrahydrouridine (THU)
- Oral bioavailability of decitabine is low due to degradation in the gut by CDA
- MDS requires continued treatment for long periods
- An oral decitabine option would provide significant benefit and convenience
- Development of a potent, safe CDA inhibitor should enable decitabine oral bioavailability
- Completed studies to support development of cedazuridine in combination with decitabine



RESULTS

Cedazuridine Proof of Concept for Enhancing Oral Bioavailability via Inhibition of CDA

Oral Decitabine with Increasing Doses of cedazuridine (E7727) in Cynomolgus Monkeys

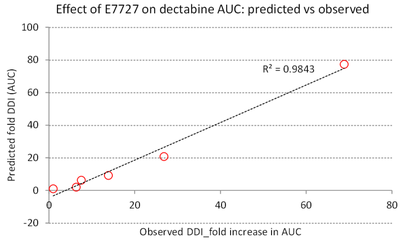
- Following cedazuridine administration, decitabine exposures increased in dose-dependent manner relative to increasing cedazuridine doses
- No saturation was evident for the effect of increasing decitabine exposures with increasing E7727 doses up to 10 mg/kg

Group	Dose (mg/kg) E7727[a]	Dose (mg/kg) Decitabine	AUC_{0-t}[b] (ng*hr/mL)	Fold increase AUC_{0-t}	C_{max}[b] (ng/mL)	Fold increase C_{max}
1	0	3	21.7 (8)	1.0	24.4 (7)	1.0
2	0.1	3	138 (43)	6.4	140 (35)	5.7
3	0.3	3	164 (112	7.6	129 (70)	5.3
4	1	3	301 (94)	13.9	281 (102)	11.4
5	3	3	582 (273)	26.8	425 (193)	17.4
6	10	3	1494 (912)	68.9	622 (256)	25.5

[a] E7727 administered 1-hr prior to decitabine
[b] Mean (SD), n = 3 per group

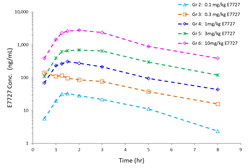
Modeling Drug-Drug Interaction Effect Between Cedazuridine and Decitabine in Cynomolgus Monkeys

- Good concordance between predicted vs observed DDI effect in monkeys with increasing doses of CDAi cedazuridine
- Modeling based on cedazuridine C_{max} and calculated K_i for CDA inhibition
- Increased confidence in probability of success for achieving similar effect in the clinic, further supported by very similar CDA status in cynomolgus monkeys and humans (identical baseline serum cytidine levels)



Cedazuridine PK Profile in Monkeys

- Mean Plasma Concentration-Time Profile for E7727 Administered Orally
- Dose-proportional increase in E7727 exposures was observed from 0.1 to 10 mg/kg



Proof of Concept Replicated for Second Species (Mouse)

- Increase in decitabine AUC achieved in 2nd preclinical species at low and clinically relevant doses
- Cynomolgus monkey is a very relevant and predictive model for human decitabine PK based on oral decitabine exposures and circulating baseline cytidine levels (marker of CDA status)

	Oral Decitabine AUC, ng·h/mL (Dose)	
	Mice (0.1 mg/kg)	Cynomolgus Monkeys (3 mg/kg)
Vehicle	23	22
E7727 (0.1 mg/kg)	45	138
E7727 (1 mg/kg)	56	301
E7727 (10 mg/kg)	126	1494

DMPK Evaluation of Cedazuridine

- Cedazuridine does not inhibit major human CYP450 enzymes
- No inhibition of major human drug transporters (efflux or uptake)
- Not a substrate of major human CYPs or transporters
- Cedazuridine did not accumulate in tissues in qWBA study
- Mass-balance study suggests excretion of circulating cedazuridine is mainly renal
- Cedazuridine-epimer is the main metabolite, with conversion occurring prior to absorption in the acidic environment of the stomach upon oral dosing
  - The epimer PK profile closely follows that of cedazuridine

Safety Pharmacology

- Cedazuridine did not show any significant inhibition in a panel (Cerep) of 80 receptors, ion channels, transporters.
- No inhibition of hERG potassium channel at up to 300 uM
- No effect on action potential parameters in guinea pig papillary muscle
- In GLP CV and respiratory safety assessment in telemetered cyno monkeys, cedazuridine had no clinical signs or changes in mean arterial blood pressure, heart rate, derived respiration parameters, or body temperature, no qualitative ECG abnormalities; no effects on the PR, QRS, or raw QT-intervals; no effect on derived QTc values and there were also no effects on respiratory parameters

Genotoxicity Evaluation

- Cedazuridine was negative in *in vitro* Ames and chromosome aberration tests at concentrations that were not cytotoxic
- Negative in mouse in vivo micronucleus study at up to 2000 mg/kg, dosed once daily for two days

GLP Toxicity Evaluation Studies for Cedazuridine

One cycle IND-enabling: well tolerated in Mouse and Monkey

Dosing regimen: 7 days once-daily, followed by 14-day recovery

Dose levels selected based on DRF studies:

- Mouse (CD1): 0, 100, 300, 1000 mg/kg
  - NOAEL 1000 mg/kg based on minimal decrease in hemoglobin, reticulocytes, with no concomitant adverse microscopic findings in bone marrow
  - Systemic exposures at NOAEL:
    - AUC_{0-24}: 122,000 (m) and 113,500 (f) ng*hr/mL
    - C_{max}: 44,600 (m) or 44,900 (f) ng/mL
- Monkey (Rhesus): 0, 30, 100, 200 mg/kg
  - NOAEL 200 mg/kg based on minimal findings
  - Systemic exposures at NOAEL:
    - AUC_{0-24}: 45,500 (m) and 36,600 (f) ng*hr/mL
    - C_{max}: 6,520 (m) or 6,150 (f) ng/mL

Four cycle subchronic (13-week) studies: tolerated in Mouse and Monkey

Dosing regimen: 7 days once-daily for every 28-day cycle for 4 dosing cycles, followed by 28-day recovery

- Mouse (CD1): 0, 100, 300, 1000 mg/kg
  - NOAEL 300 mg/kg in males and 100 mg/kg in females, based on adverse microscopic findings (all reversible) in mesenteric lymph nodes and splenic white pulp in females at the 300 mg/kg and in both sexes at 1000 mg/kg/dose; and in sternal bone marrow in females at the 1000 mg/kg/dose
  - Systemic exposures at NOAEL:
    - AUC_{0-24}: 165,000 (m) and 46,600 (f) ng*hr/mL
    - C_{max}: 21,300 (m) or 9,280 (f) ng/mL
- Monkey (Cynomolgus): 0, 20, 60, 200 mg/kg
  - NOAEL 60 mg/kg based on abnormal maturation in bone marrow, and associated changes in red blood cell parameters (reversible)
  - HNSTD was 200 mg/kg
  - Systemic exposures at NOAEL:
    - AUC_{0-24}: 27,500 (m) and 28,800 (f) ng*hr/mL
    - C_{max}: 4,150 (m) or 5,050 (f) ng/mL

Clinical exposures for comparison after 100 mg: AUC ~ 3,500 ng*hr/mL; C_{max} ~ 450 ng/mL

SUMMARY

- Cedazuridine is a potent novel inhibitor of cytidine deaminase
- Enhanced oral bioavailability achieved for CDA substrate decitabine when dosed in combination with cedazuridine in both toxicology species (mouse and monkey)
- Cedazuridine offers a large safety margin based on toxicity evaluation studies
- Benign DDI profile: no inhibition of major human CYPs or drug transporters
- Does not accumulate in tissues and undergoes minimal metabolism
- Cedazuridine offers a potential for development of decitabine as an oral hypomethylating agent at low dose levels and with an acceptable safety profile for treatment of MDS

Poster presented at: 15th International Congress of Toxicology (ICTXV), Honolulu, HI July 15 – 18, 2019

Poster can be downloaded from www.astx.com 19ASTX727-PB(108)