Effect of TERN-701 on Transporter and Cytochrome P450 Probe Substrates and the Effect of Acid-Reducing Agents on TERN-701 Pharmacokinetics

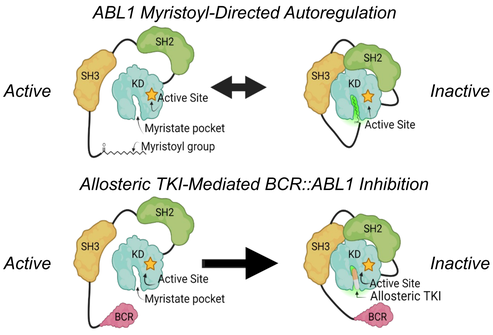
Poster #: CML-586

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BACKGROUND

- TERN-701 is a potent and selective, allosteric BCR::ABL1 kinase inhibitor in clinical development for the treatment of CML[1,2]
- TERN-701 retains activity against the BCR::ABL1^{T315I} resistance mutation (Figure 1), which confers resistance to all approved active-site inhibitors except for ponatinib[3]
- A global, two-part Phase 1 clinical trial (CARDINAL; NCT06163430) to evaluate the safety, pharmacokinetics (PK), and efficacy of TERN-701 in participants with previously treated CML is ongoing
- This drug-drug interaction (DDI) study was conducted in healthy participants to guide concomitant medication use in clinical studies

Figure 1. Schematic representation of allosteric inhibition of the BCR::ABL1 oncoprotein



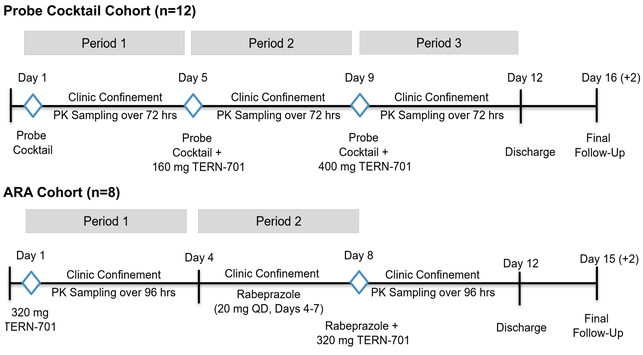
OBJECTIVES

- To evaluate the effect of TERN-701 on the PK of probe substrates of cytochrome P450 (CYP) enzymes and drug transporters
- To evaluate the effect of a representative gastric acid-reducing agent (ARA) on the PK of TERN-701

METHODS

- Phase 1, open-label, two separate crossover cohorts in healthy adult participants
- Probe substrate cocktail: midazolam (CYP3A substrate; 2 mg), montelukast (CYP2C8 substrate; 10 mg), omeprazole (CYP2C19 substrate; 40 mg), pravastatin (OATP1B1/3 substrate; 40 mg), and digoxin (P-gp substrate; 0.25 mg) (Figure 2)
- All treatments were administered in the morning under fasting conditions

Figure 2. Study design



- PK parameters were generated using noncompartmental methods (Phoenix® WinNonlin® 8.4, Certara, Princeton, NJ)
- Analysis of variance using a mixed-effects model was fitted to the natural logarithmic transformation of PK parameters for probe substrates or TERN-701; 90% confidence intervals (CIs) were constructed for the ratios of geometric least-squares means (GLSMs) between test versus reference treatment for AUC and C_{max}
- Safety assessments performed throughout the study

RESULTS

- All 20 participants completed the study
- Demographics and baseline characteristics are provided in Table 1

Table 1. Demographics and Baseline Characteristics

	Probe Substrate DDI (N=12)	ARA DDI (N=8)
Median age, years (range)	44 (29–65)	27 (23–52)
Male [n (%)]	8 (66.7)	8 (100)
Race [n (%)]		
White	7 (58.3)	5 (62.5)
Black or African-American	3 (25.0)	3 (37.5)
Multiple	2 (16.7)	0
Ethnicity, Hispanic or Latino, n (%)	2 (16.7)	2 (25.0)
Median BMI, kg/m^2 (range)	27.6 (23.7–31.5)	24.9 (21.5–29.0)

Safety

- TERN-701 was well-tolerated as single doses up to 400 mg, alone and in combination with probe substrates or rabeprazole
- All treatment-emergent adverse events (TEAEs) were mild (Grade 1). Most common TEAE was headache (n=2)
- No Grade ≥3 or serious TEAEs; no dose limiting toxicities
- No clinically meaningful changes in laboratory abnormalities, vital signs, or ECGs

RESULTS (CONT'D)

Effect of TERN-701 on Probe Substrates

- TERN-701 is not a clinically relevant inhibitor of CYP3A4, CYP2C8, CYP2C19, or OATP1B1/3
- TERN-701 is a P-gp inhibitor (Figure 3 and Table 2)

Figure 3. Effect of TERN-701 on Probe Substrates

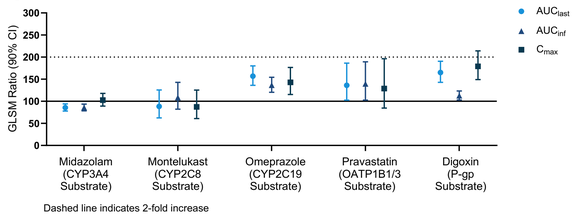


Table 2. Effect of TERN-701 on Probe Substrates

Probe Substrate	ΔAUC_{last}	ΔC_{max}	TERN-701 Clinically Relevant Inhibitor?
Midazolam (CYP3A4)	↓14%	↔	No
Montelukast (CYP2C8)	↓12%	↓13%	No
Omeprazole (CYP2C19)	↑57%	↑43%	No
Pravastatin (OATP1B1/3)	↑36%	↑29%	No
Digoxin (P-gp)	↑65%	↑79%	Yes

No clinically relevant effect of rabeprazole on TERN-701 PK

- There were no clinically relevant effects of rabeprazole on TERN-701 PK (Figure 4 and Table 3)
  - Coadministration of rabeprazole slightly increased TERN-701 AUC_{inf} by 15% and C_{max} by 20%
  - Coadministration of rabeprazole did not affect the time to peak plasma concentrations of TERN-701 (T_{max} ~2 hrs)

Figure 4. TERN-701 PK Profile Following Single 320-mg Dose with or without Rabeprazole

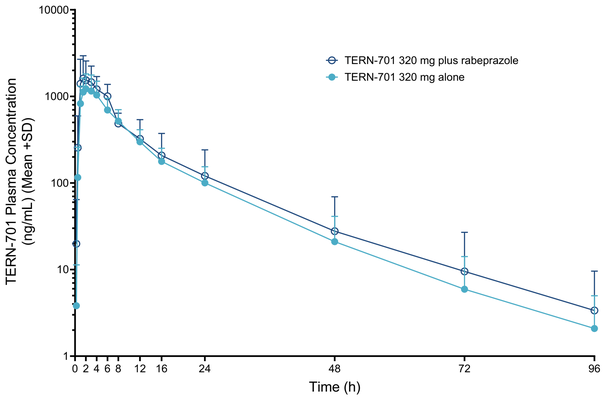


Table 3. Effect of Rabeprazole on TERN-701 PK Parameters

PK Parameter	TERN-701 Alone (Reference)	TERN-701 + Rabeprazole (Test)	% GLSM Ratio (90% CI)
AUC_{last} (h*ng/mL)	11,700 (35.8)	14,700 (65.4)	115 (95.4, 138)
AUC_{inf} (h*ng/mL)	11,800 (35.9)	14,800 (65.9)	115 (95.4, 138)
C_{max} (ng/mL)	1,560 (25.6)	2,000 (52.7)	120 (96.7, 149)
T_{max} (h)	2.00 (1.00, 6.00)	2.00 (1.00, 6.00)	--
$t_{1/2}$ (h)	8.30 (7.74, 16.3)	7.98 (6.87, 16.3)	--

AUC and C_{max} presented as mean (%CV); T_{max} and $t_{1/2}$ presented as median (min, max).

CONCLUSIONS

Pathway (Probe Drug)		TERN-701 Dosing Recommendations
Acid-reducing agents (rabeprazole)	✓	TERN-701 may be co-administered with acid-reducing agents, without dose modification of TERN-701
CYP3A4 (midazolam)	✓	TERN-701 may be co-administered with CYP3A4, CYP2C8, CYP2C19, and OATP1B1/3 substrates, without dose modification of probe substrates
CYP2C8 (montelukast)	✓	
CYP2C19 (omeprazole)	✓	
OATP1B1/3 (pravastatin)	✓	
P-gp (digoxin)	✓	TERN-701 is a P-gp inhibitor; sensitive, narrow therapeutic index substrates of P-gp can be allowed for use with TERN-701 with caution

REFERENCES

1. Parsons B, et al. *Clin Lymphoma Myeloma Leuk*. 2023;23(Suppl 1):S350.
2. Parsons BM, et al. *Blood*. 2023;142(Suppl 1):5757.
3. Alves R, et al. *Cancers (Basel)*. 2021;13(19):4820.

DISCLOSURES

- K. Anderson, L. Holes, C. Nelson, and E. Kuriakose: Employees and Shareholders of Terns Pharmaceuticals
- T. Marmon, A. Nichols: Consultants of Terns Pharmaceuticals