Safety, Tolerability, Pharmacokinetics, and the Effect of Food on TERN-701, an Oral Allosteric BCR-ABL Tyrosine Kinase Inhibitor, in Healthy Participants

Poster #: CML-396

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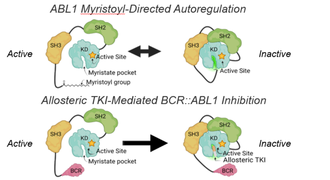
1 BACKGROUND

- Chronic myeloid leukemia (CML) is a myeloproliferative disorder characterized by a reciprocal translocation between chromosomes 9 and 22, leading to the loss of myristoyl-directed autoregulation and constitutive activation of the BCR::ABL1 oncoprotein [1,2]
- TERN-701 is an investigational, highly selective, oral allosteric BCR::ABL1 inhibitor that specifically targets the ABL myristoyl pocket that is potent against native BCR::ABL1 and most common BCR::ABL1 mutations, including T315I, in preclinical models [3,4,5]
- This Phase 1 study was conducted to evaluate the pharmacokinetics (PK), safety, and tolerability of TERN-701 and the effect of food on the PK of TERN-701 in healthy volunteers

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



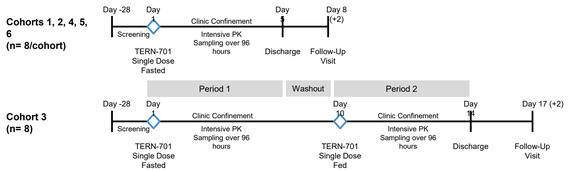
2 OBJECTIVES

- **Primary:** To evaluate the safety, tolerability, and PK of single-ascending doses of TERN-701 in healthy participants
- **Secondary:** To evaluate the effect of food on the PK of TERN-701

3 METHODS

Study Design: Phase 1, open-label, single-ascending dose escalation study in healthy male and female participants at a single center in the United States

Figure 2. Study schema across cohorts



- TERN-701 was administered fasted, except Cohort 3 (high-fat meal in crossover)
- Adverse event (AE) monitoring, clinical laboratory assessment, physical examination, and electrocardiography performed throughout the study
  - Dose escalations guided by review of safety and available PK data
- TERN-701 plasma concentrations determined using validated liquid chromatography-tandem mass spectrometry assay
- PK parameters estimated via noncompartmental methods using WinNonlin 8.4 (Certara, LP, Princeton, NJ, USA)
  - Geometric least-squares means ratios (GLSMR) and 90% confidence intervals (CIs) calculated (test [high-fat meal] vs reference [fasting]) for TERN-701 primary PK parameters

4 RESULTS

Table 1. Baseline Demographics of Study Participants

Demographics	Cohort 1 20 mg (N=8)	Cohort 2 40 mg (N=8)	Cohort 3 80 mg (N=8)	Cohort 4 160 mg (N=8)	Cohort 5 320 mg (N=8)	Cohort 6 400 mg (N=8)
Mean age, years (range)	48 (20-65)	38 (24-65)	48 (27-57)	47 (31-62)	43 (30-63)	38 (27-64)
Sex [n (%)]						
Male	3 (37.5%)	5 (62.5%)	8 (100%)	4 (50%)	5 (62.5%)	7 (87.5%)
Race [n (%)]						
White	7 (87.5%)	6 (75.0%)	5 (62.5%)	5 (62.5%)	6 (75.0%)	5 (62.5%)
Non-White	1 (12.5%)	2 (25.0%)	3 (37.5%)	3 (37.5%)	2 (25%)	3 (37.5%)

Table 2. Summary of Treatment-Emergent AEs

Participant incidence AE by category, N (%)	Cohort 1 20 mg (N=8)	Cohort 2 40 mg (N=8)	Cohort 3 Period 1 80 mg, fasted (N=8)	Cohort 3 Period 2 80 mg, fed (N=8)	Cohort 4 160 mg (N=8)	Cohort 5 320 mg (N=8)	Cohort 6 400 mg (N=8)
Any TEAE, all grades	3 (37.5%)	1 (12.5%)	1 (12.5%)	0	3 (37.5%)	1 (12.5%)	1 (12.5%)
TEAE, Grade 2	0	0	0	0	0	0	1 (12.5%)
TEAEs by relationship to study drug							
Not Related	2 (25.0%)	1 (12.5%)	0	0	1 (12.5%)	0	0
Unlikely Related	0	0	0	0	0	0	0
Possibly Related	1 (12.5%)	0	1 (12.5%)	0	2 (25.0%)	1 (12.5%)	1 (12.5%)
Related	0	0	0	0	0	0	0

CTCAE = common terminology criteria for adverse events, version 5.0

- TERN-701 was well-tolerated as single doses up to 400 mg
- Most TEAEs were mild (1 TEAE of Grade 2); most common TEAE was headache (n=5)
- No Grade ≥3 or Serious TEAEs
- No pre-defined trial or dose-escalation stopping criteria were met
- No clinically meaningful changes in vital signs or ECGs
- No clinically significant laboratory abnormalities

Figure 3. TERN-701 Single Dose Pharmacokinetic Profile

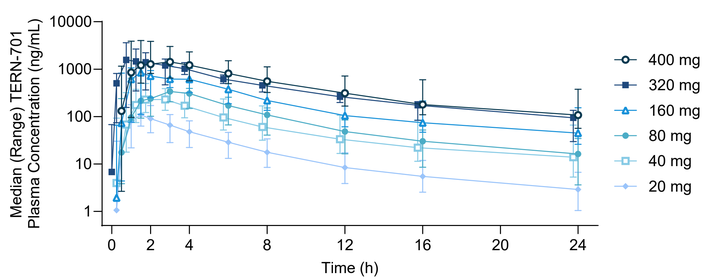


Figure 4. TERN-701 Food Effect Pharmacokinetic Profile

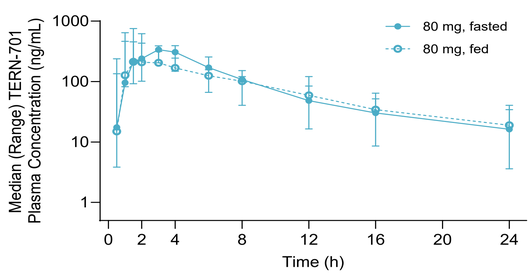


Table 3. TERN-701 Single Dose Pharmacokinetic Parameters

Parameter	Cohort 1 20 mg (N=8)	Cohort 2 40 mg (N=8)	Cohort 3 80 mg (N=8)	Cohort 4 160 mg (N=8)	Cohort 5 320 mg (N=8)	Cohort 6 400 mg (N=8)
C_{max} (ng/mL)	110 (63, 200)	250 (170, 500)	360 (240, 750)	900 (630, 1200)	1800 (810, 3600)	1600 (1300, 4000)
T_{max} (h)	1.5 (1.0, 3.0)	2.0 (1.0, 3.0)	2.0 (1.5, 4.0)	2.3 (1.0, 4.0)	1.8 (1.0, 4.0)	2.0 (1.0, 4.0)
AUC_{inf} (ng*h/mL)	560 (260, 1000)	1600 (950, 5200)	2600 (1100, 3600)	5700 (4000, 13000)	11000 (8600, 16000)	13000 (7700, 34000)
$t_{1/2}$ (h)	7.8 (5.1, 11)	11 (6.2, 17)	9.5 (4.8, 12)	12 (9.1, 15)	12 (6.3, 14)	14 (6.9, 19)

Data presented as median (range). Values reported to 2 significant figures.

- TERN-701 was rapidly absorbed, with median T_{max} occurring 1.5 to 2.3 hours postdose
- Median TERN-701 half-life ($t_{1/2}$) ranged from 8 to 14 hours
- TERN-701 exhibited approximately linear increases in AUC from 20 to 400 mg and C_{max} from 20 to 320 mg

Table 4. TERN-701 Food Effect Pharmacokinetic Parameters, 80 mg

Parameter	TERN-701 Fasted (reference) N=8	TERN-701 High-Fat Meal (test) N=8	% GLSMR (90% CI)
C_{max} (ng/mL)	380 (47)	240 (53)	62 (44, 87)
T_{max} (h)	2.0 (1.5, 4.0)	2.5 (1.0, 4.0)	--
AUC_{inf} (ng*h/mL)	2400 (36)	2100 (32)	89 (68, 120)
$t_{1/2}$ (h)	9.5 (4.8, 12)	11 (7.2, 17)	--

Data presented as geometric mean (geometric %CV). Time to maximum concentration (T_{max}) and terminal elimination half-life ($t_{1/2}$) presented as median (range). Values reported to 2 significant figures.

- When administered with a high-fat meal, TERN-701 AUC_{inf} and C_{max} were 89% and 62% of fasted state AUC_{inf} and C_{max}, respectively

5 CONCLUSIONS

- TERN-701 was safe and well-tolerated following oral doses up to 400 mg
- TERN-701 exhibited approximately linear increases in AUC over the dose range of 20 to 400 mg
- Food had no clinically meaningful impact on TERN-701 exposure, supporting administration of TERN-701 with or without food
- The PK and safety profile of TERN-701 support further evaluation in CML with once-daily dosing; including the ongoing, global, Phase 1 clinical trial (CARDINAL; NCT06163430) to evaluate TERN-701 in participants with previously treated chronic phase CML

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DISCLOSURES

- K. Anderson, L. Holes, T. Marmon, A. Nichols, C. Nelson, and E. Kuriakose: Terns Pharmaceuticals
- A. Schlegel: Terns Pharmaceuticals employee at the time of study conduct