CARDINAL: A Phase 1, Multicenter, Open-Label, Dose-Escalation and Dose-Optimization Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of TERN-701 in Chronic Myeloid Leukemia

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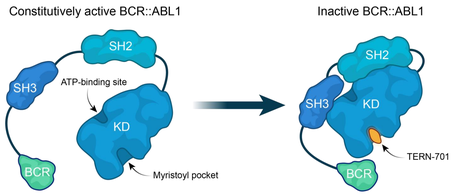
SUMMARY

- Many people with CP-CML experience suboptimal response, treatment failure, or intolerance with active site-targeting TKIs and, therefore, have limited second-line or later treatment options
- TERN-701 is a selective, allosteric BCR::ABL1 inhibitor that specifically targets the ABL myristoyl pocket
- In preclinical studies, TERN-701 showed high potency against native and mutant CML cell lines, including those with the T315Im
- CARDINAL is a two-part, global, multicenter, open-label, Phase 1 clinical trial to assess the safety, tolerability, pharmacokinetics, and efficacy of TERN-701 in participants with previously treated *BCR::ABL1*-positive CP-CML

BACKGROUND

- Chronic myeloid leukemia (CML) is characterized by the presence of the Philadelphia chromosome, caused by a translocation between chromosomes 9 and 22, resulting in the constitutive activation of the oncoprotein, BCR::ABL1 tyrosine kinase[1,2]
  - BCR::ABL1 active site-targeting tyrosine kinase inhibitors (TKIs) have transformed the treatment landscape in chronic phase CML (CP-CML) but are susceptible to BCR::ABL1 resistance mutations[1,3]
  - Treatment options for patients with CP-CML who experience suboptimal response or treatment failure with second-generation active site-targeting TKIs are limited[3]
- TERN-701 is an allosteric BCR::ABL1 inhibitor designed to specifically target the ABL myristoyl pocket (**Figure 1**), bypassing active site resistance mechanisms[4,5]
- TERN-701 showed high antiproliferative potency against native and mutant CML cell lines, including those harboring the T315I mutation (T315Im),[4,5] which confers resistance to imatinib and second-generation active site-targeting TKIs[1,2]
  - TERN-701 also demonstrated high selectivity for BCR::ABL1, with no appreciable off-target activity (>50%) against >450 purified kinase targets[4,5]
- Results from a Phase 1 dose-ascending study in healthy participants demonstrated that TERN-701 can be administered once-daily[6]
- Here we present the design of the CARDINAL trial (NCT06163430) of TERN-701 in participants with previously treated *BCR::ABL1*-positive CP-CML

Figure 1. TERN-701 mechanism of action



ATP, adenosine 5′-triphosphate; KD, kinase domain; SH2, SRC-homology-2 domain; SH3, SRC-homology-3 domain; TKI, tyrosine kinase inhibitor.

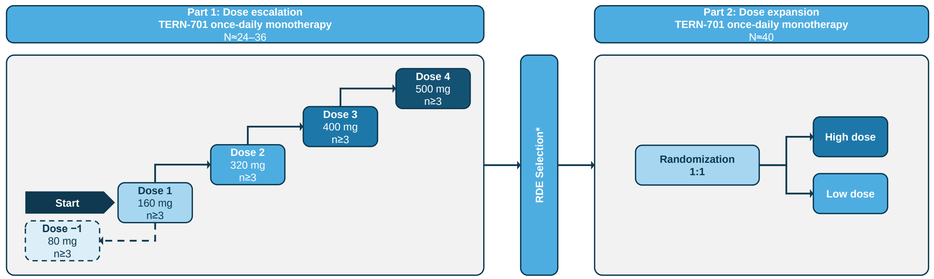
OBJECTIVE

- The Phase 1 CARDINAL trial is a global, multicenter, open-label, two-part study (**Figure 2**) that will evaluate the safety, tolerability, pharmacokinetics, and efficacy of TERN-701 as second-line or later therapy in participants with T315Im or non-T15Im *BCR::ABL1*-positive CP-CML

STUDY DESIGN AND METHODS

- TERN-701 will be administered orally, once daily, in 28-day treatment cycles until disease progression, intolerable toxicity, or other discontinuation criteria occur
- In Part 1 (dose-escalation phase), groups of ≥3 participants will be assigned to ≈4 sequential dose-escalation cohorts (starting at 160 mg); dose escalation will be guided by a Bayesian optimal interval algorithm[7]
- From Part 1, ≈2 recommended doses for expansion (RDE) will be selected for evaluation in Part 2
- In Part 2 (dose-expansion phase), ≈40 participants with non-T315Im CP-CML will be randomized 1:1 to ≈2 RDE cohorts, stratified by baseline *BCR::ABL1* transcript levels (<1% or ≥1%)
  - The safety and efficacy data will be evaluated continually
  - The optimal therapeutically active dose(s) of TERN-701 will be identified for evaluation in future studies in patients with CP-CML
- Patients may continue therapy beyond endpoint measures, through the end of the study

Figure 2. Study Design



*RDE will be selected following an interim analysis of Part 1.

RDE, recommended doses for expansion.

Eligibility criteria

- Key inclusion and exclusion criteria are presented in **Table 1**
- People with CP-CML who require second-line or later therapy are eligible for inclusion

Table 1. Eligibility Criteria

Key inclusion criteria
✓ Male or female adults (≥18 years of age)
✓ Have an ECOG performance status score of 0 to 2
✓ Have an established, cytopathologically confirmed diagnosis of *BCR::ABL1*-positive CP-CML with or without T315Im
✓ Have received treatment with at least one prior second generation active site-targeting TKI and have treatment failure, suboptimal response, or treatment intolerance*
✓ Participants who are intolerant of asciminib and do not have resistant/relapsing disease
✓ Have adequate organ function
Key exclusion criteria
× Have CML in the accelerated or blast phase
× Received treatment with systemic antineoplastic therapy or other experimental therapies 7 days before the first TERN-701 dose
× Completed previous anticancer therapy without resolution of clinically significant toxicity (to Grade ≤2 or baseline)

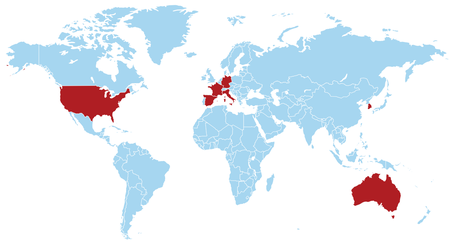
*As determined by the investigator.

CP-CML, chronic phase chronic myeloid leukemia; ECOG, Eastern Cooperative Oncology Group; T315Im, T315I mutation; TKI, tyrosine kinase inhibitor.

CURRENT STATUS

- CARDINAL is recruiting in the USA, Europe, Australia, and the Republic of Korea (**Figure 3**)

Figure 3. CARDINAL study locations



Study objectives and endpoints

- Primary and secondary objectives and endpoints are shown in **Table 2**

Table 2. Study objectives and endpoints

Part 1 (dose-escalation phase)	
Primary objective	**Primary endpoints**
• To evaluate the safety and tolerability of TERN-701 in participants with previously treated CP-CML	• The incidence of DLTs during the 1st treatment cycle • AEs and changes in vital signs, laboratory values, and ECGs
Secondary objectives	**Secondary endpoints**
• To evaluate the PK of TERN-701 in participants with previously treated CP-CML	• Plasma concentration and derived PK parameters for TERN-701
• To evaluate the efficacy of TERN-701 in participants with previously treated CP-CML	• Hematologic and molecular response • Best categorical shift in *BCR::ABL1* transcript levels from baseline
Part 2 (dose-expansion phase)	
Primary objective	**Primary endpoints**
• To evaluate the efficacy of TERN-701 in participants with previously treated CP-CML	• Hematologic and molecular response • Best categorical shift in *BCR::ABL1* transcript levels from baseline
Secondary objectives	**Secondary endpoints**
• To evaluate the safety and tolerability of TERN-701 in participants with previously treated CP-CML	• AEs and changes in vital signs, laboratory values, and ECG
• To evaluate the PK of TERN-701 in participants with previously treated CP-CML	• Plasma concentration and derived PK parameters for TERN-701

AE, adverse event; CP-CML, chronic phase chronic myeloid leukemia; DLT, dose-limiting toxicity; ECG, electrocardiogram; PK, pharmacokinetic.

SCAN HERE
Poster: CML-399

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