Poster #: AML-259

Pharmacokinetics and Bioequivalence of Two Formulations of GFH009 Maleate Injection in Sprague Dawley Rats

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BACKGROUND

- Cyclin-dependent kinase 9 (CDK9) is a serine/threonine kinase that regulates the expression of short-lived oncogene products, such as MYC and MCL1
  - MYC and MCL1 are key influencers of tumor cell proliferation and survival
- CDK9 deregulation has been reported in leukemia and other hematologic malignancies
- GFH009 maleate is a potent, highly selective, clinical-stage, small molecule that inhibits CDK9
- A 4-week toxicity study of Sprague Dawley (SD) rats tested GFH009 maleate at 2 mg/kg, 4 mg/kg, and 8 mg/kg
  - At 4 mg/kg, drug exposure was approaching the efficacious exposure, which was the rationale for the dose selection in the current study
- The objective of this study was to characterize the preclinical pharmacokinetic (PK) profiles of 2 different formulations of GFH009 maleate (pH 4.5 and pH 6.0)

METHODS

- SD rats were randomly assigned to group 1 (pH 4.5) or group 2 (pH 6.0) and matched by sex and body weight
- Each rat received a single dose of pH 4.5 or pH 6.0 formulation of GFH009 maleate (4 mg/kg) intravenously (IV) in the tail vein at a volume of 5 mL/kg
- Approximately 0.3 mL of whole blood/animal/timepoint were obtained from the jugular vein prior to dosing and at 0.083, 0.25, 0.5, 1, 2, 3, 4, 7, 10, 12, and 24 hours post dosing
- Plasma concentration of GFH009 was quantitated by a validated liquid chromatography-tandem mass spectrometry method
- PK parameters were assessed by noncompartmental analysis approach
- Bioequivalence was established if the 90% confidence interval (CI) of the ratio of geometric means of AUC_{inf}, AUC_{last}, and C_0 was within the predefined range of 0.80-1.25.

RESULTS

- The study included 12 SD rats (6 male/6 female) for each GFH009 formulation tested
- The concentration was measured by high-performance liquid chromatography, and the results are shown in **Table 1**
- The plasma concentrations of the GFH009 formulations were within 90% to 110% of the nominal concentrations
  - The coefficient of variation was ≤5.0%
- The mean plasma concentration peaked at 5 min post dose at 479 ng/mL and 486 ng/mL in groups 1 and 2, respectively, and gradually decreased in a similar profile (**Figure 1**)
- The PK profiles are shown in **Table 2**
- No gender differences in the key PK parameters were observed
- Bioequivalence analysis showed that the 90% CI values for drug concentration at 0 (C_0), area under the curve from time zero to the last quantifiable concentration (AUC_{last}), and area under the curve extrapolated to infinity (AUC_{Inf}) were within the acceptable range (80-125%)

Figure 1. Mean Plasma Concentration-Time Curve

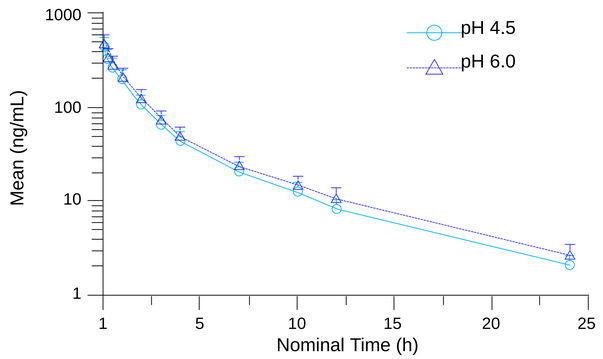


Table 1. Concentration Analysis

	pH 4.5	pH 6.0
Nominal concentration (mg/mL)	0.8	0.8
Mean (mg/mL)	0.842	0.861
Relative deviation (%)	0.2	0.0
Recovery (%)	105.3	107.6

Table 2. Mean PK Parameters

Parameter	pH 4.5			pH 6.0		
	Mean	SD	95% CI	Mean	SD	95% CI
AUC_{Inf} (h*ng/mL)	842	75.0	767, 917	946	145	801, 1091
AUC_{last} (h*ng/mL)	825	73.8	751.2, 898.8	924	144	780, 1068
C_0 (ng/mL)	586	109	477, 695	572	147	425, 719
CL (mL/h/kg)	4780	429	4351, 5209	4310	607	3703, 4917
$t_{1/2}$ (h)	5.45	0.649	4.801, 6.099	5.66	0.973	4.687, 6.633

CL = clearance; SD = standard deviation; $T_{1/2}$ = half-life.

CONCLUSIONS

- The PK profiles of GFH009 maleate were comparable following single IV administration of 2 formulations (pH 4.5 and pH 6.0) in SD rats
- The results supported the application of the pH 6.0 formulation in the currently ongoing phase 1 trial of GFH009 monotherapy in patients with relapsed/refractory hematologic conditions, including acute myeloid leukemia and lymphoma (ClinicalTrials.gov Identifier: NCT04588922)
- The pH 6.0 formulation will be used in additional studies in the clinical development program of GFH009

DISCLOSURES

Support for this study was provided from GenFleet Therapeutics. Drs. Zhou, Zhao, Lan and Lu are employees of GenFleet and Dr. Cicic is an employee of SELLAS.

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