SYNOPTIC CLINICAL STUDY REPORT
FULL VERSION FOR REGULATORY SUBMISSION

Study Title:	**A Phase 1, Multicenter, Open-Label, Dose Escalation and Expansion Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of Intravenously Administered FHD-609 in Subjects With Advanced Synovial Sarcoma or Advanced SMACRB1-Loss Tumors**
Brief Title:	A Phase 1 Study of FHD-609 in Subjects With Advanced Synovial Sarcoma or Advanced SMARCB1-Loss Tumors
Study Number:	FHD-609-C-001
Study Phase:	1
Compound:	FHD-609
Study Sponsor:	Foghorn Therapeutics Inc., Suite 700500 Technology Square Cambridge, MA 02139 USA
Sponsor's Responsible Medical Officer:	Alfonso Quintás-Cardama, MD
Study Initiation Date:	17 Aug 2021
Study Completion:	04 Dec 2023 (last subject's last visit) The analyses presented in this report are based on a database lock date of 12 Apr 2024.
Regulatory Agency Identifier Numbers:	US IND 153387 ClinicalTrials.gov NCT04965753 EudraCT Number 2021-001488-25
Report Date:	**Document Version** / **Date** Final CSR / 03 Dec 2024
This study was conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents.	

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AUC	area under the concentration-time curve
$AUC_{0\text{-}168hr}$	area under the concentration-time curve from time 0 to 168 hours postdose
$AUC_{0\text{-}72hr}$	area under the concentration-time curve from time 0 to 72 hours postdose
$AUC_{0\text{-}inf}$	area under the concentration-time curve from time 0 extrapolated to infinity
$AUC_{0\text{-}last}$	area under the concentration-time curve from time 0 to the time of the last quantifiable concentration
AUC_{tau}	area under the concentration-time curve from time 0 to the time prior to the next dose
AV	atrioventricular
BRD9	bromodomain-containing protein 9
CxDx	Cycle x Day x
CL	clearance
C_{max}	maximum concentration
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
DDS	Dose Determining Set
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
FDA	Food and Drug Administration
IND	Investigational New Drug Application
IV	intravenous
LC-MS/MS	liquid chromatography with tandem mass spectrometry
ms	millisecond(s)
MTD	maximum tolerated dose
ORR	objective response rate
OS	overall survival
PD	pharmacodynamic(s)
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response

Abbreviation	Definition
QTc	heart rate–corrected QT interval
QTcF	heart rate–corrected QT interval, Fridericia correction
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SS	synovial sarcoma
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
T_{last}	time of last observed concentration
T_{max}	observed time to reach maximum concentration
TTR	time to response
US	United States
v/v	volume-to-volume

SYNOPSIS FOR CLINICAL STUDY REPORT

Study Title

A Phase 1 Multicenter, Open-Label, Dose Escalation and Expansion Study to Assess the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of Intravenously Administered FHD-609 in Subjects With Advanced Synovial Sarcoma or Advanced SMARCB1-Loss Tumors

Study Number

FHD-609-C-001

Regulatory Agency Identifier Number(s)

US IND	153387
EudraCT number	2021-001488-25
ClinicalTrials.gov	NCT04965753

Study Phase

1

Name of Investigational Intervention

FHD-609

Name of Sponsor/Company

Foghorn Therapeutics Inc.
500 Technology Square, Suite 700
Cambridge, MA 02139 USA

Number of Study Center(s) and Countries

This study was conducted at 12 sites that enrolled subjects in the US, France, Spain, and Italy.

Publications

Livingston JA, Cote GM, Blay JY, et al. Preliminary results from a Phase 1 study of FHD-609, a bromodomain-containing protein 9 degrader, in patients with advanced synovial sarcoma or SMARCB1-loss tumors. Presentation presented at 2023 CTOS Annual Meeting; 01-04 November 2023; Dublin, Ireland.

Study Period

The study initiation date was 17 Aug 2021.

The date of the last subject's last visit was 04 Dec 2023.

The database lock date was 12 Apr 2024.

Rationale

FHD-609 is a potent, selective, heterobifunctional degrader of BRD9 being developed as an anticancer therapy in BRD9-dependent cancers, including synovial sarcoma (SS) and SMARCB1-loss tumors.

This clinical study was planned to evaluate single-agent intravenous (IV) administration of FHD-609 in subjects with advanced SS and SMARCB1-loss tumors, by providing insight into the safety, tolerability, PK, pharmacodynamics (PD), and clinical activity associated with FHD-609. The Dose Escalation Phase of the study aimed to determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose(s) (RP2D[s]) of FHD-609. This study was also intended to provide a preliminary assessment of the clinical activity of FHD-609 in subjects with advanced SS and SMARCB1-loss tumors.

The Dose Expansion Phase of the study aimed to further evaluate the safety and tolerability; however, no subjects were enrolled as enrollment was stopped by the sponsor during the Dose Escalation Phase because of safety concerns. In response, FDA placed the study on partial clinical hold in April 2023. The sponsor responded to the FDA partial clinical hold comments in October 2023 to address clinical deficiencies; however, because the sponsor decided to stop further development of FHD-609 for business reasons in November 2023, the study remains on partial clinical hold. After the decision to stop further development of FHD-609, subjects who were still on treatment were given the option to continue treatment as long as the treating physician deemed it appropriate for their patient.

Ethics

The protocol, informed consent form (ICF), Investigator's Brochure, written information given to the subjects (including diary cards), and other relevant documents were submitted to an Investigational Review Board/Independent Ethics Committee by the sponsor and reviewed and approved by the IRB before the study was initiated.

Any amendments to the protocol obtained IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

As applicable according to local regulations, the protocol and all protocol amendments were reviewed and approved by each pertinent Competent Authority.

This study was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki, applicable ICH GCP Guidelines, and other applicable laws and regulations.

The investigator or designee explained the nature of the study to the subject or their legally authorized representative and answered all questions regarding the study at the screening visit.

Subjects and/or their legally authorized representatives were informed that their participation was voluntary. Subjects or their legally authorized representative were required to sign a statement of informed consent/assent that met the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/IEC or study center.

Investigative sites were instructed to obtain written informed consent/assent before the subject was enrolled in the study and document the date the written consent was obtained. The authorized person obtaining the informed consent was also instructed to sign the ICF. Subjects were to be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) was provided to the subject or the subject's legally authorized representative.

Objectives, Endpoints, and Statistical Methods

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To determine the safety and tolerability of FHD-609 when administered as an IV monotherapy in subjects with advanced SS or advanced SMARCB1-loss tumors • To identify the MTD and/or the RP2D(s) of FHD-609	• Incidence of treatment-emergent adverse events (TEAEs), adverse events (AEs), dose-limiting toxicities (DLTs), serious AEs (SAEs), and AEs leading to discontinuation; laboratory and other safety assessments

Objectives	Endpoints
Secondary	
• To determine the PK of FHD-609 in plasma when administered as an IV monotherapy	• Plasma concentration versus time profiles of FHD-609 will be determined and the following plasma PK parameters will be calculated: • $AUC_{0\text{-last}}$: AUC (area under the concentration-time curve) from time 0 to the time of the last quantifiable concentration • AUC_{tau}: AUC from time 0 to the time prior to the next dose • $AUC_{0\text{-inf}}$: AUC from time 0 extrapolated to infinity • C_{max}: maximum concentration • C_{trough}: minimum concentration before administration of the next dose • T_{max}: observed time to reach C_{max} • $t_{1/2}$: terminal elimination half-life • V_{ss}: volume of distribution at steady state • CL: total body clearance

Objectives	Endpoints

• To characterize the preliminary clinical activity associated with FHD-609 by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1	• Preliminary clinical activity:
	  • Objective response rate (ORR): the proportion of subjects achieving a complete response (CR) or partial response (PR) per RECIST v1.1
	  • Duration of response (DOR): the time from the first documented evidence of CR or PR to the earliest date of progressive disease or death from any cause among subjects who achieve a CR or PR per RECIST v1.1
	  • Progression-free survival (PFS): the time from the date of the first dose of study treatment to the earliest date of progressive disease per RECIST v1.1 or death from any cause
	  • Time to response (TTR): the time from the date of the first dose of study treatment to the first documented evidence of CR or PR among subjects who achieve a CR or PR per RECIST v1.1
	  • Overall survival (OS): the time from the date of the first dose of study treatment to death from any cause

Exploratory	
• To determine the PK of FHD-609 in blood and urine when administered as an IV monotherapy • To explore the PK of the inactive enantiomer of FHD-609 (FHT-0011612) in plasma	• Plasma concentration of FHD-609 and/or derived PK parameters will be determined for FHD-609 blood PK and the inactive enantiomer (FHT-0011612), if possible; amount of FHD-609 in urine and fraction excreted in urine
• To characterize the PD effects of FHD-609 in tumor and blood tissues	• Levels of BRD9 and other relevant markers and change from baseline in blood and tumor tissue
• To explore the relationship of FHD-609 PK or dose with PD and other downstream markers in tumor and blood, clinical activity, and safety	• Graphical exploration of relationship between PK parameters or dose of FHD-609 with (1) blood and tumor tissue levels of, and/or change from baseline in, BRD9 (and other downstream markers), (2) tumor size reduction, and (3) adverse events
• To explore potential predictive tumor biomarkers of response/resistance and downstream impact of FHD-609 on tumor and immune cell biology	• Baseline expression and mutational status of relevant genes in tumor and blood samples and their correlation to tumor response

Objectives	Endpoints
• To assess any impact of FHD-609 on corrected QT interval (QTc) via concentration-QTc analysis	• Time-matched FHD-609 concentration and QTc measurements

Exploratory endpoints, other than the PK of FHD-609 in blood, are not reported here and may be reported separately.

Sample collection time points are described in the protocol (Appendix 16.1.1).

Statistical Analyses

Statistical analyses were descriptive. No statistical hypotheses were tested.

The planned analyses and sample size justification for the dose escalation portion of the study are described in the final version of the statistical analysis plan (SAP) (Appendix 16.1.9) and contained in the protocol (Appendix 16.1.1).

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 26.0. Toxicity severity was graded according to the National Cancer Institute Common Terminology for Adverse Events (CTCAE) version 5.0. Treatment-emergent adverse events are defined as those that occurred after the first dose of FHD-609 (C1D1) and within the 28-day follow-up period.

The following additional analysis set is not described in the SAP, and was evaluated and used for the presentation of data:

- Full Analysis Set (FAS): All subjects who were enrolled and received at least 1 dose of study treatment. (The FAS and the Safety Analysis Set are the same.)

The FAS was used for the summaries of subject disposition, protocol deviations, demographics and baseline characteristics, prior and concomitant medications and procedures, cancer-related medical history, disease history, and some analyses of efficacy data.

The Dose Determining Set (DDS) was defined as all subjects in the Dose Escalation Phase who either had a DLT during the 6-week DLT evaluation period or who received ≥9 of the 12 (for twice-weekly [BIW] dosing; 5 of the 6 for once weekly [QW] dosing) planned doses and were considered by the Clinical Study Team (CST) to have had sufficient safety data available to conclude that a DLT did not occur during the 6-week DLT evaluation period; the DDS was not used in any analyses. The Safety Analysis Set was used to summarize DLTs because DLTs could have occurred outside of the 6-week DLT evaluation period.

The following planned analyses, described in the SAP, were not conducted:

- No variables were summarized by Part I and Part II, since both parts were combined for all analyses. All analyses were summarized by dose level (dose and schedule) and overall.
- The number (%) of subjects with postbaseline response to treatment assessment was not included in the summary of disposition, as this is not a disposition characteristic. These results are presented in the summary of best overall response and ORR.

- The number (%) of subjects in the PK Analysis Set was not included in the summary of disposition, as this was determined separately.
- Best responses to prior anticancer surgery, radiotherapy, or chemotherapy/ immunotherapy and reason for discontinuation from chemotherapy/immunotherapy were not summarized. This information is contained in the by-subject listings.
- Duration of exposure was calculated in days rather than weeks because the overall median duration of exposure was short (43 days).
- Compliance variables were not summarized by cycle, but only overall (cumulative) for each dose level.
- Variables related to infusion time and infusion interruptions were not summarized. This information is contained in the by-subject listings.
- Intended dose intensity is not included in the by-subject listings or summarized in the tables, only actual and relative dose intensity.
- Clinically identical Preferred Terms were not identified and grouped; instead, grouped terms encompassing clinically similar Preferred Terms were defined (leukocytosis, rash, nausea/vomiting, increased blood bilirubin, increased blood glucose, decreased white blood cell count, decreased neutrophil count, and decreased platelet count).
- Summaries of shifts in laboratory values from baseline to worst value on treatment were categorized using CTCAE (Common Terminology Criteria for Adverse Events) grading, rather than by low, medium, and high.
- Because the study was stopped by the sponsor for safety concerns before the start of the Dose Expansion Phase, the summaries and by-subject listings of efficacy variables were more limited than outlined in the SAP.

Methodology

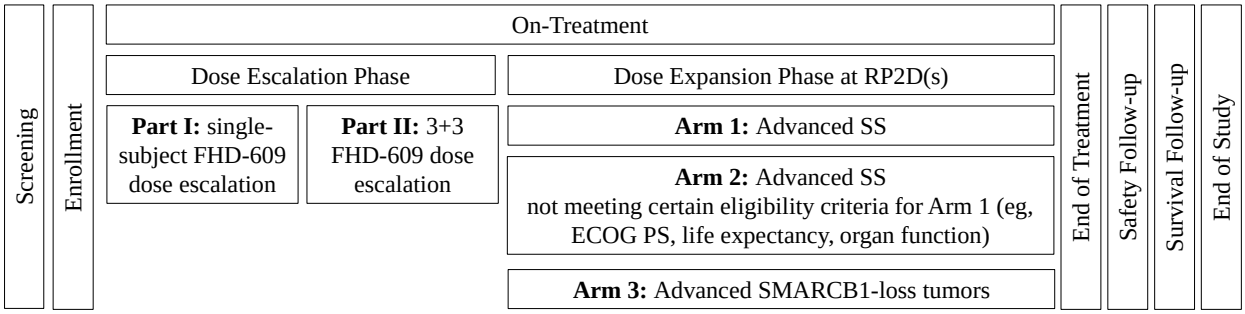
Clinical study FHD-609-C-001 was an open-label, single-arm, Phase 1 study of FHD-609 in subjects with advanced SS or SMARCB-1 loss tumor. FHD-609 was administered IV BIW or QW as monotherapy in 28-day cycles. This study was designed to assess the safety, tolerability, PK, PD, and preliminary clinical activity of FHD-609 IV monotherapy. The goal of the Dose Escalation Phase of the study was to determine the MTD and/or RP2D(s) of FHD-609. The proposed RP2D(s) was to be determined by the CST, comprising the sponsor (Responsible Medical Officer), study medical monitor, and investigators, and was to be the dose schedule identified for continued study, based on observed safety, tolerability, PK, PD, and clinical activity data. The MTD was defined as the highest dose that caused DLTs in <2 of 6 subjects.

Dose escalation occurred in 2 parts: Subjects were initially enrolled to single-subject cohorts and the study transitioned to a traditional 3+3 design once one subject exhibited any DLTs and/or 1 subject experienced treatment-related, Grade ≥2, non-DLTs, during the first 6 weeks of treatment. Dose escalation decisions were based on the safety, clinical activity, PK, and PD data available when 1 (single-subject cohorts) or 3 (3+3 design) DLT-evaluable subjects in a given cohort had completed the 6-week DLT evaluation period.

Subjects continued treatment until confirmed disease progression per RECIST v1.1 (Eisenhauer, et al 2009), death, start of alternative anticancer therapy, unacceptable toxicity, or study withdrawal. An End of Treatment visit occurred within 7 days after the last dose of study drug, and a post-treatment Safety Follow-up visit occurred 28 (±7) days after the End of Treatment visit. After discontinuing treatment with FHD-609, subjects were contacted by telephone approximately every 3 months to assess survival status and to document receipt and type of subsequent anticancer therapy, unless consent/assent was withdrawn. Figure 1 illustrates the study design.

A cohort expansion phase of the study was planned to further evaluate safety and tolerability at the MTD and/or RP2D(s), but no subjects were enrolled, as the study was stopped for business reasons. In response, FDA placed the study on partial clinical hold in April 2023. The sponsor responded to the FDA partial clinical hold comments in October 2023 to address clinical deficiencies; however, because the sponsor decided to stop further development of FHD-609 for business reasons in November 2023, the study remains on partial clinical hold.

Figure 1: Study Design Schema



Abbreviations: ECOG PS=Eastern Cooperative Oncology Group Performance Status; RP2D=recommended Phase 2 dose; SS=synovial sarcoma.

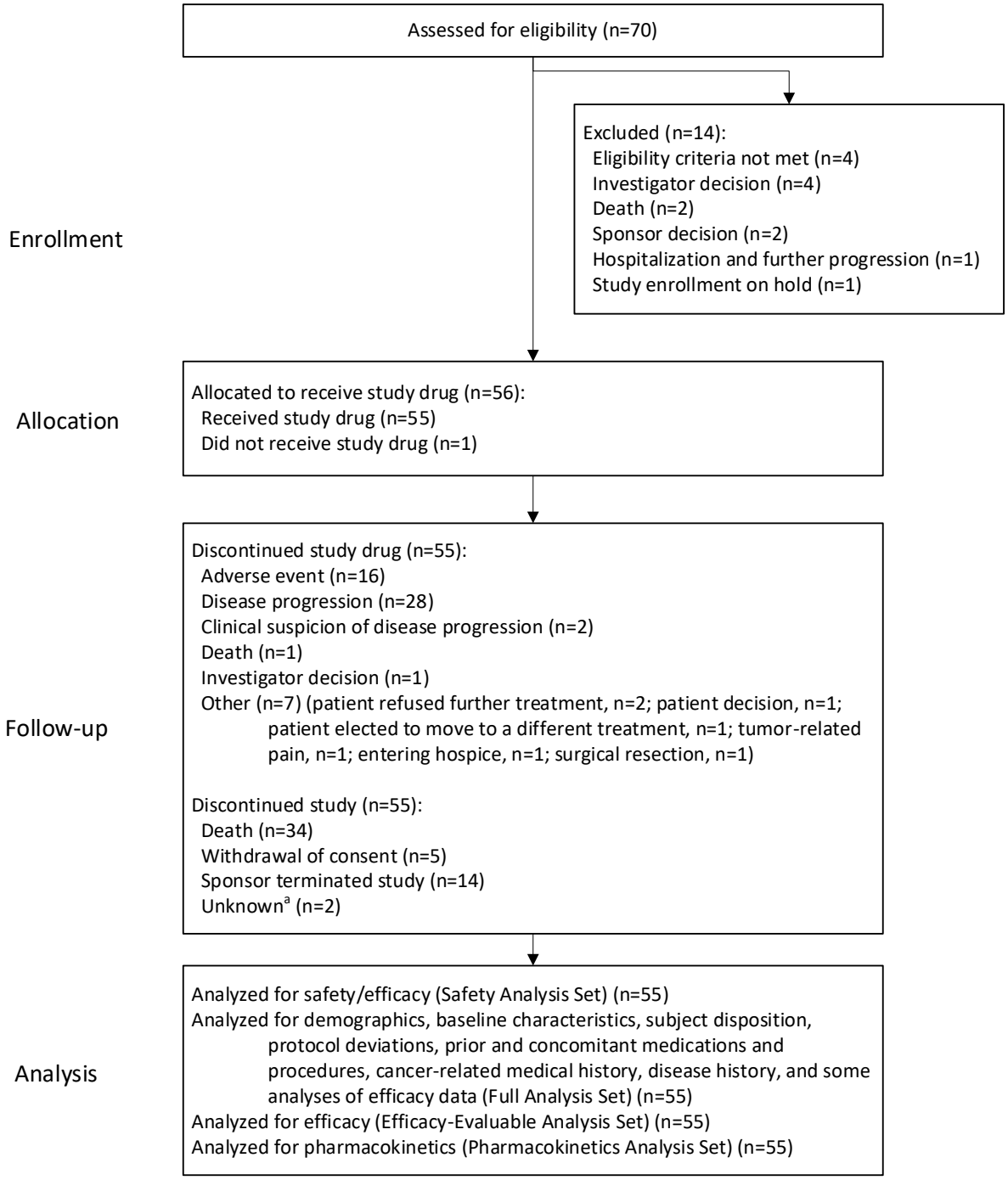
Number of Subjects (Planned and Analyzed)

A total of approximately 104 subjects were planned to be enrolled and treated in this study, including approximately 27 to 39 subjects in the Dose Escalation Phase and approximately 40 to 65 subjects in the Dose Expansion Phase.

Seventy subjects were assessed for eligibility. Fourteen were excluded, primarily because inclusion/exclusion criteria were not met. One subject was enrolled but did not receive study drug. Fifty-five subjects received ≥1 dose of FHD-609, including 38 subjects in the US and 17 subjects in the European Union (1 subject in Italy, 6 subjects in Spain, and 10 subjects in France), and were included in all analysis sets (Figure 2).

While 16 subjects in the disposition data were reported as discontinuing treatment due to an AE, 17 subjects in the AE data were reported as having a TEAE that led to treatment discontinuation. In the disposition data, 3 subjects had a reason for discontinuation of “AE;” however, in the AE data, there were no corresponding AEs leading to treatment discontinuation for these subjects. For 4 subjects, AEs had an action taken of “drug withdrawn,” however, in the disposition data, the reason for discontinuation was not “AE” (reasons were “subject is entering hospice care,” “disease progression,” “tumor related pain,” and “patient decision”).

Figure 2: Subject Disposition (Study FHD-609-C-001, Dose Escalation)



Source: Tables 14.1.1.1.1 and Table 14.1.1.2.1; Listings 16.2.1 and 16.2.3.1.
Note: The Safety Analysis Set/Full Analysis Set includes all subjects who were enrolled and received ≥1 dose of study drug. The Efficacy-Evaluable Analysis Set includes all subjects who received ≥1 dose of study drug and who completed ≥1 postbaseline assessment or had discontinued from study. The Pharmacokinetics Analysis Set includes all subjects who received ≥1 dose of study drug who had ≥1 blood sample providing efficacy PK data for FHD-609.
[a] Two subjects discontinued the study but did not have end of study disposition events in the electronic database and therefore were not included in the summary of subjects who discontinued the study.

Diagnosis and Main Criteria for Inclusion and Exclusion

Eligible subjects included those ≥18 years of age, or ≥16 years of age with a minimum body weight of 50 kg, with a confirmed pathological diagnosis of advanced SS or advanced SMARCB-1 loss tumor. Treatment-naïve subjects must have had no other reasonable therapeutic options in the opinion of the Investigator. Previously treated subjects must have had demonstrated progress of disease on their most recent therapy or discontinued their most recent therapy due to potential for cumulative toxicity, intolerability, or lack of continued clinical benefit. Subjects were required to have measurable disease by RECIST v1.1, Eastern Cooperative Oncology Group (ECOG) performance status of ≤2, and adequate organ function.

Subjects were excluded if they had active central nervous system metastases, except under certain conditions, or prior exposure to a BRD9 degrader. Systemic anticancer therapy within 2 weeks (or 5 half-lives) of the first dose of study treatment, systemic steroid therapy (other than stable doses for controlled chronic disease), and systemic immunosuppressive medications were not permitted at enrollment.

Detailed eligibility criteria are described in the protocol (Appendix 16.1.1).

Study Interventions, Dose, and Mode of Administration

Beginning on Cycle 1 Day 1 (C1D1), FHD-609 was administered as a 2-hour IV infusion at the study site on either a BIW or QW schedule. Subjects were assigned to a given dose and schedule by the sponsor in discussion with the investigator. Intrasubject dose escalation was permitted.

Increases in the dose of FHD-609 for each cohort were guided by an accelerated titration design, wherein the daily dose could be increased by a maximum of 100% from one cohort to the next. The absolute percent increase (or decrease) was determined by the CST, and was based on the available safety, PK, PD, and clinical activity data. The Dose Escalation Phase continued in this manner until the MTD and/or RP2D(s) was determined. If warranted based on the emerging data, alternative dosing schedule(s) and/or infusion times could be explored as agreed upon by the CST.

The following doses were evaluated:

- BIW:
  - 5 mg
  - 10 mg
  - 20 mg
  - 40 mg
  - 60 mg
  - 80 mg
- QW
  - 40 mg
  - 80 mg

- 120 mg

Duration of Study Intervention

Subjects continued treatment with FHD-609 until withdrawal of consent/assent, experiencing an AE and/or DLT or other unacceptable toxicity, removal at the discretion of the investigator, disease progression, start of alternative cancer therapy, development of an intercurrent medical condition or need for a concomitant medication that precluded further participation in the study, protocol violation, becoming lost to follow-up, becoming pregnant, dying, lack of efficacy, or the sponsor ending the study, whichever occurred first.

Subjects who experienced disease progression per the applicable response criteria but for whom continuing treatment was in the subject's best interest, in the opinion of the investigator, may have been allowed to continue on study drug, with sponsor approval.

Summary of Pharmacokinetic Assessments

The time points for collection of pharmacokinetic samples, and the permitted time deviations in sample collection, are provided in the protocol (Appendix 16.1.1).

Blood samples for analysis of FHD-609 concentrations in blood and plasma were collected separately into custom collection tubes containing 1% (volume-to-volume [v/v]) of 3M liquid citric acid (to stabilize the pH of the sample without causing clotting) and into EDTA (ethylenediaminetetraacetic acid) tubes, respectively. Samples for plasma analysis were then processed to obtain plasma, which was aliquoted into tubes containing 1% (v/v) 3M lyophilized citric acid (to stabilize the pH of the sample). Whole blood samples were analyzed for FHD-609 using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method with a nominal quantitative range of 3.00 to 750 ng/mL (Report V2012088.01). Plasma samples were analyzed for FHD-609 using a validated LC-MS/MS method in plasma with a quantitative nominal range of 1.00 to 250 ng/mL (Report V2012085.01).

The PK parameters of FHD-609 after a single dose on C1D1 included C_{max}, T_{max}, T_{last} (time of last observed concentration), $t_{1/2}$ (terminal elimination half-life), and $AUC_{0\text{-}72hr}$ (AUC from time 0 to 72 hours postdose) (BIW dosing) or $AUC_{0\text{-}168hr}$ (AUC from 0 to 168 hours postdose) (QW dosing). The PK parameters of FHD-609 after BIW or QW dosing on C1D22 included C_{max}, T_{max}, T_{last}, $t_{1/2}$, and $AUC_{0\text{-}72hr}$ (BIW dosing) or $AUC_{0\text{-}168hr}$ (QW dosing). Accumulation was determined by comparing the means of C_{max} and AUC after multiple doses on C1D22 versus a single dose of FHD-609 on C1D1. Noncompartmental analyses were conducted using Phoenix WinNonlin (version 8.4; Certara, Radnor, Pennsylvania, US), and concentration-time figures were generated in R (version 4.2.2). Pharmacokinetic data were analyzed using nominal doses and actual sampling time points.

Summary of Results and Conclusions

Protocol Deviations

Fourteen (25.5%) subjects had a major protocol deviation (Table 14.1.2.1.1). The major protocol deviations were "study procedure/missed procedure" (5 [9.1%]), "investigational product/IP dosing" (3 [5.5%]), "inclusion or exclusion criteria" and "SAE not reported or reported late" (2

[3.6%] each), and "study procedure/other" and "visit window" (1 [1.8%] each). There were no major protocol deviations due to COVID-19 (Table 14.1.2.2.1).

Details on major protocol deviations are provided in Listing 16.2.2.

Analysis Sets

All subjects who received at least 1 dose of study treatment were included in each analysis set (Figure 2).

Demographic and Other Baseline Characteristics

Demographics and disease characteristics were generally well balanced across dose levels. The median age was 36 years (range: 19-73). Most (96.4%) subjects were <65 years old, 22 (40%) were female, and 35 (63.4%) were White. Most (96.3%) subjects had an ECOG performance status of 0 or 1 (Table 1).

Fifty-three (96.4%) subjects had a diagnosis of advanced SS, and 2 (3.6%) subjects had SMARCB1-loss tumors (1 with epithelioid sarcoma and 1 with sarcomatoid carcinoma of the renal pelvis). The median time since the diagnosis of metastatic disease was 2.0 years (range: 0.1-11.8) (Table 2).

The medical history of the subjects in this study was reflective of the advanced synovial sarcoma/SMARCB1-loss tumor patient population (Table 14.1.4.1.1).

All subjects had previously been treated with surgery, radiotherapy, and/or chemotherapy/ immunotherapy. The median number of prior lines of chemotherapy/immunotherapy was 3 (range: 1-8); 38 (69.1%) subjects had received ≥3 prior lines of chemotherapy/immunotherapy (Table 3). Fifty-one (94.4%) subjects had previously been treated with anthracyclines (most commonly doxorubicin) (Listing 16.2.4.2.4). Information on dexrazoxane use was not collected.

The prior and concomitant medications and procedures were reflective of the advanced SS/SMARCB1-loss patient population (Tables 14.1.5.1.1, 14.1.5.2.1, 14.1.5.3.1, 14.1.5.4.1). The most common (taken by ≥30% of subjects overall) classes of concomitant medications were:

- Analgesics (48 [87.3%] subjects)
- Drugs for constipation (31 [56.4%] subjects)
- Antiemetics and antinauseants (29 [52.7%] subjects)
- Psycholeptics (28 [50.9%] subjects)
- Antibacterials for systemic use (24 [43.6%] subjects)
- Drugs for acid related disorders (24 [43.6%] subjects)
- Vitamins (19 [34.5%] subjects)

Table 1: Demographics and Other Baseline Characteristics (Study FHD-609-C-001, Dose Escalation) (Full Analysis Set)

Parameter	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Age (years)										
n (%)	4 (100)	7 (100)	5 (100)	8 (100)	7 (100)	9 (100)	2 (100)	5 (100)	8 (100)	55 (100)
Mean (SD)	45.5 (18.05)	41.1 (15.13)	41.8 (16.84)	43.1 (14.98)	34.1 (13.36)	48.2 (10.20)	38.5 (6.36)	42.6 (16.35)	35 (11.56)	41.2 (13.77)
Median	48.5	37.0	34.0	41.5	31.0	52.0	38.5	35.0	32.5	36.0
Min, max	23, 62	26, 73	27, 61	23, 62	19, 58	30, 58	34, 43	27, 66	19, 59	19, 73
Age group, n (%)										
<65 years	4 (100)	6 (85.7)	5 (100)	8 (100)	7 (100)	9 (100)	2 (100)	4 (80.0)	8 (100)	53 (96.4)
≥65 years	0	1 (14.3)	0	0	0	0	0	1 (20.0)	0	2 (3.6)
Sex, n (%)										
Male	2 (50.0)	6 (85.7)	2 (40.0)	5 (62.5)	6 (85.7)	4 (44.4)	1 (50.0)	4 (80.0)	3 (37.5)	33 (60.0)
Female	2 (50.0)	1 (14.3)	3 (60.0)	3 (37.5)	1 (14.3)	5 (55.6)	1 (50.0)	1 (20.0)	5 (62.5)	22 (40.0)
Race, n (%)										
White	4 (100)	4 (57.1)	3 (60.0)	7 (87.5)	3 (42.9)	5 (55.6)	1 (50.0)	3 (60.0)	5 (62.5)	35 (63.6)
Asian	0	1 (14.3)	1 (20.0)	1 (12.5)	0	0	0	0	0	3 (5.5)
Multiple	0	0	0	0	0	0	0	0	1 (12.5)	1 (1.8)
Not reported	0	1 (14.3)	0	0	3 (42.9)	4 (44.4)	1 (50.0)	2 (40.0)	2 (25.0)	13 (23.6)
Unknown	0	1 (14.3)	1 (20.0)	0	1 (14.3)	0	0	0	0	3 (5.5)

Table 1: Demographics and Other Baseline Characteristics (Study FHD-609-C-001, Dose Escalation) (Full Analysis Set)

Parameter	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Ethnicity, n (%)										
Hispanic or Latino	0	1 (14.3)	1 (20.0)	2 (25.0)	2 (28.6)	2 (22.2)	1 (50.0)	0	1 (12.5)	10 (18.2)
Not Hispanic or Latino	4 (100)	6 (85.7)	4 (80.0)	6 (75.0)	2 (28.6)	4 (44.4)	1 (50.0)	3 (60.0)	5 (62.5)	35 (63.6)
Not reported	0	0	0	0	3 (42.9)	3 (33.3)	0	2 (40.0)	2 (25)	10 (18.2)
ECOG performance status at baseline, n (%)										
0	1 (25.0)	3 (42.9)	3 (60.0)	3 (37.5)	6 (85.7)	3 (33.3)	0	1 (20.0)	3 (37.5)	23 (41.8)
1	3 (75.0)	3 (42.9)	2 (40.0)	4 (50.0)	1 (14.3)	6 (66.7)	2 (100)	4 (80.0)	5 (62.5)	30 (54.5)
2	0	1 (14.3)	0	1 (12.5)	0	0	0	0	0	2 (3.6)

Source: Table 14.1.3.1.
Abbreviations: BIW=twice weekly; ECOG=Eastern Cooperative Oncology Group; QW=once weekly.
Note: The Full Analysis Set includes all subjects who were enrolled and received ≥1 dose of study treatment. Categories with 0 subjects are not shown.

Table 2: Baseline Disease Characteristics (Study FHD-609-C-001, Dose Escalation) (Full Analysis Set)

Parameter	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Type of advanced cancer at screening, n (%)										
Synovial sarcoma	4 (100)	7 (100)	5 (100)	8 (100)	7 (100)	9 (100)	2 (100)	4 (80.0)	7 (87.5)	53 (96.4)
SMARCB1-loss tumor	0	0	0	0	0	0	0	1 (20.0)	1 (12.5)	2 (3.6)
Epithelioid sarcoma	0	0	0	0	0	0	0	0	1 (12.5)	1 (1.8)
Other[a]	0	0	0	0	0	0	0	1 (20.0)	0	1 (1.8)
Subtype of advanced cancer at screening, n (%)										
Metastatic	4 (100)	6 (85.7)	5 (100)	7 (87.5)	6 (85.7)	8 (88.9)	2 (100)	4 (80.0)	7 (87.5)	49 (89.1)
Local (primary disease) and unresectable	0	0	0	1 (12.5)	0	0	0	1 (20.0)	0	2 (3.6)
Local (recurrent disease) and unresectable	0	1 (14.3)	0	0	1 (14.3)	1 (11.1)	0	0	1 (12.5)	4 (7.3)
Time since initial cancer diagnosis (years)										
n (%)	4 (100)	7 (100)	5 (100)	8 (100)	7 (100)	9 (100)	2 (100)	5 (100)	8 (100)	55 (100)
Mean (SD)	4.566 (3.311)	6.719 (4.986)	2.828 (1.601)	5.555 (3.338)	4.244 (3.930)	3.323 (1.417)	3.110 (0.596)	3.279 (1.789)	3.509 (3.185)	4.258 (3.190)
Median	3.695	6.264	2.828	4.987	2.146	2.762	3.110	3.529	2.063	3.118
Min, max	1.689, 9.185	1.900, 15.923	0.994, 4.709	1.150, 10.546	1.807, 12.266	1.840, 6.292	2.689, 3.532	1.018, 5.407	1.035, 10.272	0.994, 15.923

Table 2: Baseline Disease Characteristics (Study FHD-609-C-001, Dose Escalation) (Full Analysis Set)

Parameter	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Time since metastatic diagnosis (years)										
n (%)	4 (100)	6 (85.7)	5 (100)	7 (87.5)	6 (85.7)	8 (88.9)	2 (100)	3 (60.0)	7 (87.5)	48 (87.3)
Mean (SD)	3.042 (1.120)	4.240 (3.797)	2.069 (1.016)	4.508 (2.933)	1.892 (1.467)	1.627 (0.949)	2.372 (1.512)	1.931 (1.609)	2.265 (3.200)	2.714 (2.412)
Median	3.125	2.838	1.585	4.192	1.647	1.273	2.372	1.153	0.652	2.014
Min, max	1.645, 4.271	1.914, 11.808	0.994, 3.428	0.115, 9.629	0.249, 4.638	0.832, 3.469	1.303, 3.441	0.860, 3.781	0.129, 9.183	0.115, 11.808
Stage at screening, n (%)										
Stage II	0	0	1 (20.0)	0	0	0	0	0	0	1 (1.8)
Stage III	0	0	0	0	0	1 (11.1)	0	0	2 (25.0)	3 (5.5)
Stage IV	4 (100)	6 (85.7)	4 (80.0)	8 (100)	7 (100)	8 (88.9)	2 (100)	5 (100)	6 (75.0)	50 (90.9)
Missing	0	1 (14.3)	0	0	0	0	0	0	0	1 (1.8)

Source: Table 14.1.4.3.1 and Listing 16.2.4.2.5.
Abbreviations: BIW=twice weekly; QW=once weekly.
Note: The Full Analysis Set includes all subjects who were enrolled and received ≥1 dose of study treatment. Categories with 0 subjects are not shown.
[a] Sarcomatoid carcinoma.

Table 3: Cancer-Related Medical History (Study FHD-609-C-001, Dose Escalation) (Full Analysis Set)

Parameter	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Prior anticancer therapy, n (%)										
Yes	4 (100)	7 (100)	5 (100)	8 (100)	7 (100)	9 (100)	2 (100)	5 (100)	8 (100)	55 (100)
Surgery	4 (100)	7 (100)	5 (100)	8 (100)	6 (85.7)	8 (88.9)	2 (100)	4 (80.0)	6 (75.0)	50 (90.9)
Radiotherapy	3 (75.0)	4 (57.1)	4 (80.0)	7 (87.5)	5 (71.4)	6 (66.7)	2 (100)	4 (80.0)	6 (75.0)	41 (74.5)
Chemotherapy/ immunotherapy	3 (75.0)	7 (100)	5 (100)	8 (100)	7 (100)	9 (100)	2 (100)	5 (100)	8 (100)	54 (98.2)
Number of prior lines of chemotherapy/immunotherapy, n (%)										
1	0	0	1 (20.0)	1 (12.5)	3 (42.9)	1 (11.1)	0	0	2 (25.0)	8 (14.5)
2	0	0	1 (20.0)	0	0	3 (33.3)	0	2 (40.0)	2 (25.0)	8 (14.5)
≥3	3 (75.0)	7 (100)	3 (60.0)	7 (87.5)	4 (57.1)	5 (55.6)	2 (100)	3 (60.0)	4 (50.0)	38 (69.1)
3	1 (25.0)	1 (14.3)	1 (20.0)	3 (37.5)	3 (42.9)	1 (11.1)	1 (50.0)	1 (20.0)	1 (12.5)	13 (23.6)
4	1 (25.0)	0	0	0	0	3 (33.3)	0	1 (20.0)	0	5 (9.1)
5	1 (25.0)	2 (28.6)	0	3 (37.5)	1 (14.3)	0	0	1 (20.0)	3 (37.5)	11 (20)
6	0	4 (57.1)	1 (20.0)	1 (12.5)	0	0	1 (50.0)	0	0	7 (12.7)
8	0	0	1 (20.0)	0	0	1 (11.1)	0	0	0	2 (3.6)

Table 3: Cancer-Related Medical History (Study FHD-609-C-001, Dose Escalation) (Full Analysis Set)

Parameter	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Number of prior lines of chemotherapy/immunotherapy										
n (%)	3 (75)	7 (100)	5 (100)	8 (100)	7 (100)	9 (100)	2 (100)	5 (100)	8 (100)	54 (98.2)
Mean (SD)	4.0 (1.00)	5.3 (1.11)	4 (2.92)	3.9 (1.64)	2.4 (1.51)	3.3 (2.06)	4.5 (2.12)	3.2 (1.30)	3 (1.77)	3.6 (1.85)
Median	4.0	6.0	3.0	4.0	3.0	3.0	4.5	3.0	2.5	3.0
Min, max	3, 5	3, 6	1, 8	1, 6	1, 5	1, 8	3, 6	2, 5	1, 5	1, 8

Source: Table 14.1.4.2.1.
Abbreviations: BIW=twice weekly; QW=once weekly.
Note: The Full Analysis Set includes all subjects who were enrolled and received ≥1 dose of study treatment. Percentages are based on the number of subjects in the Full Analysis Set within each dose level. Categories with 0 subjects are not shown.

A by-subject listing of demographics and baseline characteristics, medical history, prior anticancer surgery, prior anticancer radiotherapy, prior anticancer chemotherapy/ immunotherapy, disease history, prior and concomitant medications, and prior and concomitant procedures is provided in Listings 16.2.4.1, 16.2.4.2.1, 16.2.4.2.2, 16.2.4.2.3, 16.2.4.2.4, 16.2.4.2.5, 16.2.4.3, and 16.2.4.4, respectively.

Exposure and Compliance

The median duration of exposure was 43 days (range: 1-463). Among the BIW treatment cohorts, the median duration of exposure was 77.5, 50, 50, 32, 39, and 22 days for FHD-609 5, 10, 20, 40, 60, and 80 mg BIW, respectively. Among the QW treatment cohorts, the median duration of exposure was 33.5, 43, and 50 days for FHD-609 40, 80, and 120 mg QW, respectively (Table 14.1.6.1.1).

Intrasubject dose escalation occurred in 3 subjects: from 5 mg BIW to 10 mg BIW in 2 subjects and from 40 mg BIW to 80 mg BIW in 1 subject (Listing 16.2.5.1). Dose modifications that resulted from TEAEs are presented in the section entitled, "Discontinuations and/or Dose Modifications Due to AEs."

FHD-609 was administered IV; relative dose intensity was 100% (Table 14.1.6.2.1).

Safety Results

TEAE Summary

Overall, 54 (98.2%) subjects had ≥1 TEAE; 45 (81.8%) had ≥1 treatment-related TEAE (TRAE) (Table 4).

Table 4: Overall TEAE Summary (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

Parameter	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Any TEAE	4 (100)	7 (100)	5 (100)	7 (87.5)	7 (100)	9 (100)	2 (100)	5 (100)	8 (100)	54 (98.2)
Any TRAE	2 (50.0)	6 (85.7)	5 (100)	7 (87.5)	6 (85.7)	6 (66.7)	2 (100)	4 (80.0)	7 (87.5)	45 (81.8)
Any SAE	2 (50.0)	5 (71.4)	2 (40.0)	3 (37.5)	5 (71.4)	7 (77.8)	2 (100)	2 (40.0)	4 (50.0)	32 (58.2)
Any treatment-related SAE	0	0	1 (20.0)	1 (12.5)	2 (28.6)	2 (22.2)	0	1 (20.0)	1 (12.5)	8 (14.5)
Any Grade ≥3 TEAE	2 (50.0)	5 (71.4)	2 (40.0)	6 (75.0)	6 (85.7)	8 (88.9)	2 (100)	5 (100)	4 (50.0)	40 (72.7)
Any treatment-related Grade ≥3 TEAE	0	1 (14.3)	2 (40.0)	4 (50.0)	2 (28.6)	3 (33.3)	0	1 (20.0)	1 (12.5)	14 (25.5)
Any TEAE classified as a DLT	0	0	0	1 (12.5)	1 (14.3)	0	0	0	0	2 (3.6)
Any TEAE leading to dose reduction	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)
Any TRAE leading to dose reduction	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)
Any TEAE leading to dose interruption	3 (75.0)	3 (42.9)	3 (60.0)	5 (62.5)	3 (42.9)	8 (88.9)	0	3 (60.0)	5 (62.5)	33 (60.0)
Any TRAE leading to dose interruption	0	0	3 (60.0)	3 (37.5)	2 (28.6)	4 (44.4)	0	2 (40.0)	5 (62.5)	19 (34.5)

Table 4: Overall TEAE Summary (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

Parameter	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Any TEAE leading to treatment discontinuation	1 (25.0)	2 (28.6)	1 (20.0)	4 (50.0)	3 (42.9)	3 (33.3)	2 (100)	1 (20.0)	0	17 (30.9)
Any TRAE leading to treatment discontinuation	0	0	0	1 (12.5)	2 (28.6)	0	0	0	0	3 (5.5)
Any TEAE leading to death	0	2 (28.6)	1 (20.0)	2 (25.0)	1 (14.3)	4 (44.4)	1 (50.0)	1 (20.0)	1 (12.5)	13 (23.6)
Any TRAE leading to death	0	0	0	0	0	0	0	1 (20.0)	0	1 (1.8)

Source: Tables 14.3.1.1.1 and 14.3.99.1.1.
Abbreviations: BIW=twice weekly; CTCAE=Common Terminology Criteria for Adverse Events; DLT=dose-limiting toxicity; QW=once weekly; TRAE=treatment-related TEAE.
Note: The Safety Analysis Set includes all subjects who were enrolled and received ≥1 dose of study treatment. Percentages are based on the number of subjects in the Safety Analysis Set within each dose level. A TEAE is any AE either reported for the first time or worsening of a preexisting event after the first dose of study treatment and within 28 days of the last administration of study treatment. The severity of AEs or abnormal laboratory results is based on the National Cancer Institute CTCAE version 5.0.

A by-subject listing of adverse events, by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT) and by grouped PT, is provided in Listings 16.2.7.1 and 16.2.7.8, respectively.

Adverse Events

Frequency of TEAEs by SOC and PT

Overall, 54 (98.2%) subjects had ≥1 TEAE, most frequently (≥30%) in the Gastrointestinal disorders (37 [67.3%]), General disorders and administration site conditions and Investigations (35 [63.6%] each), Blood and lymphatic system disorders (29 [52.7%]), Respiratory, thoracic and mediastinal disorders and Nervous system disorders (28 [50.9%] each), Metabolism and nutrition disorders (21 [38.2%]), Cardiac disorders (20 [36.4%]), and Musculoskeletal and connective tissue disorders (17 [30.9%]) SOCs. Table 5 presents the most common TEAEs (≥10%) within these SOCs.

Table 5: Summary of TEAEs Reported in ≥30% of Subjects Overall in a Given SOC and in ≥10% of Subjects Overall for a Given PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

System Organ Class Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Any TEAE	**4 (100)**	**7 (100)**	**5 (100)**	**7 (87.5)**	**7 (100)**	**9 (100)**	**2 (100)**	**5 (100)**	**8 (100)**	**54 (98.2)**
Gastrointestinal disorders	**2 (50.0)**	**6 (85.7)**	**3 (60.0)**	**6 (75.0)**	**5 (71.4)**	**6 (66.7)**	**1 (50.0)**	**3 (60.0)**	**5 (62.5)**	**37 (67.3)**
Dry mouth	1 (25.0)	3 (42.9)	2 (40.0)	4 (50.0)	2 (28.6)	2 (22.2)	1 (50.0)	0	3 (37.5)	18 (32.7)
Constipation	1 (25.0)	2 (28.6)	1 (20.0)	2 (25.0)	0	0	0	0	2 (25.0)	8 (14.5)
Diarrhoea	1 (25.0)	0	1 (20.0)	3 (37.5)	0	3 (33.3)	0	0	0	8 (14.5)
Nausea	0	3 (42.9)	0	2 (25.0)	0	2 (22.2)	0	0	1 (12.5)	8 (14.5)
Abdominal pain	0	2 (28.6)	0	1 (12.5)	1 (14.3)	1 (11.1)	0	2 (40.0)	0	7 (12.7)
Stomatitis	0	0	0	1 (12.5)	3 (42.9)	0	0	1 (20.0)	2 (25.0)	7 (12.7)
General disorders and administration site conditions	**2 (50.0)**	**2 (28.6)**	**4 (80.0)**	**6 (75.0)**	**5 (71.4)**	**6 (66.7)**	**1 (50.0)**	**4 (80.0)**	**5 (62.5)**	**35 (63.6)**
Fatigue	1 (25.0)	2 (28.6)	4 (80.0)	1 (12.5)	4 (57.1)	2 (22.2)	1 (50.0)	1 (20.0)	4 (50.0)	20 (36.4)
Pyrexia	0	0	1 (20.0)	2 (25.0)	3 (42.9)	4 (44.4)	0	2 (40.0)	2 (25.0)	14 (25.5)
Investigations	**2 (50.0)**	**4 (57.1)**	**5 (100)**	**6 (75.0)**	**3 (42.9)**	**6 (66.7)**	**0**	**4 (80.0)**	**5 (62.5)**	**35 (63.6)**
Platelet count decreased	0	2 (28.6)	3 (60.0)	2 (25.0)	0	3 (33.3)	0	3 (60.0)	2 (25.0)	15 (27.3)
White blood cell count decreased	0	4 (57.1)	3 (60.0)	2 (25.0)	0	2 (22.2)	0	1 (20.0)	1 (12.5)	13 (23.6)
Blood creatine phosphokinase increased	0	0	1 (20.0)	3 (37.5)	0	3 (33.3)	0	2 (40.0)	2 (25.0)	11 (20.0)

Table 5: Summary of TEAEs Reported in ≥30% of Subjects Overall in a Given SOC and in ≥10% of Subjects Overall for a Given PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

System Organ Class Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Neutrophil count decreased	0	2 (28.6)	3 (60.0)	2 (25.0)	0	2 (22.2)	0	1 (20.0)	1 (12.5)	11 (20.0)
Alanine aminotransferase increased	1 (25.0)	0	1 (20.0)	4 (50.0)	0	0	0	3 (60.0)	0	9 (16.4)
Aspartate aminotransferase increased	1 (25.0)	0	2 (40.0)	3 (37.5)	0	0	0	3 (60.0)	0	9 (16.4)
Blood bilirubin increased	0	0	1 (20.0)	2 (25.0)	2 (28.6)	2 (22.2)	0	1 (20.0)	0	8 (14.5)
Lymphocyte count decreased	0	2 (28.6)	2 (40.0)	2 (25.0)	0	1 (11.1)	0	1 (20.0)	0	8 (14.5)
Blood creatinine increased	0	0	2 (40.0)	2 (25.0)	0	2 (22.2)	0	1 (20.0)	0	7 (12.7)
Blood lactate dehydrogenase increased	0	0	1 (20.0)	2 (25.0)	0	1 (11.1)	0	2 (40.0)	0	6 (10.9)
Gamma-glutamyltransferase increased	0	0	0	2 (25.0)	0	1 (11.1)	0	3 (60.0)	0	6 (10.9)
Blood and lymphatic system disorders	**1 (25.0)**	**2 (28.6)**	**4 (80.0)**	**5 (62.5)**	**4 (57.1)**	**6 (66.7)**	**1 (50.0)**	**4 (80.0)**	**2 (25.0)**	**29 (52.7)**
Anaemia	1 (25.0)	2 (28.6)	4 (80.0)	5 (62.5)	3 (42.9)	6 (66.7)	1 (50.0)	3 (60.0)	2 (25.0)	27 (49.1)

Table 5: Summary of TEAEs Reported in ≥30% of Subjects Overall in a Given SOC and in ≥10% of Subjects Overall for a Given PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

System Organ Class Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Nervous system disorders	**4 (100)**	**4 (57.1)**	**5 (100)**	**4 (50.0)**	**2 (28.6)**	**2 (22.2)**	**0**	**2 (40.0)**	**5 (62.5)**	**28 (50.9)**
Dysgeusia	3 (75.0)	4 (57.1)	4 (80.0)	4 (50.0)	2 (28.6)	2 (22.2)	0	1 (20.0)	4 (50.0)	24 (43.6)
Headache	1 (25.0)	1 (14.3)	1 (20.0)	2 (25.0)	0	1 (11.1)	0	1 (20.0)	2 (25.0)	9 (16.4)
Respiratory, thoracic and mediastinal disorders	**0**	**5 (71.4)**	**3 (60.0)**	**4 (50.0)**	**3 (42.9)**	**7 (77.8)**	**1 (50.0)**	**1 (20.0)**	**4 (50.0)**	**28 (50.9)**
Dyspnoea	0	2 (28.6)	1 (20.0)	4 (50.0)	2 (28.6)	4 (44.4)	0	0	3 (37.5)	16 (29.1)
Haemoptysis	0	0	0	4 (50.0)	1 (14.3)	1 (11.1)	0	0	0	6 (10.9)
Metabolism and nutrition disorders	**1 (25.0)**	**4 (57.1)**	**3 (60.0)**	**2 (25.0)**	**3 (42.9)**	**4 (44.4)**	**1 (50.0)**	**1 (20.0)**	**2 (25.0)**	**21 (38.2)**
Hyponatraemia	0	4 (57.1)	0	2 (25.0)	0	1 (11.1)	0	0	0	7 (12.7)
Decreased appetite	0	2 (28.6)	0	0	0	1 (11.1)	0	1 (20.0)	2 (25.0)	6 (10.9)
Hyperglycaemia	0	3 (42.9)	2 (40.0)	0	0	0	1 (50.0)	0	0	6 (10.9)
Cardiac disorders	**1 (25.0)**	**2 (28.6)**	**1 (20.0)**	**1 (12.5)**	**4 (57.1)**	**4 (44.4)**	**1 (50.0)**	**0**	**6 (75.0)**	**20 (36.4)**
Sinus tachycardia	0	1 (14.3)	0	0	2 (28.6)	2 (22.2)	1 (50.0)	0	0	6 (10.9)
Tachycardia	1 (25.0)	1 (14.3)	0	0	1 (14.3)	0	0	0	3 (37.5)	6 (10.9)

Table 5: Summary of TEAEs Reported in ≥30% of Subjects Overall in a Given SOC and in ≥10% of Subjects Overall for a Given PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

System Organ Class Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Musculoskeletal and connective tissue disorders	**3 (75.0)**	**3 (42.9)**	**2 (40.0)**	**4 (50.0)**	**0**	**1 (11.1)**	**1 (50.0)**	**1 (20.0)**	**2 (25.0)**	**17 (30.9)**
Back pain	1 (25.0)	2 (28.6)	0	2 (25.0)	0	0	0	1 (20.0)	0	6 (10.9)
Muscle spasms	0	1 (14.3)	1 (20.0)	1 (12.5)	0	0	1 (50.0)	0	2 (25.0)	6 (10.9)

Source: Table 14.3.1.2.1.
Abbreviations: BIW=twice weekly; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; QW=once weekly; SOC=System Organ Class.
Note: The Safety Analysis Set includes all subjects who were enrolled and received ≥1 dose of study drug. Subjects were analyzed according to the dose level initially assigned. Percentages are based on the number of subjects in the Safety Analysis Set within each dose level.
A TEAE is any AE either reported for the first time or worsening of a preexisting event after the first dose of study treatment and within 28 days of the last administration of study treatment. Adverse events are coded using MedDRA version 26.0. A subject is counted only once for multiple events within each MedDRA PT.

Frequency of TEAEs by PT or Grouped PT

The most frequent (≥20%) TEAEs, by PT or grouped PT, were Anaemia (27 [49.1%]), Dysgeusia (24 [43.6%]), Fatigue (20 [36.4%]), Dry mouth (18 [32.7%]), Dyspnoea (16 [29.1%]), Decreased platelet count (15 [27.3%]), Decreased neutrophil count and Pyrexia (14 [25.0%] each), Decreased white blood cell (WBC) count (13 [23.6%]), and Blood creatine phosphokinase increased (11 [20.0%]) (Table 6).

Table 6: Summary of TEAEs Reported in ≥10% of Subjects Overall, by PT or Grouped PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Any TEAE	**4 (100)**	**7 (100)**	**5 (100)**	**7 (87.5)**	**7 (100)**	**9 (100)**	**2 (100)**	**5 (100)**	**8 (100)**	**54 (98.2)**
Anaemia	1 (25.0)	2 (28.6)	4 (80.0)	5 (62.5)	3 (42.9)	6 (66.7)	1 (50.0)	3 (60.0)	2 (25.0)	27 (49.1)
Dysgeusia	3 (75.0)	4 (57.1)	4 (80.0)	4 (50.0)	2 (28.6)	2 (22.2)	0	1 (20.0)	4 (50.0)	24 (43.6)
Fatigue	1 (25.0)	2 (28.6)	4 (80.0)	1 (12.5)	4 (57.1)	2 (22.2)	1 (50.0)	1 (20.0)	4 (50.0)	20 (36.4)
Dry mouth	1 (25.0)	3 (42.9)	2 (40.0)	4 (50.0)	2 (28.6)	2 (22.2)	1 (50.0)	0	3 (37.5)	18 (32.7)
Dyspnoea	0	2 (28.6)	1 (20.0)	4 (50.0)	2 (28.6)	4 (44.4)	0	0	3 (37.5)	16 (29.1)
Decreased platelet count[a]	0	2 (28.6)	3 (60.0)	2 (25.0)	0	3 (33.3)	0	3 (60.0)	2 (25.0)	15 (27.3)
Decreased neutrophil count[b]	0	2 (28.6)	3 (60.0)	2 (25.0)	2 (28.6)	2 (22.2)	0	2 (40.0)	1 (12.5)	14 (25.5)
Pyrexia	0	0	1 (20.0)	2 (25.0)	3 (42.9)	4 (44.4)	0	2 (40.0)	2 (25.0)	14 (25.5)
Decreased WBC count[c]	0	4 (57.1)	3 (60.0)	2 (25.0)	0	2 (22.2)	0	1 (20.0)	1 (12.5)	13 (23.6)
Blood creatine phosphokinase increased	0	0	1 (20.0)	3 (37.5)	0	3 (33.3)	0	2 (40.0)	2 (25.0)	11 (20.0)
Increased blood bilirubin[d]	0	0	1 (20.0)	3 (37.5)	3 (42.9)	2 (22.2)	0	1 (20.0)	0	10 (18.2)
Alanine aminotransferase increased	1 (25.0)	0	1 (20.0)	4 (50.0)	0	0	0	3 (60.0)	0	9 (16.4)
Aspartate aminotransferase increased	1 (25.0)	0	2 (40.0)	3 (37.5)	0	0	0	3 (60.0)	0	9 (16.4)
Headache	1 (25.0)	1 (14.3)	1 (20.0)	2 (25.0)	0	1 (11.1)	0	1 (20.0)	2 (25.0)	9 (16.4)
Increased blood glucose[e]	0	3 (42.9)	2 (40.0)	1 (12.5)	0	0	1 (50.0)	2 (40.0)	0	9 (16.4)

Table 6: Summary of TEAEs Reported in ≥10% of Subjects Overall, by PT or Grouped PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Nausea/vomiting[f]	0	3 (42.9)	0	2 (25.0)	1 (14.3)	2 (22.2)	0	0	1 (12.5)	9 (16.4)
Constipation	1 (25.0)	2 (28.6)	1 (20.0)	2 (25.0)	0	0	0	0	2 (25.0)	8 (14.5)
Diarrhoea	1 (25.0)	0	1 (20.0)	3 (37.5)	0	3 (33.3)	0	0	0	8 (14.5)
Lymphocyte count decreased	0	2 (28.6)	2 (40.0)	2 (25.0)	0	1 (11.1)	0	1 (20.0)	0	8 (14.5)
Abdominal pain	0	2 (28.6)	0	1 (12.5)	1 (14.3)	1 (11.1)	0	2 (40.0)	0	7 (12.7)
Stomatitis	0	0	0	1 (12.5)	3 (42.9)	0	0	1 (20.0)	2 (25.0)	7 (12.7)
Blood creatinine increased	0	0	2 (40.0)	2 (25.0)	0	2 (22.2)	0	1 (20.0)	0	7 (12.7)
Hyponatraemia	0	4 (57.1)	0	2 (25.0)	0	1 (11.1)	0	0	0	7 (12.7)
Blood lactate dehydrogenase increased	0	0	1 (20.0)	2 (25.0)	0	1 (11.1)	0	2 (40.0)	0	6 (10.9)
Gamma-glutamyltransferase increased	0	0	0	2 (25.0)	0	1 (11.1)	0	3 (60.0)	0	6 (10.9)
Haemoptysis	0	0	0	4 (50.0)	1 (14.3)	1 (11.1)	0	0	0	6 (10.9)
Decreased appetite	0	2 (28.6)	0	0	0	1 (11.1)	0	1 (20.0)	2 (25.0)	6 (10.9)
Sinus tachycardia	0	1 (14.3)	0	0	2 (28.6)	2 (22.2)	1 (50.0)	0	0	6 (10.9)
Tachycardia	1 (25.0)	1 (14.3)	0	0	1 (14.3)	0	0	0	3 (37.5)	6 (10.9)
Back pain	1 (25.0)	2 (28.6)	0	2 (25.0)	0	0	0	1 (20.0)	0	6 (10.9)
Muscle spasms	0	1 (14.3)	1 (20.0)	1 (12.5)	0	0	1 (50.0)	0	2 (25.0)	6 (10.9)

Table 6: Summary of TEAEs Reported in ≥10% of Subjects Overall, by PT or Grouped PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

	FHD-609 dose level									
	BIW dosing						QW dosing			
Preferred Term	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	Total (N=55)

Source: Tables 14.3.1.2.1 and 14.3.1.14.1.
Abbreviations: BIW=twice weekly; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; QW=once weekly; WBC=white blood cell.
Note: The Safety Analysis Set includes all subjects who were enrolled and received ≥1 dose of study drug. Subjects were analyzed according to the dose level initially assigned. Percentages are based on the number of subjects in the Safety Analysis Set within each dose level.
A TEAE is any AE either reported for the first time or worsening of a preexisting event after the first dose of study treatment and within 28 days of the last administration of study treatment. Adverse events are coded using MedDRA version 26.0. A subject is counted only once for multiple events within each MedDRA PT.
[a] Decreased platelet count includes the PTs Thrombocytopenia and Platelet count decreased.
[b] Decreased neutrophil count includes the PTs Neutropenia and Neutrophil count decreased.
[c] Decreased WBC count includes the PTs Leukopenia and White blood cell count decreased.
[d] Increased blood bilirubin includes the PTs Blood bilirubin increased and Hyperbilirubinaemia.
[e] Increased blood glucose includes the PTs Hyperglycaemia and Blood glucose increased.
[f] Nausea/vomiting includes the PTs Nausea, Vomiting, and Retching.

Treatment-Related TEAEs

Overall, 45 (81.8%) subjects had ≥1 TRAE (Table 7).

Table 7: Summary of TRAEs Reported in ≥5% of Subjects Overall, by PT or Grouped PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

	FHD-609 dose level									
	BIW dosing						QW dosing			
Preferred Term	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	Total (N=55)
Any TRAE	**2 (50.0)**	**6 (85.7)**	**5 (100)**	**7 (87.5)**	**6 (85.7)**	**6 (66.7)**	**2 (100)**	**4 (80.0)**	**7 (87.5)**	**45 (81.8)**
Dysgeusia	2 (50.0)	4 (57.1)	4 (80.0)	3 (37.5)	2 (28.6)	2 (22.2)	0	1 (20.0)	4 (50.0)	22 (40.0)
Dry mouth	1 (25.0)	2 (28.6)	2 (40.0)	4 (50.0)	2 (28.6)	1 (11.1)	1 (50.0)	0	3 (37.5)	16 (29.1)
Fatigue	1 (25.0)	2 (28.6)	4 (80.0)	1 (12.5)	3 (42.9)	1 (11.1)	1 (50.0)	1 (20.0)	1 (12.5)	15 (27.3)
Anaemia	0	0	3 (60.0)	4 (50.0)	1 (14.3)	1 (11.1)	0	3 (60.0)	2 (25.0)	14 (25.5)
Decreased neutrophil count[a]	0	2 (28.6)	3 (60.0)	2 (25.0)	2 (28.6)	2 (22.2)	0	1 (20.0)	1 (12.5)	13 (23.6)
Decreased platelet count[b]	0	1 (14.3)	3 (60.0)	2 (25.0)	0	2 (22.2)	0	3 (60.0)	2 (25.0)	13 (23.6)
Decreased WBC count[c]	0	4 (57.1)	3 (60.0)	2 (25.0)	0	1 (11.1)	0	1 (20.0)	1 (12.5)	12 (21.8)
Alanine aminotransferase increased	1 (25.0)	0	1 (20.0)	4 (50.0)	0	0	0	2 (40.0)	0	8 (14.5)
Aspartate aminotransferase increased	1 (25.0)	0	1 (20.0)	3 (37.5)	0	0	0	2 (40.0)	0	7 (12.7)
Blood creatine phosphokinase increased	0	0	1 (20.0)	2 (25.0)	0	1 (11.1)	0	2 (40.0)	1 (12.5)	7 (12.7)
Stomatitis	0	0	0	1 (12.5)	3 (42.9)	0	0	1 (20.0)	2 (25.0)	7 (12.7)
Nausea/vomiting[d]	0	2 (28.6)	0	2 (25.0)	0	2 (22.2)	0	0	0	6 (10.9)
Asthenia	0	0	0	3 (37.5)	0	0	0	2 (40.0)	0	5 (9.1)
Electrocardiogram QT prolonged	0	0	0	2 (25.0)	1 (14.3)	1 (11.1)	0	0	1 (12.5)	5 (9.1)

Table 7: Summary of TRAEs Reported in ≥5% of Subjects Overall, by PT or Grouped PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

	FHD-609 dose level									
	BIW dosing						QW dosing			
Preferred Term	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	Total (N=55)
Alopecia	1 (25.0)	1 (14.3)	0	0	2 (28.6)	0	0	0	0	4 (7.3)
Blood creatinine increased	0	0	1 (20.0)	2 (25.0)	0	0	0	1 (20.0)	0	4 (7.3)
Diarrhoea	0	0	1 (20.0)	1 (12.5)	0	2 (22.2)	0	0	0	4 (7.3)
Electrocardiogram T wave abnormal	0	0	1 (20.0)	2 (25.0)	0	0	0	0	1 (12.5)	4 (7.3)
Electrocardiogram T wave inversion	1 (25.0)	0	0	0	2 (28.6)	0	0	0	1 (12.5)	4 (7.3)
Gamma-glutamyltransferase increased	0	0	0	2 (25.0)	0	0	0	2 (40.0)	0	4 (7.3)
Increased blood bilirubin[e]	0	0	0	2 (25.0)	1 (14.3)	1 (11.1)	0	0	0	4 (7.3)
Lymphocyte count decreased	0	0	1 (20.0)	2 (25.0)	0	1 (11.1)	0	0	0	4 (7.3)
Blood alkaline phosphatase increased	0	0	1 (20.0)	1 (12.5)	0	0	0	1 (20.0)	0	3 (5.5)
Constipation	0	0	1 (20.0)	1 (12.5)	0	0	0	0	1 (12.5)	3 (5.5)
Decreased appetite	0	0	0	0	0	0	0	1 (20.0)	2 (25.0)	3 (5.5)
Headache	0	0	1 (20.0)	0	0	0	0	0	2 (25.0)	3 (5.5)
Hyponatraemia	0	2 (28.6)	0	1 (12.5)	0	0	0	0	0	3 (5.5)
Mucosal inflammation	1 (25.0)	0	0	1 (12.5)	0	0	0	1 (20.0)	0	3 (5.5)

Table 7: Summary of TRAEs Reported in ≥5% of Subjects Overall, by PT or Grouped PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Muscle spasms	0	0	1 (20.0)	1 (12.5)	0	0	0	0	1 (12.5)	3 (5.5)
Tachycardia	0	0	0	0	0	0	0	0	3 (37.5)	3 (5.5)

Source: Tables 14.3.1.4.1 and 14.3.1.14.1.
Abbreviations: BIW=twice weekly; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; QW=once weekly; TRAE=treatment-related TEAE; WBC=white blood cell.
Note: The Safety Analysis Set includes all subjects who were enrolled and received ≥1 dose of study drug. Subjects were analyzed according to the dose level initially assigned. Percentages are based on the number of subjects in the Safety Analysis Set within each dose level.
A TEAE is any AE either reported for the first time or worsening of a preexisting event after the first dose of study treatment and within 28 days of the last administration of study treatment. Adverse events are coded using MedDRA version 26.0. A subject is counted only once for multiple events within each MedDRA PT.
[a] Decreased neutrophil count includes the PTs Neutropenia and Neutrophil count decreased.
[b] Decreased platelet count includes the PTs Thrombocytopenia and Platelet count decreased.
[c] Decreased WBC count includes the PTs Leukopenia and White blood cell count decreased.
[d] Nausea/vomiting includes the PTs Nausea, Vomiting, and Retching.
[e] Increased blood bilirubin includes the PTs Blood bilirubin increased and Hyperbilirubinaemia.

A by-subject listing of treatment-related AEs is provided in Listing 16.2.7.2.

TEAEs by Severity

Forty (72.7%) subjects had ≥1 Grade ≥3 TEAE; of these, 14 (35.0%) had ≥1 treatment-related Grade ≥3 TEAE (Table 8 and Table 9). Most treatment-related Grade ≥3 TEAEs were Grade 3; 4 were Grade 4:

- One subject in the 60 mg BIW dose group experienced Grade 4, treatment-related, serious Ventricular fibrillation (2 events), Torsade de pointes, and Electrocardiogram QT prolonged, which had worsened from dose-limiting Grade 3 Electrocardiogram QT prolonged. Study drug was withdrawn in response to these events, which recovered/resolved. After study drug was withdrawn, the subject experienced another Grade 4, treatment-related, SAE of Ventricular fibrillation and a Grade 4, treatment-related, SAE of Ventricular extrasystoles, which recovered/resolved, as well as an event of Grade 4, treatment-related, serious Ventricular fibrillation that recovered/resolved with sequelae. These events are described in more detail in the safety narrative for this subject (Section 14.3.3), and briefly summarized in the section entitled, "Dose-Limiting Toxicities." Cardiovascular events are summarized in the section entitled, "Cardiovascular Effects."

Table 8: Summary of Grade ≥3 TEAEs Reported in ≥2 Subjects Overall, by PT or Grouped PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

	FHD-609 dose level									
	BIW dosing						**QW dosing**			
Preferred Term	**5 mg (N=4)**	**10 mg (N=7)**	**20 mg (N=5)**	**40 mg (N=8)**	**60 mg (N=7)**	**80 mg (N=9)**	**40 mg (N=2)**	**80 mg (N=5)**	**120 mg (N=8)**	**Total (N=55)**
Any Grade ≥3 TEAE	**2 (50.0)**	**5 (71.4)**	**2 (40.0)**	**6 (75.0)**	**6 (85.7)**	**8 (88.9)**	**2 (100)**	**5 (100)**	**4 (50.0)**	**40 (72.7)**
Anaemia	0	2 (28.6)	1 (20.0)	2 (25.0)	1 (14.3)	2 (22.2)	1 (50.0)	0	1 (12.5)	10 (18.2)
Decreased neutrophil count[a]	0	1 (14.3)	1 (20.0)	2 (25.0)	0	1 (11.1)	0	0	0	5 (9.1)
Dyspnoea	0	1 (14.3)	0	2 (25.0)	0	2 (22.2)	0	0	0	5 (9.1)
Tumour haemorrhage	0	1 (14.3)	0	1 (12.5)	2 (28.6)	0	0	0	1 (12.5)	5 (9.1)
Haemoptysis	0	0	0	2 (25.0)	1 (14.3)	1 (11.1)	0	0	0	4 (7.3)
Hypoxia	0	1 (14.3)	0	1 (12.5)	0	2 (22.2)	0	0	0	4 (7.3)
Respiratory failure	0	1 (14.3)	0	2 (25.0)	0	1 (11.1)	0	0	0	4 (7.3)
Back pain	1 (25.0)	1 (14.3)	0	0	0	0	0	1 (20.0)	0	3 (5.5)
Electrocardiogram QT prolonged	0	0	0	1 (12.5)	1 (14.3)	1 (11.1)	0	0	0	3 (5.5)
Abdominal pain	0	1 (14.3)	0	0	1 (14.3)	0	0	0	0	2 (3.6)
Acute respiratory failure	0	1 (14.3)	0	0	0	0	0	0	1 (12.5)	2 (3.6)
Blood creatine phosphokinase increased	0	0	0	1 (12.5)	0	0	0	1 (20.0)	0	2 (3.6)
Fall	0	0	1 (20.0)	0	1 (14.3)	0	0	0	0	2 (3.6)
Fatigue	0	0	2 (40.0)	0	0	0	0	0	0	2 (3.6)

Table 8: Summary of Grade ≥3 TEAEs Reported in ≥2 Subjects Overall, by PT or Grouped PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

	FHD-609 dose level									
	BIW dosing						QW dosing			
Preferred Term	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	Total (N=55)
Gamma-glutamyltransferase increased	0	0	0	1 (12.5)	0	0	0	1 (20.0)	0	2 (3.6)
Hypotension	0	1 (14.3)	0	0	0	1 (11.1)	0	0	0	2 (3.6)
Lymphocyte count decreased	0	1 (14.3)	1 (20.0)	0	0	0	0	0	0	2 (3.6)
Pericardial effusion	0	0	0	1 (12.5)	0	0	0	0	1 (12.5)	2 (3.6)
Pleural effusion	0	0	0	0	1 (14.3)	1 (11.1)	0	0	0	2 (3.6)
Pulmonary embolism	0	1 (14.3)	0	0	0	0	1 (50.0)	0	0	2 (3.6)
Syncope	0	1 (14.3)	0	0	1 (14.3)	0	0	0	0	2 (3.6)
Tumour pain	0	0	0	0	0	1 (11.1)	0	0	1 (12.5)	2 (3.6)
Decreased WBC count[b]	0	1 (14.3)	1 (20.0)	0	0	0	0	0	0	2 (3.6)

Source: Tables 14.3.1.6.1 and 14.3.1.14.1.
Abbreviations: BIW=twice weekly; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; QW=once weekly; WBC=white blood cell.
Note: The Safety Analysis Set includes all subjects who were enrolled and received ≥1 dose of study drug. Subjects were analyzed according to the dose level initially assigned. Percentages are based on the number of subjects in the Safety Analysis Set within each dose level.
A TEAE is any AE either reported for the first time or worsening of a preexisting event after the first dose of study treatment and within 28 days of the last administration of study treatment. Adverse events are coded using MedDRA version 26.0. A subject is counted only once for multiple events within each MedDRA PT. The severity of AEs or abnormal laboratory results is based on the National Cancer Institute CTCAE version 5.0.
[a] Decreased neutrophil count includes the PTs Neutropenia and Neutrophil count decreased.
[b] Decreased WBC count includes the PTs Leukopenia and White blood cell count decreased.

Table 9: Summary of Treatment-Related Grade ≥3 TEAEs, by PT or Grouped PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Any treatment-related Grade ≥3 TEAE	**0**	**1 (14.3)**	**2 (40.0)**	**4 (50.0)**	**2 (28.6)**	**3 (33.3)**	**0**	**1 (20.0)**	**1 (12.5)**	**14 (25.5)**
Decreased neutrophil count[a]	0	1 (14.3)	1 (20.0)	2 (25.0)	0	1 (11.1)	0	0	0	5 (9.1)
Anaemia	0	0	1 (20.0)	1 (12.5)	0	1 (11.1)	0	0	1 (12.5)	4 (7.3)
Decreased WBC count[b]	0	1 (14.3)	1 (20.0)	0	0	0	0	0	0	2 (3.6)
Electrocardiogram QT prolonged	0	0	0	1 (12.5)	1 (14.3)	0	0	0	0	2 (3.6)
Decreased platelet count[c]	0	0	0	0	0	1 (11.1)	0	0	0	1 (1.8)
Electrocardiogram repolarisation abnormality	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)
Embolism venous	0	0	0	0	0	0	0	1 (20.0)	0	1 (1.8)
Fatigue	0	0	1 (20.0)	0	0	0	0	0	0	1 (1.8)
Lymphocyte count decreased	0	0	1 (20.0)	0	0	0	0	0	0	1 (1.8)
Torsade de pointes	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)
Ventricular fibrillation	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)

Table 9: Summary of Treatment-Related Grade ≥3 TEAEs, by PT or Grouped PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

	FHD-609 dose level									
	BIW dosing						QW dosing			
Preferred Term	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	Total (N=55)

Source: Tables 14.3.1.7.1 and 14.3.1.14.1.
Abbreviations: BIW=twice weekly; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; QW=once weekly; WBC=white blood cell.
Note: The Safety Analysis Set includes all subjects who were enrolled and received ≥1 dose of study drug. Subjects were analyzed according to the dose level initially assigned. Percentages are based on the number of subjects in the Safety Analysis Set within each dose level.
A TEAE is any AE either reported for the first time or worsening of a preexisting event after the first dose of study treatment and within 28 days of the last administration of study treatment. Adverse events are coded using MedDRA version 26.0. A subject is counted only once for multiple events within each MedDRA PT. The severity of AEs or abnormal laboratory results is based on the National Cancer Institute CTCAE version 5.0.
[a] Decreased neutrophil count includes the PTs Neutropenia and Neutrophil count decreased.
[b] Decreased WBC count includes the PTs Leukopenia and White blood cell count decreased.
[c] Decreased platelet count includes the PTs Thrombocytopenia and Platelet count decreased.

A summary of TEAEs by maximum severity grade is provided in Table 14.3.1.9.1.

Dose-Limiting Toxicities

Three DLT events were observed among subjects receiving FHD-609 on a BIW schedule, while no DLT events were observed among those on a QW schedule (Table 14.3.1.8.1).

One subject experienced a DLT at 40 mg BIW:

- 1 subject experienced a Grade 3 SAE of Electrocardiogram QT prolonged. Study drug was interrupted and the event recovered/resolved with sequelae.

Two subjects experienced DLTs at 60 mg BIW:

- 1 subject experienced a Grade 3 SAE of Syncope that was deemed a DLT by the sponsor. The FHD-609 dose was not changed in response to this event, which recovered/resolved.
- 1 subject experienced Grade 3 Electrocardiogram QT prolonged, which progressed to a Grade 4 SAE and manifested as torsade de pointes and reversible cardiac arrest. Study drug was interrupted and a procedure was performed (Listing 16.2.7.5).
  - After the occurrence of the Grade 3/4 Electrocardiogram QT prolonged, enrollment into the study was halted, and the FHD-609 dose was reduced to 40 mg BIW (or 80 mg QW) for all subjects receiving FHD-609 60 mg BIW, 80 mg BIW, or 120 mg QW.

Additional details are provided in the narratives for the DLTs (Section 14.3.3).

Determination of the MTD

After the 2 DLTs were observed at FHD-609 60 mg BIW, this dose level and the equivalent dose on a QW schedule (120 mg QW) were determined to be non-tolerated doses. (No DLTs occurred at 120 mg QW.) As per protocol, the next lower dose level, 40 mg BIW, and the equivalent dose on a QW schedule (80 mg QW) were therefore declared the MTDs.

Deaths

Overall, 35 (63.6%) subjects died (all-cause mortality). Thirty-day mortality was 7 of 40 (17.5%) subjects and 2 of 15 (13.3%) subjects across the BIW and QW dosing schedules, respectively. Sixty-day mortality was 11 (27.5%) and 3 (20.0%) subjects across the BIW and QW dosing schedules, respectively (Table 10).

Overall, 13 (23.6%) subjects experienced TEAEs leading to death (Table 11), all but 1 of which occurred during the first 60 days of treatment (Listing 16.2.7.7). All but 1 of the TEAEs leading to death were considered unrelated to study drug.

- One (1.8%) subject treated at the 80 mg QW dose level died on Day 53 due to a venous embolism. This event was assessed by the investigator as treatment related because, although the underlying malignancy remained a highly probable cause, a relationship to treatment could not be ruled out. The relatedness was confounded by the fact that the subject, who had recently undergone a left pneumonectomy and was

experiencing progressive disease in the right lung, had been at high risk for pulmonary embolism since before the start of study treatment.

Of the 35 subjects who died, 22 (62.8%) died due to their underlying malignancy (Listing 16.2.6.4).

Additional details are provided in the narratives for TEAEs leading to death (Section 14.3.3).

Table 10: Summary of Mortality (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Number of subjects who died, n (%)	2 (50.0)	6 (85.7)	4 (80.0)	6 (75.0)	4 (57.1)	7 (77.8)	1 (50.0)	3 (60.0)	2 (25.0)	35 (63.6)
Within 30 days of first dose	0	2 (28.6)	0	1 (12.5)	1 (14.3)	3 (33.3)	1 (50.0)	0	1 (12.5)	9 (16.4)
Within 60 days of first dose	0	3 (42.9)	1 (20.0)	2 (25.0)	1 (14.3)	4 (44.4)	1 (50.0)	1 (20.0)	1 (12.5)	14 (25.5)
Within 30 days of last dose	0	4 (57.1)	1 (20.0)	3 (37.5)	1 (14.3)	4 (44.4)	1 (50.0)	1 (20.0)	1 (12.5)	16 (29.1)
Within 60 days of last dose	0	4 (57.1)	1 (20.0)	4 (50.0)	3 (42.9)	4 (44.4)	1 (50.0)	1 (20.0)	1 (12.5)	19 (34.5)

Source: Table 14.1.99.1.1.
Abbreviations: BIW=twice weekly; QW=once weekly.
Note: The Safety Analysis Set includes all subjects who were enrolled and received ≥1 dose of study drug. Subjects were analyzed according to the dose level initially assigned. Percentages are based on the number of subjects in the Safety Analysis Set within each dose level.

Table 11: Summary of TEAEs Leading to Death, by Preferred Term (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Any TEAEs leading to death	**0**	**2 (28.6)**	**1 (20.0)**	**2 (25.0)**	**1 (14.3)**	**4 (44.4)**	**1 (50.0)**	**1 (20.0)**	**1 (12.5)**	**13 (23.6)**
Respiratory failure	0	1 (14.3)	0	2 (25.0)	0	1 (11.1)	0	0	0	4 (7.3)
Acute respiratory failure	0	1 (14.3)	0	0	0	0	0	0	1 (12.5)	2 (3.6)
Cardiac arrest	0	0	0	0	0	1 (11.1)	0	0	0	1 (1.8)
Cerebral haemorrhage	0	0	1 (20.0)	0	0	0	0	0	0	1 (1.8)
Embolism venous	0	0	0	0	0	0	0	1 (20.0)	0	1 (1.8)
Haemoptysis	0	0	0	0	0	1 (11.1)	0	0	0	1 (1.8)
Hypoxia	0	0	0	0	0	1 (11.1)	0	0	0	1 (1.8)
Sudden cardiac death	0	0	0	0	0	0	1 (50.0)	0	0	1 (1.8)
Tumour haemorrhage	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)

Source: Table 14.3.1.13.1.
Abbreviations: BIW=twice weekly; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; QW=once weekly.
Note: The Safety Analysis Set includes all subjects who were enrolled and received ≥1 dose of study drug. Subjects were analyzed according to the dose level initially assigned. Percentages are based on the number of subjects in the Safety Analysis Set within each dose level.
A TEAE is any AE either reported for the first time or worsening of a preexisting event after the first dose of study treatment and within 28 days of the last administration of study treatment. Adverse events are coded using MedDRA version 26.0. A subject is counted only once for multiple events within each MedDRA PT.

SAEs Other Than Deaths

Overall, 32 (58.2%) subjects had ≥1 SAE (Table 12); of these, 8 (25.0%) had ≥1 treatment-related SAE, of which only Anaemia and Electrocardiogram QT prolonged (2 [3.6%] subjects each) occurred in >1 subject (Table 13).

Additional details are provided in the narratives for SAEs (Section 14.3.3).

Table 12: Summary of SAEs Reported in ≥2 Subjects Overall, by PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Any SAE	**2 (50.0)**	**5 (71.4)**	**2 (40.0)**	**3 (37.5)**	**5 (71.4)**	**7 (77.8)**	**2 (100)**	**2 (40.0)**	**4 (50.0)**	**32 (58.2)**
Dyspnoea	0	1 (14.3)	0	2 (25.0)	0	2 (22.2)	0	0	0	5 (9.1)
Anaemia	0	0	1 (20.0)	1 (12.5)	0	2 (22.2)	0	0	0	4 (7.3)
Haemoptysis	0	0	0	2 (25.0)	1 (14.3)	1 (11.1)	0	0	0	4 (7.3)
Hypoxia	0	1 (14.3)	0	1 (12.5)	0	2 (22.2)	0	0	0	4 (7.3)
Respiratory failure	0	1 (14.3)	0	2 (25.0)	0	1 (11.1)	0	0	0	4 (7.3)
Tumour haemorrhage	0	1 (14.3)	0	1 (12.5)	1 (14.3)	0	0	0	1 (12.5)	4 (7.3)
Abdominal pain	0	1 (14.3)	0	0	1 (14.3)	0	0	1 (20.0)	0	3 (5.5)
Pericardial effusion	0	1 (14.3)	0	1 (12.5)	0	0	0	0	1 (12.5)	3 (5.5)
Acute respiratory failure	0	1 (14.3)	0	0	0	0	0	0	1 (12.5)	2 (3.6)
Electrocardiogram QT prolonged	0	0	0	1 (12.5)	1 (14.3)	0	0	0	0	2 (3.6)
Fall	0	0	1 (20.0)	0	1 (14.3)	0	0	0	0	2 (3.6)
Hypotension	0	1 (14.3)	0	0	0	1 (11.1)	0	0	0	2 (3.6)
Pleural effusion	0	0	0	0	1 (14.3)	1 (11.1)	0	0	0	2 (3.6)
Pulmonary embolism	0	1 (14.3)	0	0	0	0	1 (50.0)	0	0	2 (3.6)
Pyrexia	0	0	0	0	0	1 (11.1)	0	0	1 (12.5)	2 (3.6)
Syncope	0	1 (14.3)	0	0	1 (14.3)	0	0	0	0	2 (3.6)

Table 12: Summary of SAEs Reported in ≥2 Subjects Overall, by PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Tachycardia	0	1 (14.3)	0	0	0	0	0	0	1 (12.5)	2 (3.6)

Source: Table 14.3.1.3.1.
Abbreviations: BIW=twice weekly; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; QW=once weekly.
Note: The Safety Analysis Set includes all subjects who were enrolled and received ≥1 dose of study drug. Subjects were analyzed according to the dose level initially assigned. Percentages are based on the number of subjects in the Safety Analysis Set within each dose level.
A TEAE is any AE either reported for the first time or worsening of a preexisting event after the first dose of study treatment and within 28 days of the last administration of study treatment. Adverse events are coded using MedDRA version 26.0. A subject is counted only once for multiple events within each MedDRA PT.

Table 13: Summary of Treatment-Related SAEs, by PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Any treatment-related SAE	**0**	**0**	**1 (20.0)**	**1 (12.5)**	**2 (28.6)**	**2 (22.2)**	**0**	**1 (20.0)**	**1 (12.5)**	**8 (14.5)**
Anaemia	0	0	1 (20.0)	0	0	1 (11.1)	0	0	0	2 (3.6)
Electrocardiogram QT prolonged	0	0	0	1 (12.5)	1 (14.3)	0	0	0	0	2 (3.6)
Blood bilirubin increased	0	0	0	0	0	1 (11.1)	0	0	0	1 (1.8)
Electrocardiogram repolarisation abnormality	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)
Embolism venous	0	0	0	0	0	0	0	1 (20.0)	0	1 (1.8)
Neutrophil count decreased	0	0	0	0	0	1 (11.1)	0	0	0	1 (1.8)
Platelet count decreased	0	0	0	0	0	1 (11.1)	0	0	0	1 (1.8)
Tachycardia	0	0	0	0	0	0	0	0	1 (12.5)	1 (1.8)
Torsade de pointes	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)
Ventricular fibrillation	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)

Source: Table 14.3.1.5.1.
Abbreviations: BIW=twice weekly; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; QW=once weekly.
Note: The Safety Analysis Set includes all subjects who were enrolled and received ≥1 dose of study drug. Subjects were analyzed according to the dose level initially assigned. Percentages are based on the number of subjects in the Safety Analysis Set within each dose level.
A TEAE is any AE either reported for the first time or worsening of a preexisting event after the first dose of study treatment and within 28 days of the last administration of study treatment. Adverse events are coded using MedDRA version 26.0. A subject is counted only once for multiple events within each MedDRA PT.

By-subject listings of SAEs and treatment-related SAEs are provided in Listings 16.2.7.3 and 16.2.7.4, respectively.

Discontinuations and/or Dose Modifications Due to AEs

TEAEs Leading to Study Treatment Discontinuation

Overall, 17 (30.9%) subjects had ≥1 TEAE leading to treatment discontinuation (Table 14). Of these 17 subjects, 3 (17.6%) experienced TRAEs leading to treatment discontinuation (Listing 16.2.7.6):

- Grade 2 non-serious Blood creatine phosphokinase increased, Electrocardiogram QT prolonged, and Electrocardiogram T wave abnormal occurred on the same day in 1 subject in the 40 mg BIW dose group. All the events recovered/resolved.
- A Grade 3 SAE of Electrocardiogram repolarisation abnormality was reported in 1 subject in the 60 mg BIW dose group. The event recovered/resolved with sequelae.
- Grade 4 SAEs of Ventricular fibrillation, Torsade de pointes, and Electrocardiogram QT prolonged occurred in 1 subject in the 60 mg BIW dose group. These events are described in the sections entitled "TEAEs by Severity" and "Dose-Limiting Toxicities."

Additional details are provided in the narratives describing TEAEs leading to study treatment discontinuation (Section 14.3.3). Cardiovascular events are summarized in the section entitled, "Cardiovascular Effects."

Table 14: Summary of TEAEs Leading to Treatment Discontinuation, by PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Any TEAE leading to treatment discontinuation	**1 (25)**	**2 (28.6)**	**1 (20)**	**4 (50)**	**3 (42.9)**	**3 (33.3)**	**2 (100)**	**1 (20)**	**0**	**17 (30.9)**
Any TRAE leading to treatment discontinuation	**0**	**0**	**0**	**1 (12.5)**	**2 (28.6)**	**0**	**0**	**0**	**0**	**3 (5.5)**
Respiratory failure	0	1 (14.3)	0	2 (25)	0	1 (11.1)	0	0	0	4 (7.3)
Electrocardiogram QT prolonged	0	0	0	1 (12.5)	1 (14.3)	0	0	0	0	2 (3.6)
Treatment-related Electrocardiogram QT prolonged	0	0	0	1 (12.5)	1 (14.3)	0	0	0	0	2 (3.6)
Blood creatine phosphokinase increased	0	0	0	1 (12.5)	0	0	0	0	0	1 (1.8)
Treatment-related Blood creatine phosphokinase increased	0	0	0	1 (12.5)	0	0	0	0	0	1 (1.8)
Cardiac arrest	0	0	0	0	0	1 (11.1)	0	0	0	1 (1.8)
Cerebral haemorrhage	0	0	1 (20.0)	0	0	0	0	0	0	1 (1.8)
Dysphagia	0	1 (14.3)	0	0	0	0	0	0	0	1 (1.8)
Dyspnoea	0	1 (14.3)	0	0	0	0	0	0	0	1 (1.8)
Electrocardiogram repolarisation abnormality	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)
Treatment-related Electrocardiogram repolarisation abnormality	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)

Table 14: Summary of TEAEs Leading to Treatment Discontinuation, by PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Electrocardiogram T wave abnormal	0	0	0	1 (12.5)	0	0	0	0	0	1 (1.8)
Treatment-related Electrocardiogram T wave abnormal	0	0	0	1 (12.5)	0	0	0	0	0	1 (1.8)
Haemoptysis	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)
Keratitis	0	0	0	0	0	0	0	1 (20)	0	1 (1.8)
Pulmonary embolism	0	0	0	0	0	0	1 (50)	0	0	1 (1.8)
Spinal cord compression	1 (25)	0	0	0	0	0	0	0	0	1 (1.8)
Sudden cardiac death	0	0	0	0	0	0	1 (50)	0	0	1 (1.8)
Torsade de pointes	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)
Treatment-related Torsade de pointes	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)
Tumour pain	0	0	0	0	0	1 (11.1)	0	0	0	1 (1.8)
Ventricular fibrillation	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)
Treatment-related Ventricular fibrillation	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)
Vomiting	0	0	0	1 (12.5)	0	0	0	0	0	1 (1.8)

Table 14: Summary of TEAEs Leading to Treatment Discontinuation, by PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	

Source: Table 14.3.1.12.1 and Listing 16.2.7.6.
Abbreviations: BIW=twice weekly; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; QW=once weekly; TRAE=treatment-related TEAE.
Note: The Safety Analysis Set includes all subjects who were enrolled and received ≥1 dose of study drug. Subjects were analyzed according to the dose level initially assigned. Percentages are based on the number of subjects in the Safety Analysis Set within each dose level.
A TEAE is any AE either reported for the first time or worsening of a preexisting event after the first dose of study treatment and within 28 days of the last administration of study treatment. Adverse events are coded using MedDRA version 26.0. A subject is counted only once for multiple events within each MedDRA PT.

TEAEs Leading to Dose Modifications

TEAEs leading to dose reduction: Overall, 1 (1.8%) subject had ≥1 TEAE (Electrocardiogram T wave inversion) leading to dose reduction (Table 14.3.1.10.1), which occurred at the 60 mg BIW dose level, was Grade 1, and was treatment related.

TEAEs leading to dose interruption: Overall, 33 (60.0%) subjects had ≥1 TEAE leading to dose interruption (Table 15); of these, 19 (57.6%) subjects had ≥1 treatment-related TEAE leading to dose interruption (Table 16).

Table 15: Summary of TEAEs Leading to Dose Interruption in ≥2 Subjects, by PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Any TEAEs leading to dose interruption	**3 (75.0)**	**3 (42.9)**	**3 (60.0)**	**5 (62.5)**	**3 (42.9)**	**8 (88.9)**	**0**	**3 (60.0)**	**5 (62.5)**	**33 (60.0)**
Anaemia	0	0	1 (20.0)	2 (25.0)	0	1 (11.1)	0	0	1 (12.5)	5 (9.1)
Diarrhoea	1 (25.0)	0	1 (20.0)	0	0	1 (11.1)	0	0	0	3 (5.5)
Dyspnoea	0	1 (14.3)	0	1 (12.5)	0	0	0	0	1 (12.5)	3 (5.5)
Electrocardiogram QT prolonged	0	0	0	1 (12.5)	1 (14.3)	1 (11.1)	0	0	0	3 (5.5)
Electrocardiogram T wave abnormal	0	0	1 (20.0)	0	0	1 (11.1)	0	0	1 (12.5)	3 (5.5)
Tachycardia	0	0	0	0	1 (14.3)	0	0	0	2 (25.0)	3 (5.5)
Back pain	1 (25.0)	1 (14.3)	0	0	0	0	0	0	0	2 (3.6)
Haemoptysis	0	0	0	1 (12.5)	0	1 (11.1)	0	0	0	2 (3.6)
Hypoxia	0	1 (14.3)	0	1 (12.5)	0	0	0	0	0	2 (3.6)
Pyrexia	0	0	0	0	0	1 (11.1)	0	0	1 (12.5)	2 (3.6)

Source: Table 14.3.1.11.1.
Abbreviations: BIW=twice weekly; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; QW=once weekly.
Note: The Safety Analysis Set includes all subjects who were enrolled and received ≥1 dose of study drug. Subjects were analyzed according to the dose level initially assigned. Percentages are based on the number of subjects in the Safety Analysis Set within each dose level.
A TEAE is any AE either reported for the first time or worsening of a preexisting event after the first dose of study treatment and within 28 days of the last administration of study treatment. Adverse events are coded using MedDRA version 26.0. A subject is counted only once for multiple events within each MedDRA PT.

Table 16: Summary of TRAEs Leading to Dose Interruption, by PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
Any TRAEs leading to dose interruption	**0**	**0**	**3 (60.0)**	**3 (37.5)**	**2 (28.6)**	**4 (44.4)**	**0**	**2 (40.0)**	**5 (62.5)**	**19 (34.5)**
Anaemia	0	0	1 (20.0)	1 (25.0)	0	1 (11.1)	0	0	1 (12.5)	4 (7.3)
Diarrhoea	0	0	1 (20.0)	0	0	1 (11.1)	0	0	0	2 (3.6)
Electrocardiogram QT prolonged	0	0	0	1 (25.0)	1 (14.3)	0	0	0	0	2 (3.6)
Electrocardiogram T wave abnormal	0	0	1 (20.0)	0	0	0	0	0	1 (12.5)	2 (3.6)
Tachycardia	0	0	0	0	0	0	0	0	2 (25.0)	2 (3.6)
Bradycardia	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)
Electrocardiogram ST-T change	0	0	0	0	0	0	0	0	1 (12.5)	1 (1.8)
Electrocardiogram T wave inversion	0	0	0	0	0	0	0	0	1 (12.5)	1 (1.8)
Embolism venous	0	0	0	0	0	0	0	1 (11.1)	0	1 (1.8)
Fatigue	0	0	0	0	0	1 (11.1)	0	0	0	1 (1.8)
Hypophosphataemia	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)
Infusion related reaction	0	0	0	0	0	0	0	1 (11.1)	0	1 (1.8)
Decreased neutrophil count[a]	0	0	0	1 (25.0)	0	0	0	0	0	1 (1.8)
Palpitations	0	0	0	0	0	0	0	0	1 (12.5)	1 (1.8)
Decreased platelet count[b]	0	0	0	0	0	1 (11.1)	0	0	0	1 (1.8)

Table 16: Summary of TRAEs Leading to Dose Interruption, by PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

Preferred Term	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	

Source: Table 14.3.99.1.1 and Listing 16.2.7.6.
Abbreviations: BIW=twice weekly; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; QW=once weekly; TRAE=treatment-related TEAE; WBC=white blood cell.
Note: The Safety Analysis Set includes all subjects who were enrolled and received ≥1 dose of study drug. Subjects were analyzed according to the dose level initially assigned. Percentages are based on the number of subjects in the Safety Analysis Set within each dose level.
A TEAE is any AE either reported for the first time or worsening of a preexisting event after the first dose of study treatment and within 28 days of the last administration of study treatment. Adverse events are coded using MedDRA version 26.0. A subject is counted only once for multiple events within each MedDRA PT.
[a] Decreased neutrophil count includes the PTs Neutropenia and Neutrophil count decreased.
[b] Decreased platelet count includes the PTs Thrombocytopenia and Platelet count decreased.

Cardiovascular Effects

Investigator-Reported Cardiovascular TEAEs

Three cardiac-associated DLT events were observed, including Grade 3 QT interval prolongation that progressed to Grade 4, which manifested as torsade de pointes and reversible cardiac arrest in a subject in the 60 mg BIW dose group. After the occurrence of the Grade 3/4 QT interval prolongation in the 60 mg BIW cohort, enrollment into the study was halted, and the FHD-609 dose was reduced to 40 mg BIW (or 80 mg QW) for all subjects receiving FHD-609 60 mg BIW, 80 mg BIW, or 120 mg QW.

Overall, 20 (36.4%) subjects experienced TEAEs in the Cardiac disorders SOC, most commonly Sinus tachycardia and Tachycardia (6 [10.9%] subjects each). TEAEs in this SOC occurred in ≥1 subject at every dose except 80 mg QW. Thirteen of 40 (32.5%) subjects in the BIW dosing groups and 7 of 15 (46.7%) subjects in the QW dosing groups experienced TEAEs in this SOC (Table 17).

Electrocardiogram (ECG) abnormalities were observed more frequently in the BIW dosing groups.

Additional details are provided in the narratives for TEAEs of:

- Grade ≥2 Electrocardiogram T wave inversion, Electrocardiogram T wave abnormal, and Electrocardiogram ST-T change
- Grade ≥3 Electrocardiogram QT prolonged (Section 14.3.3)

Table 17: Summary of TEAEs in the Cardiac Disorders and Electrocardiogram Abnormality TEAEs in the Investigations SOC, by SOC and PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

	FHD-609 dose level									
	BIW dosing						QW dosing			
Preferred Term	**5 mg (N=4)**	**10 mg (N=7)**	**20 mg (N=5)**	**40 mg (N=8)**	**60 mg (N=7)**	**80 mg (N=9)**	**40 mg (N=2)**	**80 mg (N=5)**	**120 mg (N=8)**	**Total (N=55)**
Cardiac disorders	**1 (25.0)**	**2 (28.6)**	**1 (20.0)**	**1 (12.5)**	**4 (57.1)**	**4 (44.4)**	**1 (50.0)**	**0**	**6 (75.0)**	**20 (36.4)**
Sinus tachycardia	0	1 (14.3)	0	0	2 (28.6)	2 (22.2)	1 (50.0)	0	0	6 (10.9)
Tachycardia	1 (25.0)	1 (14.3)	0	0	1 (14.3)	0	0	0	3 (37.5)	6 (10.9)
Palpitations	0	1 (14.3)	0	0	0	0	1 (50.0)	0	1 (12.5)	3 (5.5)
Pericardial effusion	0	1 (14.3)	0	1 (12.5)	0	0	0	0	1 (12.5)	3 (5.5)
Bradycardia	0	0	0	0	2 (28.6)	0	0	0	0	2 (3.6)
Sinus bradycardia	0	0	1 (20.0)	0	0	0	0	0	1 (12.5)	2 (3.6)
Atrial tachycardia	0	0	0	0	0	0	0	0	1 (12.5)	1 (1.8)
Cardiac arrest	0	0	0	0	0	1 (11.1)	0	0	0	1 (1.8)
Pulseless electrical activity	0	0	0	0	0	1 (11.1)	0	0	0	1 (1.8)
Torsade de pointes	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)
Ventricular fibrillation	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)
Investigations (ECG abnormalities)										
Electrocardiogram QT prolonged	0	0	0	2 (25.0)	1 (14.3)	1 (11.1)	0	0	1 (12.5)	5 (9.1)
Electrocardiogram T wave abnormal	0	0	1 (20.0)	2 (25.0)	0	1 (11.1)	0	0	1 (12.5)	5 (9.1)

Table 17: Summary of TEAEs in the Cardiac Disorders and Electrocardiogram Abnormality TEAEs in the Investigations SOC, by SOC and PT (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

	FHD-609 dose level									
	BIW dosing						QW dosing			
Preferred Term	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	Total (N=55)
Electrocardiogram T wave inversion	1 (25.0)	0	0	0	2 (28.6)	0	0	0	1 (12.5)	4 (7.3)
Electrocardiogram repolarisation abnormality	0	0	0	0	1 (14.3)	0	0	0	0	1 (1.8)
Electrocardiogram ST-T change	0	0	0	0	0	0	0	0	1 (12.5)	1 (1.8)

Source: Table 14.3.1.2.1.
Abbreviations: BIW=twice weekly; ECG=electrocardiogram; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; QW=once weekly; SOC=System Organ Class.
Note: The Safety Analysis Set includes all subjects who were enrolled and received ≥1 dose of study drug. Subjects were analyzed according to the dose level initially assigned. Percentages are based on the number of subjects in the Safety Analysis Set within each dose level.
A TEAE is any AE either reported for the first time or worsening of a preexisting event after the first dose of study treatment and within 28 days of the last administration of study treatment. Adverse events are coded using MedDRA version 26.0. A subject is counted only once for multiple events within each MedDRA PT.

External Expert Cardiology Review

The sponsor engaged 2 external expert cardiologists to perform a comprehensive review of centrally collected ECG data for all 55 subjects who had received ≥1 dose of study drug (data cutoff date 03 Jul 2023). The experts developed a strategy to select subjects for in-depth review, identifying subjects with an absolute QTcF (QTc [Fridericia formula]) >480 milliseconds (ms) or a change from baseline in QTcF >60 ms and/or with at least 1 Grade ≥3 TEAE potentially associated with cardiac toxicity. These events were identified using a MedDRA search strategy designed by the sponsor with a focus on event terms that could be associated with malignant ventricular arrhythmias (syncope, cardiac arrest, sudden cardiac death, torsade de pointes, ventricular tachycardia, or ventricular fibrillation). Based on this review:

- 11 subjects were identified as potentially having had a malignant arrhythmia, at FHD-609 dose levels of 10 mg BIW (1 subject), 20 mg BIW (1 subject), 40 mg BIW (1 subject), 60 mg BIW (3 subjects), 80 mg BIW (3 subjects), 40 mg QW (1 subject), and 120 mg QW (1 subject).
- Several of the 11 subjects experienced adverse cardiovascular (CV) events in the context of multiple predisposing and/or contributing factors to their CV event, such as their advanced underlying disease; prior therapy with doxorubicin, a known cardiotoxin; and the presence of comorbidities (such as anemia, hypotension, enterocolitis, hypokalemia) and concomitant medications (such as azithromycin, amphotericin B, doxycycline).
- An association may exist between T wave inversions and the potential for a subsequent adverse CV event in subjects treated with FHD-609, as described in the section, "External Expert Cardiology Overread of Electrocardiograms."
- There was no clear relationship (based on manual review) between total study drug exposure or maximum study drug concentration, and QTcF prolongation.

The memo summarizing the results of the cardiology review is provided in Appendix 1.

Evaluation of Clinical Laboratory Tests

Clinically significant changes in laboratory values were captured as TEAEs.

Hematology Parameters

Overall, baseline erythrocyte counts were low, which was reflective of the advanced stage of the underlying disease, and levels generally remained low throughout treatment with FHD-609 (Table 14.3.4.1.1.1). TEAEs of Anaemia were reported in 27 (49.1%) subjects.

There were few notable changes in hematology parameters on study. Overall:

- 8 of 55 (14.5%) subjects with a Grade 0 or 1 baseline neutrophil (low direction) value shifted to a Grade 3 or 4 postbaseline value.
  - Decreased neutrophil count (Neutropenia, Neutrophil count decreased) was reported in 4 (7.3%) subjects.

- 4 of 32 (12.5%) subjects with a Grade 0 or 1 baseline lymphocyte (low direction) value shifted to a Grade 3 or 4 postbaseline value (Table 14.3.4.1.2.1).
  - Lymphocyte count decreased was reported in 8 (14.5%) subjects.

Appropriate measures were instituted for the management of opportunistic infections and immunologic and/or inflammatory response events. The overall frequency of TEAEs in the Infections and infestations SOC was 15 (27.3%) subjects. Among these 15 subjects, there was no trend suggesting an increased frequency of opportunistic infections.

A by-subject listing of hematology laboratory results is provided in Listing 16.2.8.1.

Serum Chemistry Parameters

At baseline, the median overall alkaline phosphatase concentration was 83.0 U/L (range: 42-421), consistent with the known effects of the underlying disease on the bone. Overall, median alkaline phosphatase levels generally remained high throughout treatment (Table 14.3.4.2.1.1). Treatment-emergent adverse events of Blood alkaline phosphatase increased were reported in 4 (7.3%) subjects.

There were no notable changes in serum chemistry parameters on study, including in parameters associated with QT interval prolongation:

- Except for 2 subjects whose postbaseline results were missing, all subjects with a Grade 0 or 1 baseline potassium (low direction) value remained Grade 0 or 1 postbaseline.
- Except for 2 subjects whose postbaseline results were missing, all subjects with a Grade 0 baseline calcium (low direction) value remained Grade 0 or 1 postbaseline (Table 14.3.4.2.2.1).

A by-subject listing of serum chemistry laboratory results is provided in Listing 16.2.8.2.

Coagulation Parameters

There were no notable changes in coagulation parameters on study (Table 14.3.4.3.2.1).

A summary of coagulation laboratory results is provided in Table 14.3.4.3.1.1. A by-subject listing of coagulation laboratory results is provided in Listing 16.2.8.3.

Inflammatory Markers

There were no notable changes in inflammatory markers (fibrinogen) on study (Table 14.3.4.4.2.1).

A summary and by-subject listing of the results of inflammatory marker assessments is provided in Table 14.3.4.4.1.1 and Listing 16.2.8.4, respectively.

Other Safety Evaluations

Clinically meaningful changes in ECG assessments were observed. Overall, there were no clinically meaningful findings in the vital sign measurements, ECOG PS assessments, echocardiogram assessments, or other observations related to safety in this study.

Vital Signs

Vital signs are summarized in Table 14.3.5.1.1. A by-subject listing of vital signs is provided in Listing 16.2.9.1.1. A by-subject listing of vital signs during the infusion period is provided in Listing 16.2.9.1.2.

ECOG PS

Results of ECOG PS assessments are summarized in Table 14.3.5.4.1.1 and a summary of shifts from baseline to worst grade is provided in Table 14.3.5.4.2.1. A by-subject listing of ECOG PS is provided in Listing 16.2.9.4.

Electrocardiograms

External Expert Cardiology Overread of Electrocardiograms

The sponsor engaged 2 external expert cardiologists to perform a comprehensive review of centrally collected ECG data (data cutoff date 03 Jul 2023). The cardiologists reviewed 2449 ECGs from all 55 subjects who had received ≥1 dose of study drug.

The cardiologists did not identify any bradycardic outliers or QRS interval outliers, or any findings of atrial fibrillation, atrial flutter, non-sustained ventricular tachycardia, Mobitz I or II second-degree atrioventricular (AV) block, 2:1 AV block, third-degree (ie, complete) heart block, complete left bundle branch block, or ST segment elevation or depression.

The cardiologists identified 1 subject with a PR interval outlier, 11 subjects with tachycardic outliers, and the following QTcF outliers:

- Absolute QTcF >500 ms: 7 subjects
- Absolute QTcF >480 to 500 ms: 9 subjects
- Absolute QTcF >450 to 480 ms: 27 subjects
- QTcF change from baseline >60 ms: 10 subjects
- QTcF change from baseline >30 to 60 ms: 18 subjects

The cardiologists identified 30 subjects with treatment-emergent T wave inversion. Among these 30 subjects, 25 had received a dose of 40 mg BIW (or 80 mg QW) or higher, 27 had received prior treatment with doxorubicin, a known cardiotoxin, and at least 1 had received dexrazoxane, a cardioprotective drug, after their second round of doxorubicin. Twenty-three subjects never developed T wave inversion after receiving study drug. Among these 23 subjects, 15 had received a dose of 40 mg BIW (or 80 mg QW) or higher, and 19 had received prior doxorubicin treatment (it is unknown whether any of these subjects may have also received dexrazoxane). T wave inversions appeared to be a precursor to an adverse CV event:

- All 11 subjects were identified as having a malignant arrhythmia developed T wave inversion 1 to 2 weeks before the CV event.
- Twenty-one of the 30 subjects who developed T wave inversions did not have an adverse CV event.

- None of the 23 subjects without a T wave inversion experienced an adverse CV event.

The cardiologists also identified 1 subject with treatment-emergent complete right bundle branch block (RBBB), noting that the subject had had incomplete RBBB at baseline; 1 subject with treatment-emergent abnormal U waves, noting that the subject was reported to have T-U fusion on C1D15 and C1D22; and "probably 0" myocardial infarctions, noting that 2 subjects were reported to have anteroseptal myocardial infarction old/age indeterminate.

The memo summarizing the results of the cardiology review is provided in Appendix 1.

Central Electrocardiogram Results

Overall, based on central ECG results, 7 (13%) subjects had a QTcF >500 ms at any time during the study; 11 (20.4%) subjects had a change from baseline in QTcF >60 at any time during the study (Table 18).

Additional details are provided in the narratives for the following:

- Absolute QTcF >500 ms at any time on study
- Change from baseline in QTcF >60 ms at any time on study (Section 14.3.3)

Table 18: Summary of QTcF Outliers at Any Time During the Study (Study FHD-609-C-001, Dose Escalation) (Safety Analysis Set)

Parameter	FHD-609 dose level									Total (N=55)
	BIW dosing						QW dosing			
	5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)	40 mg (N=2)	80 mg (N=5)	120 mg (N=8)	
M	4	7	5	8	7	9	2	5	7	54
QTcF >450, n (%)	1 (25.0)	2 (28.6)	3 (60.0)	4 (50.0)	4 (57.1)	3 (33.3)	0	2 (40.0)	3 (42.9)	22 (40.7)
QTcF >480, n (%)	0	0	2 (40.0)	1 (12.5)	2 (28.6)	2 (22.2)	0	0	2 (28.6)	9 (16.7)
QTcF >500, n (%)	0	0	2 (40.0)	1 (12.5)	2 (28.6)	2 (22.2)	0	0	0	7 (13.0)
Change from baseline in QTcF >30, n (%)	1 (25.0)	2 (28.6)	3 (60.0)	5 (62.5)	4 (57.1)	3 (33.3)	0	2 (40.0)	3 (42.9)	23 (42.6)
Change from baseline in QTcF >60, n (%)	0	1 (14.3)	2 (40.0)	1 (12.5)	3 (42.9)	2 (22.2)	0	0	2 (28.6)	11 (20.4)

Source: Table 14.3.5.3.3.1.
Abbreviations: BIW=twice weekly; M=number of subjects with non-missing value; QTcF=heart rate–corrected QT interval, Fridericia correction; QW=once weekly.
Note: The Safety Analysis Set includes all subjects who were enrolled and received ≥1 dose of study drug. Subjects were analyzed according to the dose level initially assigned. Percentages are based on the number of subjects in the Safety Analysis Set within each dose level.

A summary of ECG results and interpretations is provided in Tables 14.3.5.3.1.1 and 14.3.5.3.2.1, respectively. By-subject listings of 12-lead ECG results and interpretations are provided in Listings 16.2.9.3.1 and 16.2.9.3.2, respectively.

Echocardiograms

The following subjects had a >10 percentage point decrease in left ventricular ejection fraction (LVEF) from baseline:

- 5 mg BIW:
  - Baseline 63%, EOT 50%; both values were in the normal range
  - Baseline 71%, EOT 58%; both values were in the normal range
- 60 mg BIW:
  - Baseline 61%, C4D1 50%; the latter was deemed abnormal, not clinically significant
  - Baseline 58%, unscheduled assessment on Day 34 40%; both values were in the normal range
  - Baseline 65%, C4D1 52%, EOT 53%; the last value was deemed abnormal, not clinically significant
  - Baseline 73%, EOT 18%; the latter was deemed abnormal, clinically significant. No results are available for previous assessments for this subject, who subject also experienced a DLT of Grade 3 Electrocardiogram QT prolonged that progressed to Grade 4 ("Dose-Limiting Toxicities").
- 80 mg BIW: baseline 63%, EOT 51%; the latter value was deemed abnormal, not clinically significant (Listing 16.2.9.2)

A summary of LVEF data is presented in Table 14.3.5.2.1.

Other Observations Related to Safety

A by-subject listing of the results of pregnancy tests is provided in Listing 16.2.8.5.

A by-subject listing of laboratory parameter results potentially meeting criteria for Hy's law is provided in Listing 16.2.8.6. The data did not reflect Hy's Law, as the elevations in liver function parameters occurred in the setting of severe medical complications (respiratory failure, pulseless electrical activity, septic shock, and metabolic acidosis) in a subject with metastatic synovial sarcoma with poor prognosis.

A by-subject listing of results of COVID-19 testing and vaccine administration is provided in Listing 16.2.9.6.

Pharmacokinetic Results

After IV infusion, FHD-609 concentrations in blood and plasma increased with dose from 5 mg to 120 mg on C1D1 and C1D22 (Figure 3 and Figure 4). The median T_{max} was similar across the dose levels and matrices (blood and plasma), and was observed at the end of the 2-hour infusion (Table 19, Table 20, Table 21, and Table 22). The C_{max} and AUC of FHD-609 increased with increasing dose. FHD-609 preferentially distributed into the blood, with mean blood-to-plasma ratios ranging from 1.35 to 2.34 for C_{max} and 2.25 to 6.33 for AUC during Cycle 1. The mean terminal half-life of FHD-609 at doses from 40 to 80 mg BIW ranged from 31.1 to 38.3 hours in blood and from 19.6 to 26.6 hours in plasma on C1D22. Similar half-lives of FHD-609 were observed in blood and plasma on C1D1 for both dosing schedules. The terminal half-life was difficult to estimate at doses <40 mg, given the observed flat concentration-time profile in blood and plasma. No significant accumulation of FHD-609 was observed in blood or plasma on C1D22 after dosing with FHD-609 (C_{max} and AUC accumulation ratios <2.0 at all doses) (Table 21, Table 22, and Figure 5).

Table 19: FHD-609 Blood and Plasma Pharmacokinetic Parameters After IV Infusion of FHD-609 5 mg, 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg BIW on C1D1 (Study FHD-609-C-001; Pharmacokinetics Analysis Set)

Matrix	Parameter	FHD-609 dose level BIW dosing 5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)
Blood	C_{max} (ng/mL)	25.1 (35.9); 4	54.7 (33.4); 7	107 (53.5); 5	268 (44.8); 8	375 (63.9); 7	530 (51.8); 9
	T_{max} (hr)	2.05 (2.00-2.33); 4	2.10 (2.05-2.68); 7	2.07 (2.00-2.25); 5	2.03 (1.98-2.17); 8	2.07 (2.00-2.42); 7	2.07 (1.82-2.17); 9
	T_{last} (hr)	8.09 (7.83-8.32); 4	48.6 (4.22-70.7); 7	71.3 (67.1-72.2); 5	69.6 (45.0-74.0); 8	68.9 (48.4-93.3); 7	70.7 (68.0-76.4); 9
	$AUC_{0\text{-}72hr}$ (hr•ng/mL)	108 (33.6); 4	331 (72.2); 7	867 (38.2); 5	2240 (47.1); 8	3810 (39.6); 7	4440 (50.3); 9
	$AUC_{0\text{-}last}$ (hr•ng/mL)	71.7 (37.8); 4	284 (88.7); 7	854 (37.7); 5	2160 (45.0); 8	3790 (49.5); 7	4420 (50.1); 9
	$AUC_{0\text{-}inf}$[a] (hr•ng/mL)	NC	740; 1	NC	3200 (39.3); 3	NC	4720; 1
	$t_{1/2}$ (hr)[b]	4.32-6.79; 2	19.3 (155); 4	40.7-44.4; 2	33.4 (41.0); 8	51.3 (51.6); 7	38.6 (13.0); 7
	V_z (L)	387 (54.3); 4	520 (47.8); 7	793 (50.4); 5	662 (61.6); 8	746 (34.9); 7	776 (61.7); 9
	CL (L/hr)[a]	NC	13.5; 1	NC	12.5 (39.3); 3	NC	17.0; 1

Table 19: FHD-609 Blood and Plasma Pharmacokinetic Parameters After IV Infusion of FHD-609 5 mg, 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg BIW on C1D1 (Study FHD-609-C-001; Pharmacokinetics Analysis Set)

Matrix	Parameter	FHD-609 dose level BIW dosing 5 mg (N=4)	10 mg (N=7)	20 mg (N=5)	40 mg (N=8)	60 mg (N=7)	80 mg (N=9)
Plasma	C_{max} (ng/mL)	15.4 (42.0); 4	27.4 (61.8); 7	58.3 (64.4); 5	145 (61.7); 8	161 (85.8); 7	305 (79.1); 9
	T_{max} (hr)	2.00 (0.00-2.33); 4	2.10 (2.05-2.68); 7	2.07 (2.00-2.25); 5	2.07 (2.00-2.17); 8	2.02 (2.00-3.38); 7	2.07 (1.82-2.30); 9
	T_{last} (hr)	7.93 (3.98-8.32); 4	8.13 (4.63-74.7); 7	71.3 (48.7-72.2); 5	57.8 (23.6-72.4); 8	68.9 (48.4-93.3); 7	70.7 (48.0-76.4); 9
	$AUC_{0\text{-}72hr}$ (hr•ng/mL)	44.6 (29.8); 4	94.1 (76.9); 7	307 (22.5); 5	629 (62.5); 8	601 (30.1); 7	1050 (90.1); 9
	$AUC_{0\text{-}last}$ (hr•ng/mL)	33.9 (32.8); 4	82.1 (85.3); 7	291 (22.4); 5	593 (70.3); 8	603 (31.0); 7	1050 (91.4); 9
	$AUC_{0\text{-}inf}$[a] (hr•ng/mL)	30.7; 1	24.9-71.8; 2	NC	938 (35.6); 5	626 (39.6); 4	1040 (90.0); 8
	$t_{1/2}$ (hr)[b]	0.816; 1	5.08 (303); 4	NC	18.1 (30.3); 5	19.4 (35.5); 4	19.9 (38.2); 8
	V_z (L)	391 (77.5); 4	1060 (68.8); 7	1860 (48.3); 5	1400 (56.0); 8	2450 (37.3); 7	2100 (113.0); 9
	CL (L/hr)[a]	163; 1	139-402; 2	NC	42.6 (35.6); 5	95.8 (39.6); 4	77.0 (90.0); 8
Blood-to-plasma ratio	C_{max}	1.63 (17.3); 4	2.00 (33.1); 7	1.84 (14.1); 5	1.84 (28.6); 8	2.34 (19.9); 7	1.74 (25.5); 9
	$AUC_{0\text{-}72hr}$	2.43 (23.8); 4	3.51 (112); 7	2.83 (36.4); 5	3.57 (48.2); 8	6.33 (34.1); 7	4.22 (49.0); 9

Abbreviations: AUC=area under the concentration-time curve; $AUC_{0\text{-}72hr}$=AUC from time 0 to 72 hours postdose; $AUC_{0\text{-}inf}$=AUC from time 0 extrapolated to infinity; $AUC_{0\text{-}last}$= AUC from time 0 to the time of the last quantifiable concentration; BIW=twice weekly; C1D1=Cycle 1 Day 1; CL=clearance; C_{max}=maximum concentration; CV=coefficient of variation; IV=intravenous; N=number of subjects in cohort; n=number of subjects with calculable PK parameter; NC=not calculated; $t_{1/2}$=terminal elimination half-life; T_{max}=observed time to reach C_{max}; T_{last}=time of last observed concentration; V_z=volume of distribution.
Notes: Parameters are presented as "geometric mean (geometric CV%); n," except for T_{max} and T_{last}, which are presented as "median (minimum-maximum); n" and blood-to-plasma ratios, which are presented as "arithmetic mean (CV%); n." Individual values are reported when n ≤2 subjects in cohort.
[a] Subjects are excluded from summary statistics if % extrapolation of AUC >20% and/or R2 adjusted value <0.8.
[b] Subjects are excluded from summary statistics if R2 adjusted value <0.8.

Table 20: FHD-609 Blood and Plasma Pharmacokinetic Parameters After IV Infusion of FHD-609 40 mg, 80 mg, and 120 mg QW on C1D1 (Study FHD-609-C-001; Pharmacokinetics Analysis Set)

Matrix	Parameter	FHD-609 dose level		
		QW dosing		
		40 mg (N=2)	80 mg (N=5)	120 mg (N=8)
Blood	C_{max} (ng/mL)	114-216; 2	530 (15.2); 5	530 (45.0); 8
	T_{max} (hr)	2.17-2.37; 2	2.13 (2.07-2.38); 5	2.07 (1.93-2.27); 8
	T_{last} (hr)	171-192; 2	168 (121-171); 5	168 (120-174); 8
	$AUC_{0\text{-}168hr}$ (hr•ng/mL)	2350-2380; 2	5270 (26.9); 5	7980 (39.8); 8
	$AUC_{0\text{-}last}$ (hr•ng/mL)	2400-2450; 2	5220 (29.1); 5	7900 (38.3); 8
	$AUC_{0\text{-}inf}$ (hr•ng/mL)[a]	2750; 1	5370 (27.1); 4	8950 (46.4); 6
	$t_{1/2}$ (hr)[b]	58.8-95.1; 2	49.6 (24.4); 5	55.2 (31.2); 8
	V_z (L)	1240-1770; 2	962 (8.9); 5	1030 (43.0); 8
	CL (L/hr)[a]	14.6; 1	14.9 (27.1); 4	13.4 (46.4); 6

Table 20: FHD-609 Blood and Plasma Pharmacokinetic Parameters After IV Infusion of FHD-609 40 mg, 80 mg, and 120 mg QW on C1D1 (Study FHD-609-C-001; Pharmacokinetics Analysis Set)

Matrix	Parameter	FHD-609 dose level		
		QW dosing		
		40 mg (N=2)	80 mg (N=5)	120 mg (N=8)
Plasma	C_{max} (ng/mL)	37.4-120; 2	314 (34.2); 5	371 (77.9); 8
	T_{max} (hr)	2.17-2.37; 2	2.13 (2.07-2.38); 5	2.11 (1.93-2.27); 8
	T_{last} (hr)	26.6-171; 2	121 (116-168); 5	121 (48.5-173); 8
	$AUC_{0\text{-}168hr}$ (hr•ng/mL)	323-1060; 2	1540 (31.6); 5	1670 (52.3); 8
	$AUC_{0\text{-}last}$ (hr•ng/mL)	295-1070; 2	1510 (32.2); 5	1580 (57.1); 8
	$AUC_{0\text{-}inf}$ (hr•ng/mL)[a]	NC	1740 (26.1); 4	1720 (59.9); 7
	$t_{1/2}$ (hr)[b]	215; 1	40.9 (72.7); 5	30.3 (36.4); 7
	V_z (L)	1370-5860; 2	2850 (89.8); 5	3070 (41.0); 8
	CL (L/hr)[a]	NC	46.0 (26.1); 4	69.7 (59.9); 7
Blood-to-plasma ratio	C_{max}	1.80-3.05; 2	1.55 (30.3); 5	1.43 (45.2); 8
	$AUC_{0\text{-}168hr}$	2.25-7.27; 2	3.41 (28.2); 5	4.78 (52.1); 8

Abbreviations: AUC=area under the concentration-time curve; $AUC_{0\text{-}168hr}$=AUC from time 0 to 168 hours postdose; $AUC_{0\text{-}inf}$=AUC from time 0 extrapolated to infinity; $AUC_{0\text{-}last}$= AUC from time 0 to the time of the last quantifiable concentration; C1D1=Cycle 1 Day 1; CL=clearance; C_{max}=maximum concentration; CV=coefficient of variation; IV=intravenous; N=number of subjects in cohort; n=number of subjects with calculable PK parameter; NC=not calculated; QW=once weekly; $t_{1/2}$=terminal elimination half-life; T_{max}=observed time to reach C_{max}; T_{last}=time of last observed concentration; V_z=volume of distribution
Notes: Parameters are presented as "geometric mean (geometric CV%); n," except for T_{max} and T_{last}, which are presented as "median (minimum-maximum); n" and blood-to-plasma ratios, which are presented as "arithmetic mean (CV%); n." Individual values are reported when n ≤2 subjects in cohort.
[a] Subjects are excluded from summary statistics if % extrapolation of AUC >20% and/or R2 adjusted value <0.8.
[b] Subjects are excluded from summary statistics if R2 adjusted value <0.8.

Table 21: FHD-609 Blood and Plasma Pharmacokinetic Parameters After IV Infusion of FHD-609 5 mg, 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg BIW on C1D22 (Study FHD-609-C-001; Pharmacokinetics Analysis Set)

Matrix	Parameter	FHD-609 dose level (mg)					
		BIW dosing					
		5 mg (N=3)	10 mg (N=5)[c]	20 mg (N=5)	40 mg (N=5)	60 mg (N=5)	80 mg (N=5)
Blood	C_{max} (ng/mL)	21.0 (115); 3	62.8 (24.5); 4	136 (48.9); 5	206 (86.5); 5	348 (45.9); 5	530 (34.7); 5
	T_{max} (hr)	2.08 (2.00-2.37); 3	2.04 (2.00-2.12); 4	2.07 (1.93-2.17); 5	2.13 (2.02-2.22); 5	2.08 (2.00-2.35); 5	2.22 (2.02-2.75); 5
	T_{last} (hr)	7.97 (7.88-8.10); 3	59.0 (25.5-76.5); 4	71.2 (66.8-72.7); 5	71.3 (66.2-95.9); 5	71.1 (67.9-74.2); 5	68.1 (25.1-72.4); 5
	AUC_{0-72hr} (hr•ng/mL)	105 (44.5); 3	403 (69.6); 4	987 (26.0); 5	1490 (75.4); 5	3620 (27.8); 5	6510 (73.7); 5
	AUC_{0-last} (hr•ng/mL)	67.4 (58.0); 3	374 (83.4); 4	978 (25.1); 5	1500 (77.3); 5	3590 (27.9); 5	5600 (64.4); 5
	AUC_{0-inf} (hr•ng/mL)[a]	NC	NC	1045; 1	1890-3340; 2	NC	4230; 1
	$t_{1/2}$ (hr)[b]	4.17-5.71; 2	35.4; 1	44.4 (23.3); 4	38.3 (28.3); 5	36.2 (11.4); 4	31.1 (58.8); 4
	V_{ss} (L)[a]	NC	NC	699; 1	460-711; 2	NC	677; 1
	CL (L/hr)[a]	NC	NC	19.1; 1	12.0-21.1; 2	NC	18.9; 1
	AR C_{max}	0.885 (65.1); 3	1.05 (26.9); 4	1.27 (50.4); 5	0.821 (63.7); 5	0.939 (31.9); 5	1.00 (17.0); 5
	AR AUC_{0-72hr}	0.899 (14.7); 3	1.33 (70.4); 4	1.14 (21.9); 5	0.804 (25.8); 5	1.08 (14.2); 5	1.32 (37.6); 5

Table 21: FHD-609 Blood and Plasma Pharmacokinetic Parameters After IV Infusion of FHD-609 5 mg, 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg BIW on C1D22 (Study FHD-609-C-001; Pharmacokinetics Analysis Set)

Matrix	Parameter	FHD-609 dose level (mg)					
		BIW dosing					
		5 mg (N=3)	10 mg (N=5)[c]	20 mg (N=5)	40 mg (N=5)	60 mg (N=5)	80 mg (N=5)
Plasma	C_{max} (ng/mL)	13.0 (94.4); 3	43.4 (19.5); 4	68.5 (51.1); 5	130 (127); 5	182 (75.7); 5	271 (43.1); 5
	T_{max} (hr)	2.08 (2.00-2.37); 3	2.04 (2.00-2.12); 4	2.07 (1.93-2.17); 5	2.18 (2.13-2.27); 5	2.15 (2.02-4.50); 5	2.17 (2.00-2.25); 5
	T_{last} (hr)	7.88 (4.23-24.3); 3	68.9 (8.15-76.5); 4	66.8 (47.7-72.4); 5	66.2 (8.15-95.9); 5	71.1 (67.9-74.2); 5	68.1 (25.1-72.4); 5
	$AUC_{0\text{-}72hr}$ (hr•ng/mL)	37.8 (113); 3	142 (68.9); 4	279 (17.1); 5	480 (132); 5	942 (40.4); 5	1060 (60.1); 5
	$AUC_{0\text{-}last}$ (hr•ng/mL)	29.6 (116.4); 3	138 (76.7); 4	268 (18.6); 5	439 (167.0); 5	941 (39.8); 5	1030 (60.4); 5
	$AUC_{0\text{-}inf}$ (hr•ng/mL)[a]	NC	62.5; 1	230; 1	767 (86.6); 4	1170 (27.1); 4	870 (48.1); 3
	$t_{1/2}$ (hr)[b]	1.31; 1	17.0 (429); 3	17.2; 1	26.6 (35.1); 4	22.4 (59.2); 4	19.6 (187); 4
	V_{ss} (L)[a]	NC	350; 1	1740; 1	1390 (102.0); 4	1100 (51.0); 4	1000 (59.1); 3
	CL (L/hr)[a]	NC	160; 1	86.8; 1	52.1 (86.6); 4	51.3 (27.1); 4	91.9 (48.1); 3
	AR C_{max}	0.940 (63.1); 3	1.52 (66.0); 4	1.17 (36.8); 5	0.903 (55.7); 5	1.16 (32.1); 5	0.886 (28.9); 5
	AR $AUC_{0\text{-}72hr}$	0.878 (73.9); 3	1.08 (18.4); 4	0.911 (16.3); 5	0.744 (46.1); 5	1.58 (38.2); 5	0.924 (33.6); 5

Table 21: FHD-609 Blood and Plasma Pharmacokinetic Parameters After IV Infusion of FHD-609 5 mg, 10 mg, 20 mg, 40 mg, 60 mg, and 80 mg BIW on C1D22 (Study FHD-609-C-001; Pharmacokinetics Analysis Set)

Matrix	Parameter	FHD-609 dose level (mg)					
		BIW dosing					
		5 mg (N=3)	10 mg (N=5)[c]	20 mg (N=5)	40 mg (N=5)	60 mg (N=5)	80 mg (N=5)
Blood-to-plasma ratio	C_{max}	1.62 (16.8); 3	1.45 (23.0); 4	1.99 (10.6); 5	1.59 (47.1); 5	1.91 (25.8); 5	1.95 (8.36); 5
	$AUC_{0\text{-}72hr}$	2.78 (51.4); 3	2.83 (45.1); 4	3.53 (24.1); 5	3.11 (51.0); 5	3.84 (36.1); 5	6.15 (52.9); 5

Abbreviations: AUC=area under the concentration-time curve; AR=accumulation ratio (Day 22/Day 1); $AUC_{0\text{-}72hr}$=AUC from time 0 to 72 hours postdose; $AUC_{0\text{-}inf}$=AUC from time 0 extrapolated to infinity; $AUC_{0\text{-}last}$= AUC from time 0 to the time of the last quantifiable concentration; BIW=twice weekly; C1D22=Cycle 1 Day 22; CL=clearance; C_{max}=maximum concentration; CV=coefficient of variation; IV=intravenous; N=number of subjects in cohort; n=number of subjects with calculable PK parameter; NC=not calculated; $t_{1/2}$=terminal elimination half-life; T_{max}=observed time to reach C_{max}; T_{last}=time of last observed concentration; V_{ss}=volume of distribution at steady state.
Notes: Parameters are presented as "geometric mean (geometric CV%); n," except for T_{max} and T_{last}, which are presented as "median (minimum-maximum); n" and blood-to-plasma ratios, which are presented as "arithmetic mean (CV%); n." Individual values are reported when n ≤2 subjects in cohort.
[a] Subjects are excluded from summary statistics if % extrapolation of AUC >20% and/or R2 adjusted value <0.8.
[b] Subjects are excluded from summary statistics if R2 adjusted value <0.8.
[c] Excluded 1 subject profile from summary statistics due to insufficient PK sampling.

Table 22: FHD-609 Blood and Plasma Pharmacokinetic Parameters After IV Infusion of FHD-609 40 mg, 80 mg, and 120 mg QW on C1D22 (Study FHD-609-C-001; Pharmacokinetics Analysis Set)

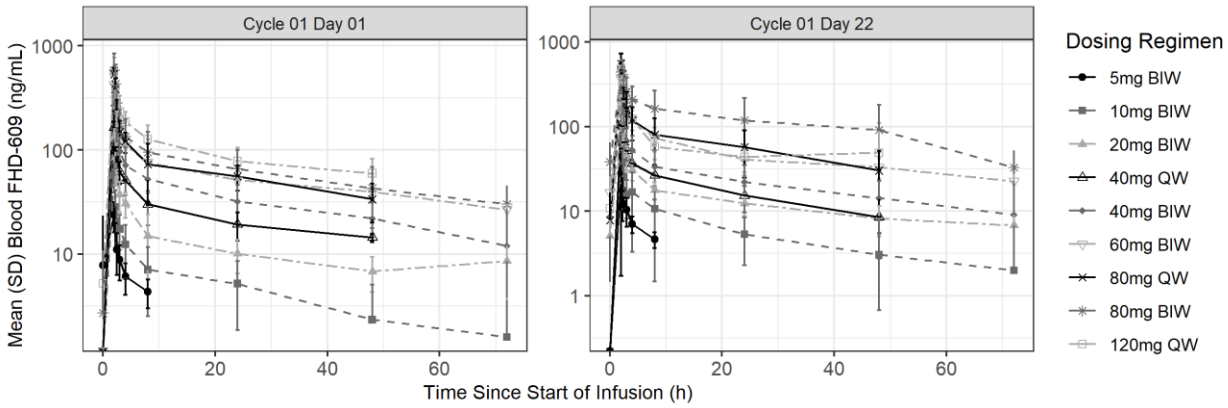
Matrix	Parameter	FHD-609 dose level		
		QW dosing		
		40 mg (N=1)	80 mg (N=5)	120 mg (N=4)
Blood	C_{max} (ng/mL)	105; 1	561 (24.5); 5	416 (43.6); 4
	T_{max} (hr)	2.35; 1	2.02 (2.00-2.30); 5	2.01 (1.92-2.50); 4
	T_{last} (hr)	47.6; 1	114 (47.2-168); 5	169 (167-195); 4
	$AUC_{0\text{-}168hr}$ (hr•ng/mL)	1490; 1	4540 (52.1); 5	5050 (23.3); 4
	$AUC_{0\text{-}last}$ (hr•ng/mL)	973; 1	3980 (36.9); 5	5090 (22.9); 4
	$AUC_{0\text{-}inf}$ (hr•ng/mL)[a]	NC	4230 (40.8); 4	5730 (20.4); 3
	$t_{1/2}$ (hr)[b]	23.9; 1	44.0 (33.2); 5	40.6 (50.5); 4
	V_{ss} (L)[a]	NC	975 (53.6); 4	1210 (22.1); 3
	CL (L/hr)[a]	NC	18.9 (40.8); 4	21.0 (20.4); 3
	AR C_{max}	0.921; 1	1.06 (25.6); 5	0.875 (61.8); 4
	AR $AUC_{0\text{-}168hr}$	1.58; 1	1.16 (28.4); 5	1.22 (64.0); 4

Table 22: FHD-609 Blood and Plasma Pharmacokinetic Parameters After IV Infusion of FHD-609 40 mg, 80 mg, and 120 mg QW on C1D22 (Study FHD-609-C-001; Pharmacokinetics Analysis Set)

Matrix	Parameter	FHD-609 dose level		
		QW dosing		
		40 mg (N=1)	80 mg (N=5)	120 mg (N=4)
Plasma	C_{max} (ng/mL)	42.5; 1	338 (52.2); 5	307 (85.6); 4
	T_{max} (hr)	2.47; 1	2.17 (2.02-2.30); 5	2.01 (1.92-2.50); 4
	T_{last} (hr)	47.6; 1	114 (47.0-114); 5	120 (24.9-167); 4
	$AUC_{0\text{-}168hr}$ (hr•ng/mL)	434; 1	1330 (36.5); 5	1230 (30.9); 4
	$AUC_{0\text{-}last}$ (hr•ng/mL)	242; 1	1250 (37.8); 5	1190 (33.5); 4
	$AUC_{0\text{-}inf}$ (hr•ng/mL)[a]	NC	1170 (26.9); 4	1400 (33.0); 3
	$t_{1/2}$ (hr)[b]	NC	17.7 (45.2); 5	42.1 (38.3); 4
	V_{ss} (L)[a]	NC	1100 (43.1); 4	2940 (28.9); 3
	CL (L/hr)[a]	NC	68.5 (43.1); 4	85.6 (33.0); 3
	AR C_{max}	1.14; 1	0.992 (30.5); 5	0.787 (140.0); 4
	AR $AUC_{0\text{-}168hr}$	0.744; 1	1.16 (20.1); 5	1.28 (66.4); 4
Blood-to-plasma ratio	C_{max}	2.47; 1	1.66 (32.8); 5	1.35 (54.7); 4
	$AUC_{0\text{-}168hr}$	3.42; 1	3.42 (47.0); 5	4.12 (30.3); 4

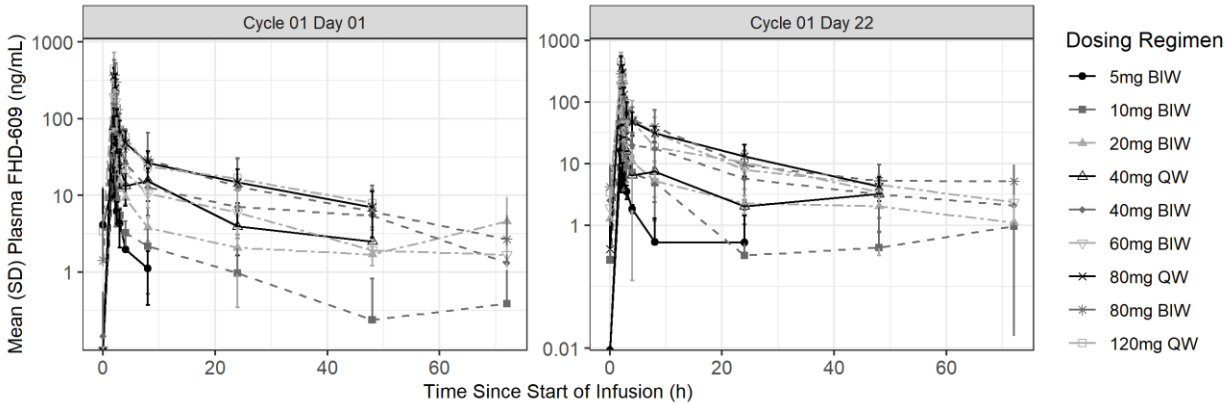
Abbreviations: AUC=area under the concentration-time curve; AR=accumulation ratio (Day 22/Day 1); $AUC_{0\text{-}168hr}$=AUC from time 0 to 168 hours postdose; $AUC_{0\text{-}inf}$=AUC from time 0 extrapolated to infinity; $AUC_{0\text{-}last}$= AUC from time 0 to the time of the last quantifiable concentration; C1D22=Cycle 1 Day 22; CL=clearance; C_{max}=maximum concentration; CV=coefficient of variation; IV=intravenous; N=number of subjects in cohort; n=number of subjects with calculable PK parameter; NC=not calculated; QW=once weekly; $t_{1/2}$=terminal elimination half-life; T_{max}=observed time to reach C_{max}; T_{last}=time of last observed concentration; V_{ss}=volume of distribution at steady state.
Notes: Parameters are presented as "geometric mean (geometric CV%); n," except for T_{max} and T_{last}, which are presented as "median (minimum-maximum); n" and blood-to-plasma ratios, which are presented as "arithmetic mean (CV%); n." Individual values reported when n ≤2 subjects in cohort.
[a] Subjects are excluded from summary statistics if % extrapolation of AUC >20% and/or R2 adjusted value <0.8.
[b] Subjects are excluded from summary statistics if R2 adjusted value <0.8.

Figure 3: Mean (SD) FHD-609 Blood Concentrations After IV Infusion of FHD-609 on C1D1 and C1D22, by Dosing Schedule (Study FHD-609-C-001; Pharmacokinetics Analysis Set)



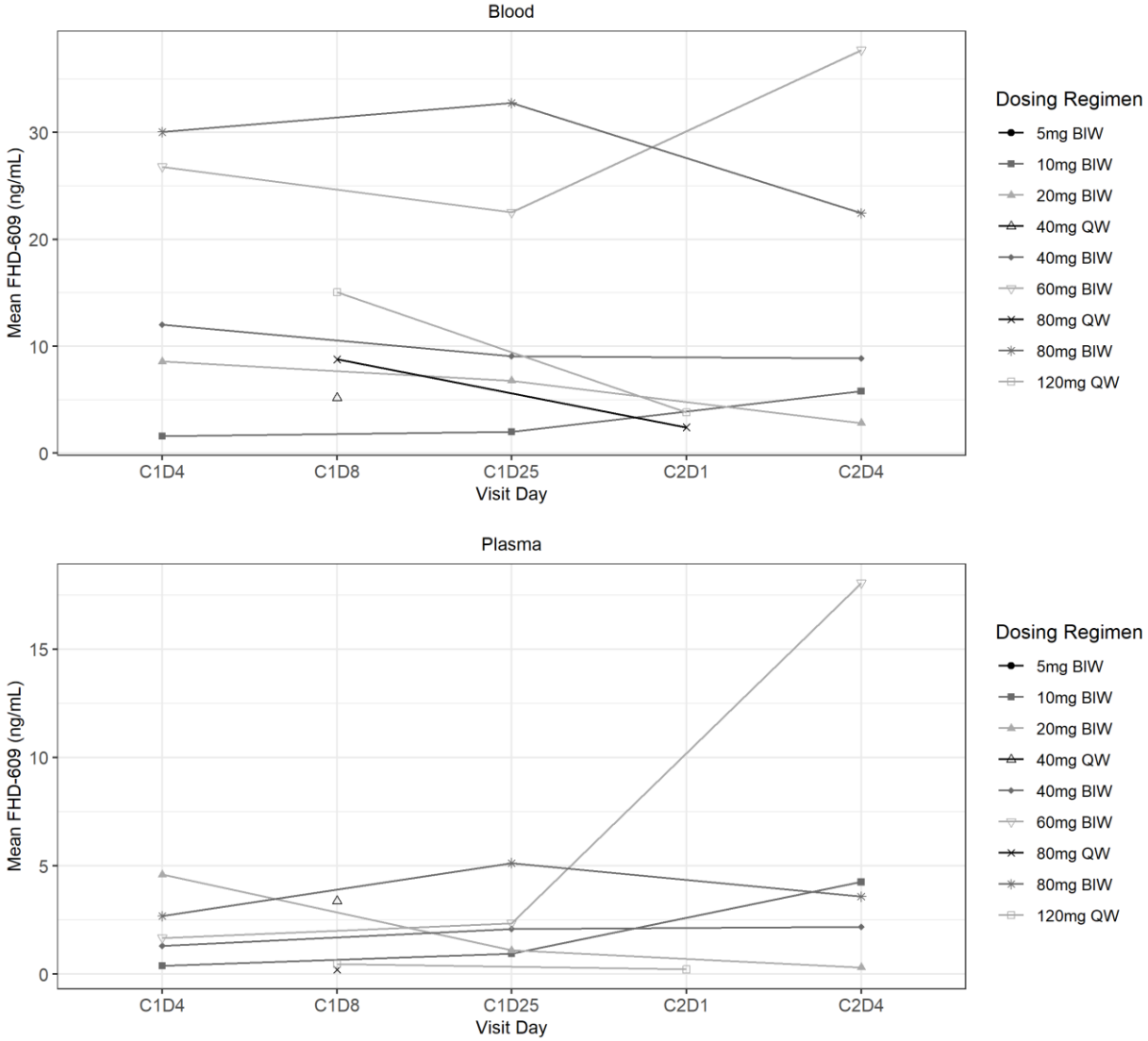
Abbreviations: BIW=twice weekly; CxDx=Cycle x, Day x; IV=intravenous; QW=once weekly.

Figure 4: Mean (SD) FHD-609 Plasma Concentrations After IV Infusion of FHD-609 on C1D1 and C1D22, by Dosing Schedule (Study FHD-609-C-001; Pharmacokinetics Analysis Set)



Abbreviations: BIW=twice weekly; CxDx=Cycle x, Day x; IV=intravenous; QW=once weekly.

Figure 5: Mean FHD-609 C_{trough} Concentrations in Blood and Plasma After IV Infusion of FHD-609, by Dosing Schedule (Study FHD-609-C-001; Pharmacokinetics Analysis Set)



Abbreviations: BIW=twice weekly; C_{trough}=minimum concentration before administration of the next dose; CxDx=Cycle x, Day x; IV=intravenous; QW=once weekly.

Preliminary Clinical Activity Results

One (2%) subject had a best overall response of PR per RECIST v1.1, which was achieved on C1D9 and maintained for 4 cycles (Listings 16.2.6.1.1 and 16.2.6.1.2), and 8 (15%) subjects had a best overall response of stable disease (Table 14.2.1.1). Stable disease lasted longer than 6 months in 2 subjects (Listing 16.2.6.1.2). A swimlane plot of treatment response is provided in Figure 14.2.1; a waterfall plot of change in tumor burden is provided in Figure 14.2.2.

The subject who experienced the PR was assigned to the 60 mg BIW dose group. Their dose was reduced to 40 mg BIW on Day 109 due to the report of QT interval prolongation in another subject in the 60 mg BIW dose group. The size of the target lesion was decreased versus baseline at C5D1, and continued to decrease consistently over the course of treatment, through the end of the subject's participation in the study (Listings 16.2.6.2.1.1 and 16.2.6.2.1.2); the non-target lesions in the pleural wall were undetectable starting on C3D1 (Listing 16.2.6.2.2). A cardiac repolarization abnormality appeared during C13, resulting in treatment discontinuation.

Summaries of DOR, TTR, PFS, and OS are provided in Tables 14.2.3.1, 14.2.4.1, 14.2.5.1, and 14.2.6.1, respectively.

Plots of Kaplan-Meier estimates for PFS and OS are provided in Figures 14.2.5.1 and 14.2.5.2, and 14.2.6.1 and 14.2.6.2, respectively. Plots are presented separately by disease type (SS and SMARCB1-loss tumors).

By-subject listings of new lesion assessment; PFS, DOR, and TTR; and OS data are provided in Listings 16.2.6.2.3, 16.2.6.3, and 16.2.6.4, respectively.

A by-subject listing of tumor biopsy information is provided in Listing 16.2.9.5.

Conclusions

Fifty-five subjects with advanced SS or SMARCB1-loss tumors received ≥1 dose of FHD-609 and were evaluated for safety, preliminary clinical activity, and PK in the dose escalation portion of this Phase 1 study. With respect to race and ethnicity, the largely White, not Hispanic or Latino patient population enrolled in this study was probably reflective of the epidemiology of metastatic SS: While data are scarce, the incidence of metastatic SS is believed to be slightly higher among patients who are White than among those who are Black or Hispanic (Blay, et al 2023). (Race and ethnicity were not reported for 13 [23.6%] subjects because of local regulations.) The medical history and prior and concomitant medications and procedures were reflective of the comorbidities associated with and natural history of SS.

FHD-609 was administered either BIW or QW, at doses of 5, 10, 20, 40, 60, or 80 mg BIW, or 40, 80, or 120 mg QW. A cohort expansion phase of the study was planned to further evaluate safety and tolerability at the MTD and/or RP2D(s), but no subjects were enrolled as enrollment was stopped by the sponsor during the Dose Escalation Phase because of safety concerns. In response, FDA placed the study on partial clinical hold in April 2023. The sponsor responded to the FDA partial clinical hold comments in October 2023 to address clinical deficiencies; however, because the sponsor decided to stop further development of FHD-609 for business reasons in November 2023, the study remains on partial clinical hold.

Three DLT events were observed among subjects receiving FHD-609 on a BIW schedule, while no DLT events were observed among those on a QW schedule: One subject in the 40 mg BIW group experienced a Grade 3 SAE of Electrocardiogram QT prolonged; 1 subject in the 60 mg BIW dose group experienced a Grade 3 SAE of Syncope that was deemed a DLT by the sponsor; and 1 subject in the 60 mg BIW group experienced Grade 3 Electrocardiogram QT prolonged, which progressed to a Grade 4 SAE and manifested as torsade de pointes and reversible cardiac arrest. After the occurrence of the latter, enrollment into the study was halted and the FHD-609 dose was reduced to 40 mg BIW (or 80 mg QW) for all subjects receiving FHD-609 60 mg BIW, 80 mg BIW, or 120 mg QW. The 60 mg BIW dose level and the equivalent dose on a QW

schedule (120 mg QW) were determined to be non-tolerated doses. As per protocol, the next lower dose level, 40 mg BIW, and the equivalent dose on a QW schedule (80 mg QW) were therefore declared the MTDs.

Other than cardiac TEAEs, the TEAEs observed in this study were generally consistent with the advanced underlying disease, comorbidities, and concomitant medications of the patient population. An external expert cardiology review determined that an association may exist between T wave inversions and the potential for a subsequent adverse CV event in subjects treated with FHD-609.

After IV infusion, blood and plasma concentrations of FHD-609 increased with increasing dose from 5 mg to 120 mg on C1D1 and C1D22. FHD-609 preferentially distributed in the blood. No significant accumulation of FHD-609 was observed in the blood or plasma on C1D22 at doses up to 80 mg BIW and up to 120 mg QW.

Per RECIST v1.1, 1 (2%) subject had a best overall response of PR, achieved on C1D9 and maintained for 4 cycles, and 8 (15%) subjects had a best overall response of stable disease, which lasted longer than 6 months in 2 subjects.

Date and Version of This Report

Document version	**Date**
Final CSR	03 Dec 2024

References

Blay JY, von Mehren M, Jones RL, et al. Synovial sarcoma: characteristics, challenges, and evolving therapeutic strategies. *ESMO Open.* 2023;8(5). doi: 10.1016/j.esmoop.2023.101618

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009;45(2):228-247. doi: 10.1016/j.ejca.2008.10.026

APPENDIX 1. CARDIAC SAFETY MEMORANDUM

Review of cardiac safety data for FHD-609 program. Clario (Philadelphia, Pennsylvania). 23 Oct 2023.

APPENDIX 2. LISTINGS NOT REFERENCED IN THE TEXT

Listing number	Listing title
16.2.3.2	Analysis Population (All Screened Subjects)
16.2.5.2	Study Drug Exposure and Dose Intensity (Safety Analysis Set)

APPENDIX 3. TABLES AND FIGURES

14 Tables and Figures

APPENDIX 4. APPENDICES

16 Appendices