SYNOPTIC CLINICAL STUDY REPORT

Study Title:	An Open-Label, Multicenter, Phase 2 Study of the Safety and Efficacy of KRT-232 in Subjects with Relapsed or Refractory Small Cell Lung Cancer (SCLC)
Brief Title:	Phase 2 Study of KRT-232 in Relapsed/Refractory SCLC
Study Number:	KRT-232-112
Study Phase:	Phase 2
Compound	Navtemadlin (KRT-232)
Indication:	Relapsed or refractory (R/R) SCLC
Study Sponsor:	Kartos Therapeutics, Inc. 275 Shoreline Drive, Suite 300 Redwood City, CA 94065
Study Initiation Date:	07 February 2022 (first subject first dose)
Early Study Termination Date:	26 August 2022 (last subject end of study)

Regulatory Agency Identification Numbers

Name	**Identification Number**
IND	155417
Eudra CT	2021-001530-19
ClinicalTrials.gov	NCT05027867

Report Date

Document Version	**Date**
Original version	07 February 2023

This study was conducted in accordance with the principles of International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents.

SYNOPSIS

Study Title: An Open-Label, Multicenter, Phase 2 Study of the Safety and Efficacy of KRT-232 in Subjects with Relapsed or Refractory Small Cell Lung Cancer (SCLC)

Study Number: KRT-232-112

Introduction: This phase 2 study KRT-232-112 was initiated to assess the safety and efficacy of navtemadlin in subjects with relapsed or refractory $TP53^{WT}$ SCLC. Because of slow enrollment due to a high screen failure rate, this study was terminated early by the Sponsor after enrollment of 3 subjects. Therefore, formal efficacy and pharmacokinetic (PK) analyses were not performed, and this clinical study report is in synoptic format.

All subjects treated on study had halted study treatment prior to the Sponsor decision to terminate the study.

Regulatory Agency Identification Numbers:

Name	Identification Number
IND	155417
Eudra CT	2021-001530-19
ClinicalTrials.gov	NCT05027867

Study Phase: 2

Name of Investigational Intervention: Navtemadlin (KRT-232)

Name of Sponsor: Kartos Therapeutics, Inc.
275 Shoreline Drive, Suite 300
Redwood City, CA 94065

Number of Study Centers and Countries: This study was conducted at 3 centers that enrolled subjects in France, South Korea, and Spain.

Publications:

Dowlati A, Juan-Vidal O, Hiret S, et al. An open-label, multicenter, phase 2 study of the safety and efficacy of navtemadlin (KRT-232) in patients with TP53 wild-type relapsed/refractory small cell lung cancer. Journal of Clinical Oncology. 2022;40(16_suppl):TPS8600-TPS8600. doi:10.1200/JCO.2022.40.16_suppl.TPS8600.

Study Period

Study Initiation Date: 07 February 2022 (first subject first dose)

Early Study Termination Date: 26 August 2022 (last subject end of study)

Rationale:

Patients with $TP53^{WT}$ SCLC may be defined as a subset of patients with unique biology and a high unmet medical need. Navtemadlin is an orally bioavailable, small molecule, targeted drug that binds to murine double minute 2 homologue (MDM2) and inhibits the MDM2/tumor protein 53 (p53) protein-protein interaction, which permits p53 to be activated and exert its tumor suppressor function, apoptosis of malignant cells. Activation of p53 by treatment with navtemadlin can result

in multiple transcription-dependent and -independent mechanisms that induce apoptosis in cancer cells and may be an effective strategy for patients with $TP53^{WT}$ SCLC.

Objectives, Endpoints, and Statistical Methods

Primary and Secondary Objectives and Endpoints

Primary Objective	**Primary Endpoint**
To determine the objective response rate (ORR) of each arm	Investigator-assessed response per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
Secondary Objectives	**Secondary Endpoints**
To determine the duration of response (DOR) for each arm	DOR among subjects who achieve a response, defined as the time from the initiation of response to disease progression or death.
To evaluate the progression-free survival (PFS) for each arm	PFS defined as the time from first dose date to disease progression or death
To evaluate the overall survival (OS) for each arm	OS defined as the time from first dose date to death
To determine the disease control rate (DCR) for each arm	Investigator-assessed response (of stable disease or better at any time while on study) per RECIST 1.1
To evaluate the safety and tolerability of navtemadlin for each arm	• Incidence, nature, and severity of adverse events (AEs) and serious adverse events (SAEs) • Changes in laboratory values, ECGs and vital signs
To determine the PK profile of navtemadlin for each arm	Navtemadlin and acyl glucuronide metabolite (M1) PK parameters, including but not limited to: • Maximum observed concentration (C_{max}) • Minimum observed concentration (C_{min}) • Area under the plasma concentration-time curve (AUC)

Statistical Analyses:

For the primary efficacy endpoint (ORR), the number and percentages of subjects who achieved a confirmed partial or complete response was to be provided, with corresponding 2-sided 90% exact binomial confidence intervals (CIs). Due to early study termination, formal analyses were not performed for efficacy endpoints.

Analysis and summary of the data was performed using the safety analysis set, which was defined as all treated subjects who received at least 1 dose of navtemadlin.

Assessment of safety data was descriptive and included summaries of treatment-emergent adverse events (TEAEs) by severity, seriousness, relationship to study drug, and adverse events (AEs) leading to discontinuation from any study drug, vital signs, and clinical laboratory tests.

Methodology:

This open-label, global, multi-center phase 2 study of navtemadlin monotherapy in subjects with $TP53^{WT}$ R/R SCLC was to be conducted in two parts. Part 1 was to evaluate the efficacy and safety of 2 dosing schedules for navtemadlin, with up to 10 subjects in each arm. Part 2 was to

further evaluate efficacy and safety of the dosing regimen(s) selected for expansion, with up to 18 additional subjects enrolled in each arm.

The study was closed after enrolling 3 subjects in Part 1. Part 2 of the study was not initiated.

Efficacy was assessed by CT/MRI every 6 weeks and response was evaluated by RECIST v1.1 criteria.

Adverse events were classified using the Medical Dictionary for Regulatory Activities (MedDRA) classification system Version 22.0 or higher. The toxicity severity was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. TEAEs were defined as AEs starting on or after the first dose of navtemadlin, up to 28 days after the last dose of the study treatment. Related SAEs reported after the treatment-emergent period were treated as TEAEs. Safety data summaries by toxicity grade were counted and displayed as the worst grade observed per subject per preferred term (PT). Overall, AE PTs by the order of frequency as well as AEs classified by system organ class (SOC) and preferred terminology according to MedDRA, were the base format for AE summaries.

Number of Participants (Planned and Analyzed):

Planned enrollment was up to 56 subjects. A total of 3 subjects were enrolled and were evaluable for safety.

Main Inclusion and Exclusion Criteria

Subjects must have been adults (≥ 18 years of age) with histologically or cytologically confirmed $TP53^{WT}$ SCLC with at least 1 measurable lesion per RECIST v1.1. Subjects must have had radiographic progression after prior platinum-containing chemotherapy and must have previously received a checkpoint inhibitor (PD-1 or PD-L1) if available and not contraindicated. Subjects with symptomatic or uncontrolled CNS metastases or prior treatment with MDM2 inhibitors were excluded from the study.

Study Interventions, Dose, Modes of Administration and Batch Number(s)

In part 1, subjects were randomized to receive 1 of two dosing schedules of navtemadlin:

- 240 mg QD on days 1-7 with 14 days off on a 21-day treatment cycle
- 180 mg QD on days 1-7 with 14 days off on a 21-day treatment cycle

Navtemadlin was administered orally.

Navtemadlin batch numbers used in this study included 4420096, 4420095, 4522454, 44420095, and 4017901.

Duration of Study Intervention

The planned duration of study treatment was up to 12 months for each subject.

Summary of Results and Conclusions

Disposition, Demographics and Other Characteristics:

Disposition. All 3 subjects enrolled in the study were randomized and treated with at least one dose of navtemadlin: 1 subject in the 180 mg navtemadlin arm and 2 subjects in the 240 mg navtemadlin

arm. All 3 subjects discontinued treatment prior to study completion due to progressive disease (2 subjects) or withdrawal of consent (1 subject; Table 14.1.1, Listing 16.2.4.1).

Demographics. Subject 3601-001 randomized to the 180 mg navtemadlin arm was 51 years old, female, and Asian. Subject 4000-001 randomized to the 240 mg navtemadlin arm was 69 years old and female; the subject's race was not reported. Subject 7000-001 randomized to the 240 mg navtemadlin arm was 55 years old, male, and White (Table 14.1.1, Listing 16.2.4.1).

Baseline disease and prior therapy. Subject 3601-001 had stage 4 metastatic SCLC at the time of initial diagnosis, including disease in the liver, and had received 1 prior line of systemic chemotherapy. Subject 4000-001 had stage 3 SCLC at the time of initial diagnosis and had received 2 prior lines of systemic chemotherapy. Subject 7000-001 had stage 3 SCLC at the time of initial diagnosis and had received 2 prior lines of systemic chemotherapy (Listing 16.2.4.3, Listing 16.2.4.4).

Exposure:

Subject 3601-001 received 4 cycles of treatment over 70 days before discontinuing due to disease progression. Subject 4000-001 received 1 cycle of treatment over 4 days before discontinuing due to withdrawal by subject. Subject 7000-001 received 3 cycles of treatment over 43 days before discontinuing due to disease progression (Listing 16.2.4.1, Listing 16.2.4.21).

Efficacy Results:

Two (2) subjects had at least 1 postbaseline imaging assessment and were evaluable for efficacy. Subject 4000-001 withdrew consent prior to the first imaging assessment at week 6 and was not evaluated for efficacy.

For subject 3601-001 (administered 180 mg navtemadlin), best overall response was stable disease (SD) at week 6. For subject 7000-001 (240 mg navtemadlin), best overall response was PD at week 6 (Listing 16.2.4.7).

Safety Results:

All 3 subjects had at least one TEAE. The most frequently reported TEAEs were asthenia (occurring in all 3 subjects) and constipation, nausea, and vomiting (each occurring in 2 subjects; 1 administered 180 mg navtemadlin and 1 administered 240 mg navtemadlin). The most frequently reported treatment-related TEAEs were asthenia, nausea, and vomiting (each occurring in 2 subjects; 1 administered 180 mg navtemadlin and 1 administered 240 mg navtemadlin) (Listing 16.2.4.8).

A single subject (subject 4000-001, administered 240 mg navtemadlin) had grade 3/4 TEAEs. These included asthenia, nausea, rectal haemorrhage, and vomiting (all grade 3) and thrombocytopenia (grade 4). Asthenia, nausea, and vomiting were considered treatment related. All grade 3/4 TEAEs resolved (Listing 16.2.4.8).

A single subject (subject 4000-001) had TEAEs that resulted in treatment interruption. These included nausea, vomiting, and asthenia (all grade 3). All these TEAEs were considered treatment related (Listing 16.2.4.8).

There were no TEAEs leading to treatment discontinuation.

A single subject (subject 4000-001) had an SAE of grade 4 thrombocytopenia. This SAE was not considered treatment related and resolved after 5 days. This SAE occurred on 24 July 2022, 28 days

after last navtemadlin treatment (26 June 2022), and 13 days after the subject initiated poststudy treatment with topotecan (11 July 2022) (Listing 16.2.4.1, Listing 16.2.4.9, and Listing 16.2.4.20).

No deaths were reported for this study (Listing 16.2.4.11).

There were no clinically meaningful changes in clinical laboratory values for chemistry (Listing 16.2.4.12), hematology (Listing 16.2.4.13), coagulation (Listing 16.2.4.14), urinalysis (Listing 16.2.4.15), vital signs (Listing 16.2.4.16) and ECGs (Listing 16.2.4.17).

Conclusions:

Interpretation of safety results is limited by the small number of subjects enrolled. However, the most frequently reported treatment-related TEAEs (asthenia, nausea, and vomiting) were consistent with the known safety profile of navtemadlin derived from clinical studies. No new or additional safety signals were observed in this study.

Date and Version of This Report: 07 February 2023, Original synoptic CSR

LIST OF ABBREVIATIONS

AE	Adverse event
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DOR	Duration of response
GCP	Good Clinical Practice
ICH	International Council for Harmonisation
MDM2	Murine double minute 2 homologue
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
PK	Pharmacokinetic
PT	Preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SCLC	Small cell lung cancer
SOC	System organ class
TEAE	Treatment-emergent adverse event

14. TABLES AND FIGURES

For consistency across programs, Kartos has a uniform numbering system for the data displays presented in this section. Tables and figures are categorized and numbered in accordance with ICH E3 guidance. The number sequence may have gaps and tables/figures do not necessarily appear in the order in which they are cited in the text. Similarly, the number sequence for subsections below may have gaps.

Tables omitted from this synoptic study report are indicated below by "Not applicable".

14.1. Demographic Data

Table 14.1.1 Demographics Safety Analysis Set

Table 14.1.2 Baseline Disease Characteristics Safety Analysis Set

14.2. Efficacy Data

Not applicable.

14.3. Safety Data

Table 14.3.1 Subject Incidence of Serious TEAE by SOC and PT Safety Analysis Set

14.4. Narratives of Deaths, Serious Adverse Events, and Certain Other Clinically Meaningful Adverse Events

The subject below had an SAE:

Subject 4000-001

15. REFERENCE LIST

Dowlati A, Juan-Vidal O, Hiret S, et al. An open-label, multicenter, phase 2 study of the safety and efficacy of navtemadlin (KRT-232) in patients with TP53 wild-type relapsed/refractory small cell lung cancer. Journal of Clinical Oncology. 2022;40(16_suppl):TPS8600-TPS8600. doi:10.1200/JCO.2022.40.16_suppl.TPS8600.

16. APPENDICES

Appendices omitted from this synoptic study report are indicated below by "Not applicable".

16.1 Study Information

16.1.1 Protocol and Protocol Amendments

Title	Protocol Version	Version Date
An Open-Label, Multicenter, Phase 2 Study of the Safety and Efficacy of KRT-232 in Subjects with Relapsed or Refractory Small Cell Lung Cancer (SCLC)	Original Protocol	19 March 2021
	Amendment 1	07 May 2021

16.1.2 Sample Case Report Form

16.1.3 List of IECs and IRBs and Representative Written Information for Subjects

Not applicable.

16.1.4 List and Description of Investigators and Other Important Study Participants

Not applicable.

16.1.5 Signatures of Principal Investigator or Sponsors Responsible Medical Officer

16.1.6 Listing of Subjects Receiving Study Drug from Specific Batches

Not applicable.

16.1.7 Randomization Scheme and Codes

Not applicable.

16.1.8 Audit Certificates

Not applicable.

16.1.9 Documentation of Statistical Methods

16.1.10 Documentation of Inter-laboratory Standardization Methods and Quality Assurance Procedures

Not applicable.

16.1.11 Publications Based on the Study

16.1.12 Important Publications Referenced in the Report

Not applicable.

16.2 Subject Data Listings

16.3 Case Report Forms

16.3.1 CRFs for Deaths, Other Serious Adverse Events, and Withdrawals for Adverse Events

The subject below had an SAE:

Subject 4000-001

16.4 Individual Subject Data Listings