SYNOPTIC CLINICAL STUDY REPORT

Study Number KRT-232-117

<table>
<tr><td>Study Title:</td><td colspan="2">An Open-Label, Multicenter, Phase 1b/2 Study of the Safety and Efficacy of KRT-232 (Navtemadlin) Combined with a Tyrosine Kinase Inhibitor (TKI) in Patients with Relapsed or Refractory Ph+ Chronic Myeloid Leukemia (CML)</td></tr>
<tr><td>Brief Title</td><td colspan="2">Navtemadlin Combined with a TKI in Patients with Relapsed or Refractory Ph+ CML</td></tr>
<tr><td>Study Phase:</td><td colspan="2">Phase 1b/2</td></tr>
<tr><td>Product Name:</td><td colspan="2">Navtemadlin (KRT-232)</td></tr>
<tr><td>Indication:</td><td colspan="2">Relapsed or Refractory Ph+ Chronic Myeloid Leukemia in Chronic Phase</td></tr>
<tr><td>Study Sponsor</td><td colspan="2"></td></tr>
<tr><td>Study Initiation Date:</td><td colspan="2">16 November 2021 (first subject, first dose)</td></tr>
<tr><td>Early Study Termination Date</td><td colspan="2">14 September 2023 (last subject, last visit)</td></tr>
<tr><td>Regulatory Agency Identification Numbers</td><td colspan="2"><table><tr><th>Name</th><th>Identification Number</th></tr><tr><td>IND</td><td>153137</td></tr><tr><td>Eudra CT</td><td>2020-004699-16</td></tr><tr><td>ClinicalTrials.gov</td><td>NCT04835584</td></tr></table></td></tr>
<tr><td>Report Date</td><td colspan="2"><table><tr><th>Document Version</th><th>Date</th></tr><tr><td>Original version</td><td>07 Nov 2023</td></tr></table></td></tr>
<tr><td colspan="3">This study was conducted in accordance with the principles of International Council for Harmonization (ICH) Good Clinical Practice (GCP).</td></tr>
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SYNOPSIS

Study Title: An Open-Label, Multicenter, Phase 1b/2 Study of the Safety and Efficacy of KRT-232 (Navtemadlin) Combined with a Tyrosine Kinase Inhibitor in Patients with Relapsed or Refractory Ph+ Chronic Myeloid Leukemia

Study Number: KRT-232-117

Introduction: This phase 1b/2 study KRT-232-117 was initiated to assess the safety and efficacy of navtemadlin combined with a second-generation tyrosine kinase inhibitor (TKI) in subjects with relapsed or refractory (R/R) Ph+ chronic myeloid leukemia (CML). A decision was made by the sponsor to terminate the study because of reallocation of resources; phase 2 of the study did not initiate. The decision to terminate the study was not based on any safety concerns. Therefore, formal efficacy and PK analyses were not performed, and this clinical study report is in synoptic format.

Regulatory Agency Identification Numbers:

Name	Identification Number
IND	153137
Eudra CT	2020-004699-16
ClinicalTrials.gov	NCT04835584

Study Phase: 1b/2

Name of Investigational Drug: Navtemadlin (KRT-232)

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

Number of Study Centers and Countries: This study was conducted at 27 centers that enrolled subjects in US, France, and Russia.

Study Period: 16 November 2021 (first subject, first dose) to 14 September 2023 (last subject, last visit)

Rationale: The defining genetic marker of CML is the presence of the Philadelphia chromosome (Ph), which involves the fusion of the Abelson murine leukemia (ABL1) gene on chromosome 9 with the breakpoint cluster region (BCR) gene on chromosome 22. The resulting oncoprotein, BCR-ABL1, is a constitutively active tyrosine kinase that utilizes downstream signaling, such as RAS, RAF, JUN kinase, MYC and STAT to promote growth and replication. The BCR-ABL fusion protein is restricted to the cytoplasm, effectively subverting the normal nuclear functions of c-ABL.

Chronic myeloid leukemia is classified into 3 phases: chronic phase (CML-CP), accelerated phase (CML-AP), and blast crisis (CML-BC). Approximately 90% to 95% of patients present with CML-CP, which can be asymptomatic or characterized by splenomegaly, anemia, fatigue, weight loss, early satiety and left upper quadrant fullness or pain. CML-AP represents a more advanced form of CML, and disease transformation may be asymptomatic or present with anemia, splenomegaly, or organ infiltration.

The largest improvements in survival have been observed with the introduction of the TKI imatinib. TKIs impede the interaction of BCR-ABL1 and adenosine triphosphate, preventing signal transduction by the kinase and blocking proliferation of the malignant clone. A number of

second generation TKIs have been approved and recommended for use in both the first-line and R/R setting.

At least 25% of patients with CML-CP develop resistance to TKIs. For patients who acquire resistance or who fail treatment with second generation TKIs, allogenic stem cell transplant (ASCT) is the treatment recommendation. Currently, ASCT is the only potential curative treatment for patients in CML-AP and CML-BC.

For patients with CML who respond to treatment, indefinite continuation of treatment with TKIs is recommended. In the second line setting and beyond, changing therapy is warranted for treatment failure or resistance, should options be available. Once patients enter the third line setting and beyond, while the determination of an acceptable response has not been established, achievement of anything less than a complete cytogenetic response (CCyR) or a BCR-ABL transcript level of <1% is suboptimal for survival outcomes.

Patients who progress from CML-CP to CML-AP while on TKI therapy have a higher rate of progression to CML-BP and poor survival. In recent studies of patients with CML-AP, many of whom had received at least 3 prior TKIs, treated with omacetaxine and ponatinib, led to a major hematologic response (MaHR) in 14% to 57% of patients, respectively. Duration of response may diminish in these patients, and ASCT is often pursued.

The introduction of TKIs has dramatically improved outcomes for patients with CML, but most will ultimately become resistant or intolerant. Improvements in onset and depth of response have been achieved with second and third generation TKIs, however clinically significant treatment-related toxicities can be associated with these therapies. Chronicity of CML and the indefinite nature of treatment, coupled with the need for available safe and effective therapies after the failure of at least 1 prior TKI indicates an unmet need for patients in whom ASCT or other TKIs are not appropriate.

In this study, convergence of the BCR-ABL and murine double minute 2 homologue (MDM2)/p53 signaling pathways in CML, suitable patient demographics (high p53 wild type [WT] frequency) and preclinical studies demonstrating marked sensitivity of leukemic stem cells provide a strong rationale to evaluate navtemadlin as an add-on to selected TKIs in patients with CML who are resistant, refractory, or intolerant to TKI treatment. Inhibition of BCR-ABL signaling in CML cells, combined with inhibition of MDM2 and activation of p53, leads to a reduction in MYC-mediated transcription and rapid induction of apoptosis via mitochondrial pathways. By reducing the leukemic burden and targeting leukemic stem cells, the combination of navtemadlin with a TKI has the potential to be a disease-modifying therapy for patients with R/R CML.

Objectives, Endpoints, and Statistical Methods

Primary and Secondary Objectives and Endpoints

Phase 1b	
Primary Objectives	**Endpoint/Outcome Measures**
To determine the navtemadlin maximum tolerated dose (MTD)/maximum administered dose (MAD) and RP2D in combination with dasatinib or nilotinib.	Determination of the dose limiting toxicities (DLTs) will be used to establish the MTD/MAD of navtemadlin in combination with dasatinib or nilotinib.
Secondary Objectives	**Endpoint/Outcomes Measure**
To determine the pharmacokinetics (PK) of navtemadlin	Navtemadlin and acyl glucuronide metabolite (M1) PK parameters including but not limited to: • Maximum observed concentration • Minimum observed concentration • Area under the plasma concentration-time curve • Time to maximum plasma concentration
[redacted]	[redacted]
[redacted]	[redacted]
Phase 2	
Primary Objective	**Endpoint/Outcomes Measure**
To determine the rate of major molecular response in Arms A and B	The proportion of subjects who achieve a major molecular response according to modified European LeukemiaNet (ELN) criteria (Protocol Appendix 5).
To determine the rate of MaHR in Arm C	The proportion of subjects who achieved MaHR according to modified ELN criteria (Protocol Appendix 5).
Secondary Objectives	**Endpoint/Outcomes Measures**
To determine the rate of CCyR in Arms A and B	The proportion of subjects who achieve a CCyR according to modified ELN criteria (Protocol Appendix 5).
To determine the rate of major cytogenetic response rate (MCyR) in Arm C	The proportion of subjects who achieved CCyR or PCyR according to modified ELN criteria (Protocol Appendix 5).
To determine the duration of response in each Arm	Duration of response (Kaplan-Meier estimate) defined as the time from first observation of response to progression/relapse or death, whichever comes first

To determine progression-free survival in each Arm	Progression-free survival is defined as the time from the first treatment dose date to progression/relapse or death, whichever comes first
To determine overall survival in each Arm	Overall survival is defined as the time from the first treatment dose date to death from any cause
To determine the proportion of subjects who transition to ASCT in each Arm	The proportion of subjects who transition to allogeneic transplant
To determine the safety and tolerability of navtemadlin in combination with dasatinib or nilotinib	Analyses of the safety endpoints will include the following measurements or assessments: physical examinations, laboratory tests, adverse events (AEs), serious adverse events (SAEs), electrocardiograms (ECGs), and vital signs
[redacted]	[redacted]
[redacted]	[redacted]

Methodology:

This was a phase 1b/2 study of navtemadlin in combination with a second-generation TKI (either dasatinib or nilotinib) in adults ≥ 18 years of age with:

- $TP53^{wt}$ Ph+ CML-CP who were resistant or intolerant to ≥ 1 prior TKI and who met either ELN criteria for treatment failure on their current TKI or who had a warning response on their current TKI therapy at or beyond 12 months.
- $TP53^{wt}$ Ph+ CML-AP who failed to obtain a MaHR 3 months after initiating their current TKI, with no alternative therapeutic options likely to produce clinical benefit.

Subjects underwent TP53 mutation status testing at screening if their TP53 mutation status was unknown.

The study consisted of 2 phases, however due to early termination of the study, only the phase 1b portion of the study enrolled subjects.

The phase 1b portion of the study employed a dose-escalation design of navtemadlin in combination with the subject's current TKI (either dasatinib or nilotinib) in subjects with CML-CP, with expansion to at least 6 subjects at the MTD/ MAD (Table 1).

[redacted]

The Screening Period assessments were performed within 28 days prior to study treatment initiation. Subjects who satisfied all eligibility criteria were eligible to enroll in the study following approval by the Sponsor's medical monitor or designee.

The Treatment Period extended from the first dose of study treatment through the End of Treatment visit which was to occur within 28 days from the last dose of study drug or prior to the start of a new anticancer treatment. Initiation of study treatment was to occur following enrollment approval by the Sponsor's medical monitor or designee. [redacted] Navtemadlin began on Cycle 1 Day 1 for all subjects. All subjects were to continue study treatment until criteria for permanent discontinuation of study drug were met, such as relapse or disease progression requiring alternate therapy, study drug was no longer tolerated by the subject, or study end.

The Follow-up Period began once a subject discontinued study treatment and continued until death, lost to follow-up, consent withdrawal, or study end, whichever occurred first.

The Response Follow-up Period occurred for subjects who discontinued treatment for reasons other than relapse or disease progression and included efficacy assessments at a minimum of every 12 weeks ± 7 days until relapse, disease progression, withdrawal of consent, or start of subsequent anticancer therapy.

The Long-term Follow-up Period occurred for subjects with relapse or disease progression who were followed for survival and subsequent anti-cancer therapy every 12 weeks ± 14 days until study end.

The primary objective of the phase 1b portion of the study was to determine the MTD / MAD and recommended phase 2 dose of navtemadlin in combination with dasatinib or nilotinib. Dose limiting toxicities were used to inform the doses, and the DLT observation period was the first cycle (28 days). The following adverse events were considered DLTs if they were treatment emergent, occurred during the specified DLT observation period, or were considered related to study drug:

[redacted]

- [redacted]
- [redacted]

[redacted]

Number of Subjects (Planned and Analyzed): [redacted] the actual number of subjects analyzed was 5 dosed subjects (all DLT evaluable).

Diagnosis and Main Criteria for Inclusion and Exclusion:

Phase 1b: Adults with TP53^{wt} Ph+ CML in chronic phase who were resistant (refractory or relapsed) or intolerant to ≥ 1 prior TKI and who met either ELN criteria for treatment failure on their current TKI or who have had a warning response on their current TKI therapy at or beyond 12 months.

Study Treatments, Dose, Mode of Administration, and Lot Numbers

In Phase 1b, the dose of navtemadlin was determined by the dose level assigned at the time of enrollment (180, 240, or 300 mg).

Navtemadlin was administered orally once daily with a glass of water on Days 1 to 7 of a 28-day cycle. Tablets were not to be crushed, chewed, or dissolved in water, and taken with or without food. [redacted]

Dasatinib or nilotinib in combination with navtemadlin were administered at the dose taken prior to study entry and according to the local prescribing information.

Duration of Study Intervention

Subjects were to continue treatment until relapse, disease progression or lack of tolerability. The definition of disease progression was based on the modified ELN response criteria (Protocol Appendix 5). All subjects who discontinued study treatment were followed for response, as applicable, and survival.

Statistical Analyses:

The dose escalation under the 3+3 design tested up to 3 dose levels. The number of subjects for Phase 1b ranged from 3 to 18 subjects before reaching the MTD/MAD. Before determining the

RP2D, [redacted] Intrapatient dose escalation was not permitted in the dose-escalation phase of this study.

Because a decision was made by the sponsor to terminate the study, phase 2 of the study did not initiate. The termination of the study was to allow reallocation of resources and was not due to any safety concerns.

The assessment of safety data is descriptive and based on the summarization of TEAEs by severity, seriousness, relationship to study drug, and AEs leading to discontinuation from any study drug, vital signs, and clinical laboratory tests. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) classification system version 25.0. The severity of the toxicities was graded according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Treatment-emergent AEs are defined as AEs starting on or after the first dose of navtemadlin, up to 28 days after the last dose of the study treatment. Treatment-emergent SAEs reported up to 28 days after the end of the treatment period were also included as TEAEs.

Summary of Results and Conclusions

The last subject last visit occurred on 14 Sep 2023, and this was also the study termination date.

Disposition, Demographics, and Other Characteristics:

Five subjects were enrolled and treated in Phase 1b of the study (Dose Level 1: 3 subjects; Dose Level 2: 2 subjects). All subjects discontinued the study; 1 subject discontinued due to death, 1 subject discontinued due to investigator decision, and 3 subjects discontinued due to study termination by sponsor (Listing 16.2.4.2).

Three subjects were male, 2 were female. The median age was 51 years (range: 39 to 67 years) (Listing 16.2.4.3).

Baseline Disease, Medical History and Therapy

Baseline disease, medical history, and prior / subsequent anti-cancer therapy are summarized for each subject in the following listings:

Listing 16.2.4.3	Listing of Demographics and Baseline Disease Characteristics Safety Analysis Set
Listing 16.2.4.4	Listing of Medical History Safety Analysis Set
Listing 16.2.4.15	Listing of Concomitant Medications Safety Analysis Set
Listing 16.2.4.16	Listing of Prior Systemic Therapy Safety Analysis Set
Listing 16.2.4.17	Listing of Subsequent Anti-Cancer Therapy Safety Analysis Set
Listing 16.2.4.18	Listing of ECOG Safety Analysis Set

Exposure

The median number of cycles of navtemadlin treatment was 10 (range: 5 to 21). Three subjects received treatment with navtemadlin 180 mg QD on Days 1-7 of a 28-day cycle for 5, 19 and 21 cycles; 2 subjects received treatment with navtemadlin 240 mg QD on Days 1-7 of a 28-day cycle for 5 and 10 cycles. Four subjects were treated concurrently with dasatinib, and 1 subject was treated with nilotinib.

Two subjects had navtemadlin dose interruptions due to adverse events (1 subject with COVID-19 and fatigue; 1 subject with decreased absolute neutrophil count) and 2 subject had a dose reduction due to adverse events (1 subject each, fatigue and vomiting).

Summaries of study drug exposure are provided for each subject in the following listings:

Listing 16.2.4.13 Listing of KRT-232 Exposure Safety Analysis Set

Listing 16.2.4.14 Listing of TKI Exposure Safety Analysis Set

Efficacy Results

Because of the early termination and small number of subjects, no formal efficacy analysis occurred. Of the 5 subjects enrolled, 2 subjects experienced complete hematologic response, 1 subject experienced minimal cytogenetic response, 1 subject experienced molecular response 1, and 1 subject had no improvement (maintained pre-treatment status of MR1). See Appendix 16.1.13 for individual subject efficacy narratives.

Safety Results

The primary objective of the phase 1b portion of the study was to determine the MTD / MAD and recommended phase 2 dose of navtemadlin in combination with dasatinib or nilotinib. These doses were to be established by DLTs occurring during the first cycle (28 days). No subject experienced a DLT during the phase 1b portion of the study.

Further safety evaluation was assessed through summaries of TEAEs, laboratory test results, vital signs, physical examinations, and ECGs, and are summarized by subject in the following listings:

Listing 16.2.4.5 Listing of Adverse Events Safety Analysis Set

Listing 16.2.4.6 Listing of Death Safety Analysis Set

Listing 16.2.4.7 Listing of AST/ALT/BILI Subjects Having Clinically Significant Abnormal Post-Baseline Values in Safety Analysis Set

Listing 16.2.4.8 Listing of Lipase/Amylase Subjects Having Clinically Significant Abnormal Post-Baseline Values in Safety Analysis Set

Listing 16.2.4.9 Listing of Lab Safety Analysis Set

Listing 16.2.4.10 Listing of ECG Safety Analysis Set

Listing 16.2.4.11 Listing of ECG Subjects with any Post-baseline Single Reading QTcF > 450 msec in Safety Analysis

Listing 16.2.4.12 Listing of Vital Signs Safety Analysis Set

Listing 16.2.4.19 Listing of Physical Exam Safety Analysis Set

All 5 subjects (100.0%) experienced at least 1 TEAE. Those TEAEs experienced by ≥ 2 subjects included nausea [redacted], vomiting, fatigue, and diarrhea [redacted], anemia, asthenia, cough, dehydration, dry skin, dyspnea, nasal congestion, and fever (Listing 16.2.4.5). [redacted]

[redacted]

Three subjects experienced serious adverse events (SAEs); 1 subject experienced COVID-19 and dehydration [redacted]; 1 subject experienced pulmonary arterial hypertension and mitral valve incompetence [redacted]; and 1 subject experienced vomiting [redacted] (Listing 16.2.4.5). Narratives for subjects experiencing SAEs are provided in Section 14.2.

No subjects experienced significant abnormal post-baseline levels of aspartate aminotransferase, alanine aminotransferase, or bilirubin (Listing 16.2.4.7). One subject experienced abnormal post-baseline levels of both amylase and lipase (Listing 16.2.4.8). Neither increase was considered by the investigator to be related to study treatment.

No subjects were discontinued from the study due to any TEAE, and no deaths occurred due to any TEAE (Listing 16.2.4.6).

Conclusions:

Interpretation of safety results is limited by the small number of subjects enrolled. No DLTs were observed with the combination of navtemadlin and either nilotinib or dasatinib. The most frequently reported navtemadlin-related TEAEs (asthenia, nausea, 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. While no formal efficacy analysis was performed, there was evidence of clinical activity in 4 of 5 subjects treated with the combination therapy.

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

LIST OF ABBREVIATIONS

ABL1	Abelson murine leukemia
AE	Adverse event
AML	Acute Myeloid Leukemia
ASCT	allogenic stem cell transplant
BCR	breakpoint cluster region
BID	Twice daily
BTK	Bruton's tyrosine kinase
BMX	X-linked bone marrow kinase
CCyR	complete cytogenetic response
CI	Confidence interval
CML	Chronic myeloid leukemia
CML-CP	Chronic myeloid leukemia-chronic phase
CML-AP	Chronic myeloid leukemia-accelerated phase
CML-BC	Chronic myeloid leukemia-blast crisis
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ELN	European Leukemia Net
KRT-232	Navtemadlin
MAD	Maximum administered dose
MaHR	major hematologic response
MCyR	Major cytogenetic response
MDM2	Murine double minute chromosome 2
MTD	Maximum tolerated dose
p53	protein 53
PCyR	Partial cytogenetic response
Ph	Philadelphia chromosome
PK	Pharmacokinetics
QD	Once daily
R/R	Relapsed/Refractory
SAE	Serious adverse event
TEAE	Treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
TP53	Tumor protein 53
$TP53^{wt}$	Wild-type tumor protein 53

14. TABLES AND FIGURES

14.1 Tables

Table 14.1.7.1 Summary of Lot Numbers for KRT-232
Safety Analysis Set

Lot Number
72669.2
72671.2
72671.3
72671.6

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

The subjects below had an SAE(s):

Subject No.:	KRT-232-117-1072-001
Treatment:	Navtemadlin 180 mg once daily (QD) on Days 1 to 7 of a 28-day cycle + TKI (Nilotinib)
Demographics:	39 years, male
Events:	Lung Infection-COVID-SAE (SAE), Dehydration -- SAE (SAE)
CIOMS Mfr. Control Numbers:	2022KARUS0001, 2022KARUS0021

This 39-year-old male subject was diagnosed with relapsed/refractory Ph+ chronic myeloid leukemia (CML) in 2006.

Subject 1072-001 signed the informed consent to enroll in Study KRT-232-117. On 14 Oct 2021, the subject received his first dose of tyrosine kinase inhibitor (TKI) nilotinib at a dosage of 300 mg, twice daily (BID). He began study treatment on 16 Nov 2021 (Cycle 1 Day 1) and received treatment with navtemadlin 180 mg once daily (QD) on Days 1 to 7 of a 28-day cycle + TKI (nilotinib). The subject received a total of 5 cycles of navtemadlin treatment, with the last dose taken on 03 Apr 2022.

Prior anti-cancer therapy included:

Therapy	Start Date	Stop Date
Hydrea, Imatinib	01 Aug 2006	25 Jul 2011
Imatinib	26 Jul 2007	11 Feb 2011
Dasatinib	11 Feb 2011	09 Dec 2011
Nilotinib	09 Dec 2011	16 Nov 2017
L buttock radiation	14 Apr 2017	19 Apr 2017
Ponatinib	16 Nov 2017	03 Oct 2018
Total Body Irradiation	15 Oct 2018	15 Oct 2018
Cytoxan, Fludarabine, Total Body Irradiation	16 Oct 2018	16 Oct 2018
Donor lympocyte infusions (x2)	01 May 2019	06 Jun 2019
Ponatinib	20 May 2019	08 Aug 2019
Omacetaxine	26 Aug 2019	UN UNK 2019
Granulocyte Infusions (x3)	UN Nov 2019	UN Nov 2019
Ponatinib	11 Nov 2019	15 Nov 2019
Imatinib	15 Nov 2019	18 Nov 2019
Bosutinib	22 Jan 2020	02 Aug 2021
Nilotinib	14 Oct 2021	

At screening, the subject's medical history included:

Condition	Onset Date	End Date (or Ongoing)
Tetanus immune globulin allergy	UNKNOWN	Ongoing
Anxiety	UN 2006	Ongoing
Chronic pain	UN 2016	Ongoing
Nausea	UN 2018	Ongoing
Fatigue	UN 2018	Ongoing
Insomnia	UN 2018	Ongoing
Fungal pneumonia	UN Sep 2019	UN Sep 2019
Hypertension	UN 2020	Ongoing
Gastrointestinal reflux disease	UN 2020	Ongoing
Aspergillus	25 Jun 2020	25 Jun 2020
Splenectomy	02 Nov 2020	2 Nov 2020
Pulmonary embolism x2	UN Dec 2020	UN Dec 2020
Pulmonary embolism	UN Feb 2021	UN Feb 2021
Transaminitis	02 Aug 2021	6 Aug 2021
Increased PTT	21 Oct 2021	Ongoing
Decreased ionized calcium	25 Oct 2021	Ongoing
Increased GGT	25 Oct 2021	Ongoing
Decreased WBC	25 Oct 2021	16 Nov 2021
Decreased ANC	25 Oct 2021	16 Nov 2021
Anemia	25 Oct 2021	6 Dec 2021
Increased LDH	25 Oct 2021	20 Dec 2021
Increased alkaline phosphatase	28 Oct 2021	Ongoing
Increased AST	28 Oct 2021	16 Nov 2021
Increased ALT	28 Oct 2021	16 Nov 2021

Concomitant medications taken by the subject included:

Medication Name	Start Date (Study Day)	End Date or Ongoing (Study Day)	Indication	Reason Given
Acetylsalicylic Acid	UN Aug 2021 (-106)	Ongoing	Anticoagulation	Anticoagulation
Aciclovir	UN 2018 (-1414)	Ongoing	Anti-viral	Prophylaxis
Allopurinol	UN Aug 2021 (-106)	Ongoing	TLS	Prophylaxis
Amitriptyline	UN 2018 (-1414)	Ongoing	Pain	Medical History (Left Hip, Abdomen Pain)
Amlodipine	UN 2020 (-684)	Ongoing	Hypertension	Medical History

Medication Name	Start Date (Study Day)	End Date or Ongoing (Study Day)	Indication	Reason Given
Anagrelide HCl	1 Nov 2021 (-14)	27 Dec 2021 (42)	Increased platelets; anti-coagulation, anti-coagulant	Anticoagulant
Sotrovimab Monoclonal Antibodies	3 Jan 2022 (49)	3 Jan 2022 (49)	Lung infection; COVID	Adverse Event
Aprepitant	17 Nov 2021 (2)	17 Nov 2021 (2)	Nausea	Medical History
Cefepime	3 Jan 2022 (49)	3 Jan 2022 (49)	Fever	Adverse Event
Clonazepam	UN 2006 (-5797)	Ongoing	Anxiety	Medical History
Diphenhydramine	16 Nov 2021 (1)	28 Mar 2022 (133)	Pre-Med	Pre-Med Blood Products
Docusate Sodium	UN 2019 (-1049)	Ongoing	Constipation	Prophylaxis
Famotidine	16 Nov 2021 (1)	Ongoing	Gerd	Medical History
Fentanyl	16 Feb 2022 (93)	16 Feb 2022 (93)	Pain	BMB Procedure
Fentanyl	7 Apr 2022 (143)	07 Apr 2022 (143)	Procedure -- BMB	Pain, BMB Procedure
Fluoxetine HCl	UN 2018 (-1414)	Ongoing	Anxiety	Medical History
Fondaparinux Sodium	UN Feb 2021 (-287)	09 Mar 2022 (114)	Anticoagulation	Anticoagulation
Furosemide	5 Jan 2022 (51)	Ongoing	Edema	Adverse Event
Furosemide	6 Dec 2021 (21)	6 Dec 2021 (21)	Lower extremity Edema	Adverse Event
Granisetron HCl	16 Nov 2021 (1)	04 Apr 2022 (140)	Nausea, Vomiting	Prophylaxis
Haloperidol	04 Apr 2022 (140)	04 Apr 2022 (140)	Vomiting, Nausea	Adverse Event
Loperamide HCl	16 Nov 2021 (1)	04 Apr 2022 (140)	Pre-Med	Pre-Med
Lorazepam	UN Sep 2021 (-75)	17 Nov 2021 (2)	Nausea, Vomiting, Anxiety	Medical History
Lorazepam	28 Mar 2022 (133)	28 Mar 2022 (133)	Anxiety	Medical History
Methadone	UN 2020 (-684)	Ongoing	Left hip and abdomen pain	Medical History
Midazolam HCl	16 Feb 2022 (93)	16 Feb 2022 (93)	Sedative	BMB Procedure
Midazolam HCl	07 Apr 2022 (143)	07 Apr 2022 (143)	Procedure -- BMB	Pain, BMB Procedure
Olanzapine	UN 2018 (-1414)	Ongoing	Insomnia	Medical History
Omeprazole	UN 2020 (-684)	16 Nov 2021 (1)	Gerd	Medical History
Ondansetron	UN 2018 (-1414)	Ongoing	Nausea	Medical History
Ondansetron	04 Apr 2022 (140)	Ongoing	Nausea, Vomiting	Adverse Event
Oxycodone	UN UNK 2019 (-1049)	Ongoing	Left Hip and Abdomen Pain	Medical History

Medication Name	Start Date (Study Day)	End Date or Ongoing (Study Day)	Indication	Reason Given
Paracetamol	16 Nov 2021 (1)	28 Mar 2022 (133)	Pre-Med	Pre-Med Blood Products
Pregabalin	UN 2019 (-1049)	Ongoing	Left Hip and Abdomen Pain	Medical History
Remdesivir	04 Jan 2022 (50)	05 Jan 2022 (51)	Lung infection; COVID	Adverse Event
Sodium Chloride	04 Apr 2022 (140)	04 Apr 2022 (140)	Dehydration	Adverse Event
Sulfamethoxazole; Trimethoprim	UN 2018 (-1414)	Ongoing	Anti-bacterial	Prophylaxis
Ursodeoxycholic Acid	02 Aug 2021 (-105)	Ongoing	Liver protectant	Prophylaxis

Event: Lung Infection-COVID-SAE (Grade 3; SAE)

The most recent dose of navtemadlin, prior to the onset of lung infection-COVID-SAE (PT: COVID-19) was administered on 20 Dec 2021 (Study Day 35; C2D7).

On 03 Jan 2022 (Study Day 49), the subject presented to the emergency department (ED) with fever 100.9˚F and a 4-day history of nasal congestion, chills, and malaise (reported as non-serious adverse events). While in the ED, the subject was administered intravenous (IV) monoclonal antibody sotrovimab. He was subsequently hospitalized for evaluation and treatment. Chest X-ray was negative. PCR test was positive for COVID-19. Treatment with cefepime and remdesivir was initiated.

On 05 Jan 2022, the subject remained afebrile. Vital signs were within normal ranges. Labs included white blood cell (WBC) 1.9 x10^9/L, hemoglobin (Hgb) 8.5 g/dL, platelets 52 x 10^9/L, absolute neutrophil count (ANC) 1.0 x 10^9/L, alkaline phosphatase (ALP) 176 U/L. Blood culture revealed no growth for 2 days; PCR was negative. The same day, lung infection-COVID was considered resolved, and the subject was discharged from the hospital in stable condition.

Action taken with study drug navtemadlin and nilotinib due to this event was reported as drug interrupted.

The investigator assessed the event lung infection-COVID-SAE as severe (PT: COVID-19; Grade 3) in severity and not related to navtemadlin and nilotinib.

Kartos assessed the serious adverse event lung infection-COVID as not related to navtemadlin or nilotinib. Lung infection- COVID-19 is unexpected for navtemadlin.

Event: Dehydration -- SAE (Grade 3; SAE)

On 03 Apr 2022 (C5D7), the subject received his last dose of navtemadlin and nilotinib prior to dehydration (PT: Dehydration, Grade 3) onset.

On 04 Apr 2022, the subject presented to the clinic with shortness of breath on exertion and tachycardia. Results of the subject's chest computed tomography (CT) were negative for pulmonary embolism, echocardiogram was unremarkable with ejection fraction of 55 to 60%, troponin negative, and electrocardiogram was unchanged, with a negative infection work-up. The subject had a 7-day history of worsening nausea and vomiting since the cycle began not relieved

by ondansetron, granisetron, or lorazepam. He was diagnosed with dehydration due to vomiting and was treated with 1 L of normal saline, haloperidol (IV), and ondansetron (IV).

On 07 Apr 2022, the event dehydration was considered resolved. Dyspnea, tachycardia, nausea, and vomiting were also considered resolved, and the subject was discharged from the hospital.

Action taken with study drug navtemadlin was reported as dose not changed; action taken with study drug nilotinib was reported as drug interrupted.

The investigator assessed the event of dehydration as Grade 3 in severity and related to navtemadlin and not related to nilotinib.

Kartos assessed the SAE of dehydration as likely related to navtemadlin given the temporal relationship with no other source identified and not related to nilotinib. Dehydration is expected per the Investigator Brochure for navtemadlin.

Subject No.:	KRT-232-117-4012-001
Treatment:	KRT-232 240 mg once daily (QD) on Days 1-7 with 21 days off 28-day cycle + TKI (Dasatinib)
Demographics:	49 years, Male
Events:	Mitral valve insufficiency, pulmonary arterial hypertension
CIOMS Mfr. Control Number:	2023KARFR0127

This 49-year-old male subject was diagnosed with chronic myelogenous leukemia (CML) on 16 Oct 2018.

Subject 4012-001 signed the informed consent to enroll in Study KRT-232-117 and began study treatment with both drugs on 23 Jun 2022 (Cycle 1 Day 1). He received treatment with navtemadlin 240mg once daily (QD) on Days 1to 7 of a 28-day cycle + TKI (dasatinib). The subject received a total of 10 cycles of navtemadlin treatment, with the last dose taken on 08 Mar 2023.

Prior anti-cancer therapy included:

Therapy	**Start Date**	**Stop Date**
Imatinib (Glivec)	UN Nov 2018	UN Jun 2019
Dasatinib (Sprycel)	16 Jul 2019	UN Dec 2019
Ponatinib	UN Dec 2019	UN Dec 2019
Ponatinib	UN Jan 2020	UN UNK 2020
Ponatinib	UN Feb 2020	UN Jul 2020
Asciminib	21 Jul 2020	25 Sep 2020
Asciminib	UN Sep 2020	UN Dec 2020
Asciminib	UN Dec 2020	UN Feb 2021
Asciminib	24 Feb 2021	UN May 2022

At screening, the subject's medical history included:

Condition	**Onset Date**	**End Date (or Ongoing)**
Hepatic Steatosis	un UNK unkn	Ongoing
Streptococcal Infection In Childhood	UN UNK UNKN	un UNK unkn
Mitral Stenosis	03 Dec 2018	Ongoing
Facial Palsy	30 Sep 2021	Ongoing
Lithiasis Cholecystitis	01 Oct 2021	27 Jan 2022
Cholecystectomy	27 Jan 2022	27 Jan 2022

Concomitant medications taken by the subject included:

Medication Name	Start Date (Study Day)	End Date or Ongoing (Study Day)	Indication	Reason Given
Furosemide	12 Sep 2022 (82)	30 Nov 2022 (161)	Medical History	Mitral stenosis
Loperamide	23 Jun 2022 (1)	19 Oct 2022 (119)	Antidiarrheal	Prophylaxis
Ondansetron	23 Jun 2022 (1)	02 Mar 2023 (253)	Prophylaxis	Nausea / vomiting

Event: Pulmonary arterial hypertension (Grade 2; SAE); Mitral valve insufficiency (Grade 2; SAE)

On 08 Feb 2023 (C9D7) and on 23 Feb 2023 (C9D22), the subject received his most recent doses of navtemadlin and dasatinib, respectively, prior to the onset of the serious adverse events.

On 21 Feb 2023, (C9D20) the subject had a echocardiographic check-up which revealed an increase in pulmonary arterial pressure. He was otherwise asymptomatic.

On 23 Feb 2023 (C9D22), the subject was hospitalized for right heart catheterization (pulmonary arterial hypertension, Grade 2), to assess the type (pre versus post capillary) and imputability of dasatinib versus cardiopathy (valvular and hypertrophic). The subject had a history of rheumatic mitral disease associating tight mitral stenosis and moderate-significant mitral regurgitation not accessible for percutaneous commissurotomy. Subject's heart rate: 84 bpm, blood pressure: 167/ 80-115 mmHg, P-cap (a/v mean): 47/ 34-34 mmHg, abdominal perfusion pressure: 70/ 38-49 mmHg, cardiac output: (thermodilution): 7.47 L/min (140% of the theoretical cardiac output), systemic vascular resistance: 13.9 IU, pulmonary vascular resistance: 2.0 IU Wood, Cardiac index: 4.0 L/min/m^2. In addition, the subject underwent drainage of left pleura, with 1.5L of serohematic fluid removed. The post drain X-ray did not reveal any pneumothorax.

On 24 Feb 2023 (C9D23), the event right heart catheterization was resolved, and subject was discharged with a final diagnosis of post-capillary pulmonary hypertension (pulmonary arterial hypertension, Grade 2) related to the rheumatic mitral disease and genetic hypertrophic cardiomyopathy.

On 28 Feb 2023, (C9 D27) labs included WBC 13.21 x 10^9/L, Hgb 13.9 g/dL, platelets 247 x 10^9/L, and ANC 5.75 x 10^9/L.

On 08 Mar 2023 (C10D7), the subject received the most recent and last dose of navtemadlin before report of mitral valve incompetence onset.

On 19 Mar 2023, (C10D18) the subject was hospitalized for preoperative assessment of rheumatic mitral insufficiency (PT: mitral valve incompetence, Grade 2). Subject was afebrile, hemodynamically stable, eupneic in ambulant air, with no signs of overload and no signs of peripheral hypoperfusion. Subject's ECG on admission showed sinus rhythm, physiological axis, no atrioventricular block, narrow QRS, no repolarization disorder. Subject's lab results showed WBC: 11 G/L, CRP: 27 mg/L, D-dimer: 1.4. The next day, pulmonary function test revealed slight decrease in mobilizable volumes.

On 21 Mar 2023, the subject had a Doppler ultrasound of the supra-aortic trunk, which showed no abnormality. Subject had arterial examination of the neck, which showed no hemodynamically significant lesion in carotid arteries, no evidence of vertebrobasilar artery steal or pre-steal

syndrome, no hemodynamically significant stenosis in subclavian arteries. Arterial doppler ultrasound examination of the lower limbs showed non-aneurysmal abdominal aorta, no sign of significant stenosis in resting flow, triphasic signal in external iliac.

On 22 Mar 2023, (Study Day 273) the event preoperative assessment of rheumatic mitral insufficiency was reported as resolved and subject was discharged. He was assessed to have post-capillary pulmonary hypertension secondary to rheumatic mitral disease. On 30 Mar 2023, subject received the last dose of dasatinib prior to permanent discontinuation.

On 26 Jun 2023, mitral valve replacement surgery occurred.

Action taken with study drug navtemadlin and dasatinib due to the events pulmonary arterial hypertension (Grade 2) and mitral valve incompetence (Grade 2), was reported as dose not changed. Both events were reported to have recovered/resolved.

The investigator reported that the events of pulmonary arterial hypertension (Grade 2) and mitral valve incompetence (Grade 2), seriousness criteria (hospitalization), were considered not related to study treatment navtemadlin and dasatinib.

Kartos assessed the serious adverse events of pulmonary arterial hypertension (Grade 2) and mitral valve insufficiency (Grade 2) as not related to navtemadlin and dasatinib. Both events were unexpected per IBs for navtemadlin and for dasatinib.

Subject No.:	KRT-232-117-4022-002
Treatment:	Navtemadlin 240 mg once daily (QD) on Days 1 to 7 of a 28-day cycle + TKI (Dasatinib)
Demographics:	64 years, female
Event:	Vomiting
CIOMS Mfr. Control Number:	2022KARFR0054

This 64-year-old female subject was diagnosed with relapsed/refractory Ph+ chronic myeloid leukemia (CML) on 27 Sep 2020.

Subject 4022-002 signed the informed consent to enroll in Study KRT-232-117. On 27 Apr 2022, the subject received her initial dose of dasatinib 100 mg daily (QD). She began study treatment on 15 Jun 2022 (Cycle 1 Day 1). She received treatment with navtemadlin 240 mg once daily (QD) on Days 1 to 7 of a 28-day cycle + TKI (dasatinib). The subject received a total of 5 cycles of navtemadlin treatment, with the last dose taken on 05 Oct 2022.

Prior anti-cancer therapy included:

Therapy	**Start Date**	**Stop Date**
Dasatinib	UNKNOWN	04 Mar 2013 (-3390)
Imatinib	UN Sep 2000	28 Nov 2001 (-7504)
Imatinib	29 Nov 2001	13 Dec 2002 (-7124)
Imatinib	14 Dec 2002	13 Apr 2003 (-7003)
Imatinib	14 Apr 2003	17 Dec 2003 (-6755)
Imatinib	18 Dec 2003	10 Jun 2005 (-6214)
Peginterferon alfa-2a recombinant	24 Mar 2005	09 Jun 2005
Imatinib, Peginterféron alfa-2a recombinant	23 Jun 2005 (-6201)	20 Apr 2006
Nilotinib	07 Jun 2006	05 Oct 2006 (-5732)
Nilotinib	UN Nov 2006	17 Jan 2007 (-5628)
Dasatinib	12 Feb 2007	
Ponatinib	06 Mar 2013 (-3388)	27 Nov 2013
Dasatinib	02 Dec 2013	18 Mar 2020 (-819)
Hydroxyurea	02 Apr 2020	19 Jul 2020 (-696)
K0706	21 Jul 2020	26 Apr 2022 (-50)
Dasatinib	27 Apr 2022	

At screening, the subject's medical history included:

Condition	**Onset Date**	**End Date (or Ongoing)**
Arterial hypertension	UN 2019	Ongoing
Diabetes	UN Mar 2020	UN Jul 2020
Pericarditis	02 Mar 2020	18 Mar 2020

Condition	Onset Date	End Date (or Ongoing)
Pleural effusion	02 Mar 2020	18 Mar 2020
Hypocalcemia	31 May 2022	Ongoing
Hyperphosphoremia	31 May 2022	Ongoing
QTc prolongation grade 1	31 May 2022	13 Jun 2022
Hypokalemia	31 May 2022	15 Jun 2022
QTc prolongation grade 2	14 Jun 2022	14 Jun 2022
QTc prolongation	15 Jun 2022	Ongoing

Concomitant medications taken by the subject included:

Medication Name	Start Date (Study Day)	End Date or Ongoing (Study Day)	Indication	Reason Given
Allopurinol	14 Nov 2022 (153)	Ongoing	Cell lysis prophylaxis	Prophylaxis
Allopurinol	15 Jun 2022 (1)	22 Jul 2022 (38)	Cellular lysis	Prophylaxis
Alpha-Amylase Swine Pancreas	04 Oct 2022 (112)	11 Oct 2022 (119)	COVID-19 related pharyngeal pain	Adverse Event
Amphotericin B	23 Jul 2022 (39)	26 Jul 2022 (42)	Oral mucositis	Adverse Event
Calcium	31 May 2022 (-14)	Ongoing	Hypocalcemia	Adverse Event
Calcium Gluconate	23 Jul 2022 (39)	25 Jul 2022 (41)	Hypocalcemia	Adverse Event
Cefixime	25 Jul 2022 (41)	01 Aug 2022 (48)	Urinary infection	Adverse Event
Darbepoetin Alfa	12 Jul 2022 (28)	Ongoing	Anemia	Adverse Event
Diosmectite	23 Jul 2022 (39)	03 Nov 2022 (142)	Diarrhea	Adverse Event
Glycerol;Paraffin, Liquid;White Soft Paraffin	04 Oct 2022 (112)	03 Nov 2022 (142)	Macular Rash	Adverse Event
Hydrochlorothiazide	18 Mar 2020 (-818)	14 Jun 2022 (0)	Arterial hypertension	Medical History
Loperamide	23 Jun 2022 (9)	03 Nov 2022 (142)	Diarrhea	Adverse Event
Magnesium	03 Nov 2022 (142)	Ongoing	Hypomagnesemia	Adverse Event
Magnesium	31 May 2022 (-14)	14 Jun 2022 (-1)	Hypocalcemia	Medical History
Magnesium	12 Jul 2022 (28)	21 Jul 2022 (37)	Hypomagnesemia	Adverse Event
Ondansetron	22 Jul 2022 (38)	22 Jul 2022 (38)	Vomiting	Adverse Event
Ondansetron	09 Aug 2022 (56)	04 Oct 2022 (112)	Vomiting	Prophylaxis
Potassium Chloride	31 May 2022 (-14)	Ongoing	Hypkalemia	Adverse Event
Racecadotril	22 Jul 2022 (38)	25 Jul 2022 (41)	Diarrhea	Adverse Event
Sodium Bicarbonate	23 Jul 2022 (39)	26 Jul 2022 (42)	Oral mucositis	Adverse Event
Sodium Chloride	21 Jul 2022 (37)	25 Jul 2022 (41)	Hydratation	Adverse Event
Sodium Polystyrene Sulfonate	23 Jul 2022 (39)	23 Jul 2022 (39)	Hypokalemia	Adverse Event
Spironolactone	02 Aug 2022 (49)	4 Oct 2022 (112)	Lower limb edema	Adverse Event

Event: Vomiting (Grade 3; SAE)

On 13 Jul 2022 (C2D2), the subject had onset of vomiting (Grade 2; non-serious) and nausea (Grade 2; non-serious).

On 18 Jul 2022 (C2D7), the subject received her last dose of navtemadlin 240 mg prior to hospitalization of the subject due to the event of vomiting.

On 21 Jul 2022 (C2D10), the subject was hospitalized for treatment and monitoring of vomiting (Grade 3) with dehydration due to significant diarrhea (Grade 2) associated with vomiting (Grade 2) for several days. Vomiting immediately subsided after first treatment with intravenous (IV) ondansetron and hydration (IV). During her hospital course, she remained afebrile and was treated with 5HT3-antagonist, sodium chloride (IV) and potassium supplementation due to hypokalemia. Diarrhea was treated with racecadrotil and diosmectite with resolution. Stool cultures were negative, including Clostridium difficile toxin. She was diagnosed with an intercurrent lower urinary tract infection, positive for Escherichia coli with 10^4 leukocyte elements/mL and treated with cefixime. The subject's general condition improved significantly.

On 22 Jul 2022 (C2D11), the event of vomiting was reported as resolved. On 25 Jul 2022 (C2D14), the dose of dasatinib was reduced to 50 mg QD due to diarrhea, and the dose of navtemadlin was reduced to 180 mg for Cycle 3 due to adverse event of vomiting.

On 26 Jul 2022, (C2D15), the subject was afebrile with normal vitals and oxygen saturation. She was treated for oral thrush that resolved with oral amphotericin B suspension. Labs included a white blood cell (WBC) 3,900/mm^3, 52.6% neutrophils, hemoglobin (Hgb) 88 g/L on erythropoietin, platelets 197,000/mm^3, potassium 2.8 mmol/L, calcium 1.78 mmol/L (corrected) despite calcium supplementation, albumin decreasing to 21 g/L, magnessium 0.5 mmol/L (low), creatinine 761 µmol/L (nL) and C-reactive protein (CRP) 30.1 mg/L. On the same day, the subject was discharged from the hospital on calcium carbonate, potassium chloride, diosmectite, loperamide, and cefixime.

Action taken with study drug navtemadlin was reported as dose reduced (to 180 mg for Cycle 3). Action taken with dasatinib was reported as dose not changed due to vomiting.

The investigator assessed the event of vomiting as severe (Grade 3) in intensity and related to navtemadlin and not related to dasatinib.

Kartos assessed the SAE of vomiting as likely related to navtemadlin and dasatinib. Vomiting is expected for navtemadlin and dasatinib per the Investigator Brochures.

15. REFERENCES

Not applicable.

16. APPENDICES

16.1 Study Information

16.1.1. Protocol and Protocol Amendments

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

Not applicable.

16.1.12. Important Publications Referenced in the Report

Not applicable.

16.1.13. Efficacy Narratives

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

Not applicable.

16.4 Individual Subject Data Listings

Not applicable.