AMENDED CLINICAL TRIAL MASTER PROTOCOL 01

Protocol title:	**A Phase 1/Phase 2, randomized, open-label, multi cohort, multi center, study assessing the safety, tolerability and preliminary efficacy of SAR443579 a natural killer cell engager (NKCE) targeting CD123, administered with different agents in participants with CD123 expressing Hematological malignancies - Master protocol**
Protocol number:	**TCD17796 - Master**
Amendment number:	**01**
Compound number (INN/Trademark):	**SAR443579** **Not applicable**
Brief title:	**A study to investigate natural killer cell engager (SAR443579) with different agents in participants with hematological malignancies – Master protocol**
Acronym:	**Not applicable**
Study phase:	**Phase 1/Phase 2**
Sponsor name:	**Sanofi-Aventis Research & Development**
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Monitoring team's representative name and contact information	

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 01		09 April 2024, version 2 (electronic 2.0)
Amended Clinical Trial Protocol 01		19 March 2024, version 1 (electronic 1.0)
Original Protocol		05 February 2024, version 1 (electronic 1.0)

Amended protocol 01 (09 April 2024)

This amended protocol 01 (Amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment is to align with health authorities' recommendations combining SAR443579 with other drugs in participants with CD123 expressing hematological malignancies.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page, Protocol amendment summary of changes and headers throughout the document	The description of the protocol was updated to Amended Clinical Trial Protocol 01.	Administrative change.
Throughout the document	Reference to monotherapy has been removed: • By removing "without" in the wording "with ~~or without~~ different agents" ""with ~~or without~~ its combination partners"; "with ~~or without~~ additional investigational medicinal products (IMPs)"; "with ~~or without~~ approved standard of care (SOC)" • By rewording the following secondary objectives wording "and/or its respective combination with other drugs partners" to "SAR443579 in combination with other drugs" • By removing "or" in the following wording "and/or its combination"	To align with health authorities' (HA) recommendation to remove monotherapy from Master protocol and make precision on type of study population for hematological malignancies.

Section # and Name	Description of Change	Brief Rationale
	• "CD123 expressing" has been added where appropriate.	
Throughout document	Each time maintenance is cited a precision was added as "Maintenance/continued therapy"	As per HA recommendation to clarify and precise that patient who reach CRi/CRh are also allowed to continue treatment, so then the treatment plan will be considered continued therapy rather than maintenance for those patients.
Section 1.1 Synopsis	In Objectives and Endpoints table, the primary objectives have been modified to list only one primary objective: "To determine the RDE of SAR443579 in combination with other drugs in participants with CD123 expressing hematological malignancies."	To align with HA's recommendation to revise the primary objective as the master protocol document is not an interventional plan and should not include any treatment activities precision in objectives.
Section 1.1 Synopsis	In Objectives and Endpoints table: The following modifications have been made to the secondary objectives: "CD123 expressing" has been added.	To align with health authorities' (HA) recommendation to make precision on type of study population for hematological malignancies.
Section 1.1 Synopsis: Statistical considerations.	In "Analysis of primary endpoint": The following text has been replaced by "Please refer to sub-study for details": Dose escalation/Safety run-in: The primary endpoints is the incidence of dose limiting toxicity (DLTs). All DLT modeling will be performed on the DLT-evaluable population or those who experienced a DLT (dose escalation or safety run-in phase). Statistical descriptive analysis will be used to summarize the incidence of DLT by dose level and overall. Dose optimization (when applicable): Please refer to sub-study protocol for details. Dose expansion: Please refer to sub-study protocol for details.	To align with HA's recommendation to accommodate substudy-specific needs that may not be applicable to all settings.
Section 1.1 Synopsis; Brief summary and Study board. Section 9.2.2.4 Main analytical approach	After the modified toxicity probability interval 2 (mTPI-2) design the following text has been added "or other appropriate dose-finding designs"	Per HA's recommendation to accommodate substudy-specific needs. As the mTPI-2 may not be an appropriate dose escalation design for all treatments and all disease settings.
Section 1.2 Schema	Figure 1 – General graphical study design has been updated to remove monotherapy and include only SAR443579 in combination with other drugs.	To align with HA's recommendation to remove monotherapy from Master protocol

Section # and Name	Description of Change	Brief Rationale
Section 1.2 Schema	"Substudy X: Place holder for future sub-studies" title was removed, as it is not needed	For typo correction, following Health authorities (HA) notification
Section 4.1 Overall design and 6.1 Study intervention(s) administered	We have replaced the word "will" to "may": • In Section 4.1, in the sentences: "the dose finding part ~~will~~ follow the mTPI-2 design to identify a pRDE"; "Each substudy ~~will~~ include three parts"; "At least 3 to 6 DLT evaluable participants ~~will~~ be treated at each DL and safety data for these participants ~~will~~ be reviewed by a Study Board. Details"; "additional participants ~~will~~ be enrolled in the dose" • And in Section 6.1 in the sentence "Participants ~~will~~ may receive study treatment until disease progression"	Under HA's recommendation to accommodate substudy-specific needs that may not be applicable to all settings.
Section 5.1 Inclusion Criteria	The following inclusion criteria was add to "Type of participant and disease characteristics" subsection: "Participants with CD123-expressing hematological neoplasm per the 5th edition of the WHO Classification of Hematolymphoid Tumors."	To align with HA's recommendation in specifying the patient population.
Section 6.1.1 Investigational medicinal product(s)	Additional text for description of SAR443579 preparation, volume and storage condition has been added.	As per HA recommendation to complete study intervention instructions
Section 6.1.2 Auxilliary medicinal product(s)	Cytokine release syndrome (CRS) has been removed from the sentence: " [...] to prevent or reduce the acute effect of infusion-related reactions (IRR) ~~or cytokine release syndrome (CRS~~	Correction under HA notification as the proposed premedications do not affect the risk of CRS.
Section 6.6.1 General rules	Section text has been removed from Master protocol to be detailed in sub-study. And the sentence "Please refer to sub-study protocol for general rules on dose modifications." has been added	Per HA's recommendation that dose modifications will need to be comprehensive for all study drugs in a combination. Therefore, specific instructions on dose modifications in the Master Protocol document should be deleted and full instructions should be included in each substudies instead.
Section 6.6.2 Cycle delay and dose omission	Section text has been removed from Master protocol to be detailed in sub-study. And the sentence "Please refer to sub-study protocol for specific details." has been added	Per HA's recommendation to keep details at sub-study level than in the Master protocol.
Section 6.9.1 Acceptable concomitant medication	Section text has been removed from Master protocol to be detailed in sub-study. And the sentence "See individual sub-studies for details." has been added	Per HA's recommendation to keep details at sub-study level than in the Master protocol.
Section 8.4.8 Adverse events of special interest	Paragraph text about elevated AST or ALT lab value has been removed. A note on the instructions for the recommended management of IRR, CSR, and ICANS has been added.	For consistency with inclusion criteria (participant may be included with ALT/AST Grade ≥2)

Section # and Name	Description of Change	Brief Rationale
Section 9 Statistical analyses	Reference to sub-study statistical analysis plan for additional statistical considerations has been added. And it has been added that "No pooled data analysis across sub-studies is planned in the master protocol."	Per HA recommendation for better clarification and reflecting the objective revision.
Section 9.2.2.1 Dose escalation/safety run-in	The following text has been removed and replaced by "Please refer to individual sub-studies for detailed specification of primary endpoints".	Per HA recommendation to keep details at sub-study level than in the Master protocol.
Section 10.4.2 Contraception guidance	Table for contraceptive guidance has been revised and acceptable methods for contraception removed. The footnotes have been updated accordingly.	To align with study requirements where only Highly effective contraception are allowed
Section 10.6 Appendix 6: other safety: suggested actions and follow-up assessment	The appendix sections on CRS and ICANS have been moved to be integrated as sub section in the main protocol Section 8.4.8 Adverse events of special interest. Therefore, the following sub section have been created: Section 8.4.8.1 CRS and Section 8.4.8.2 ICANS.	Under HA recommendation to keep safety information in main protocol section as assessing safety is critical for this study.
Section 10.6: Appendix 6: other safety: suggested actions and follow-up assessment	Wording Not Applicable has been added as information corresponding to this section has been moved in main protocol Section 8.4.8 (cf above row)	Administrative change

In addition, minor typographical error/editorial corrections were implemented throughout the protocol.

TABLE OF CONTENTS

AMENDED CLINICAL TRIAL MASTER PROTOCOL 01 1

PROTOCOL AMENDMENT SUMMARY OF CHANGES 2

TABLE OF CONTENTS 6

LIST OF TABLES 11

LIST OF FIGURES 11

LIST OF ABBREVIATIONS 12

1 PROTOCOL SUMMARY 13

1.1 SYNOPSIS 13

1.2 SCHEMA 19

1.3 SCHEDULE OF ACTIVITIES (SOA) 20

2 INTRODUCTION 21

2.1 STUDY RATIONALE 21

2.2 BACKGROUND 22

2.2.1 SAR443579 22

2.2.2 Benefit assessment 23

2.3 BENEFIT/RISK ASSESSMENT 23

2.3.1 Risk assessment 23

2.3.2 Overall benefit/risk conclusion 25

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS 26

3.1 APPROPRIATENESS OF MEASUREMENTS 26

4 STUDY DESIGN 27

4.1 OVERALL DESIGN 27

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN 27

4.3 JUSTIFICATION FOR DOSE 28

4.4 END-OF-STUDY DEFINITION 28

5 STUDY POPULATION 29

5.1 INCLUSION CRITERIA 29

5.2 EXCLUSION CRITERIA 30
5.3 LIFESTYLE CONSIDERATIONS....32
5.4 SCREEN FAILURES....32
5.5 CRITERIA FOR TEMPORARILY DELAYING SCREENING, ENROLLMENT AND ADMINISTRATION OF STUDY INTERVENTION 32
6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY 33
6.1 STUDY INTERVENTION(S) ADMINISTERED 33
6.1.1 Investigational medicinal product(s)....33
6.1.2 Auxiliary medicinal product(s) 34
6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY 34
6.3 ASSIGNMENT TO STUDY INTERVENTION 35
6.4 BLINDING 36
6.5 STUDY INTERVENTION COMPLIANCE 36
6.6 DOSE MODIFICATION....36
6.6.1 General rules....36
6.6.2 Cycle delay and dose omission 36
6.6.3 Guidelines for the management of treatment-related adverse events....37
6.6.4 Guidelines for the management of specific adverse events 37
6.6.5 Retreatment criteria....37
6.7 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY....37
6.8 TREATMENT OF OVERDOSE....37
6.9 PRIOR AND CONCOMITANT THERAPY 38
6.9.1 Acceptable concomitant medication 38
6.9.2 Prohibited concomitant medication 38
6.9.3 Concomitant therapy requiring careful monitoring 38
6.9.4 Rescue medicine....38
7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 39
7.1 DISCONTINUATION OF STUDY INTERVENTION 39
7.1.1 Permanent discontinuation 39
7.1.2 Liver chemistry stopping criteria 40
7.1.3 QTc stopping criteria 40

7.1.4 Temporary discontinuation 40
7.1.5 Rechallenge 41
7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY 41
7.3 LOST TO FOLLOW UP 42
8 STUDY ASSESSMENTS AND PROCEDURES 43
8.1 ADMINISTRATIVE PROCEDURES 43
8.2 EFFICACY ASSESSMENTS 43
8.3 SAFETY ASSESSMENTS 43
8.3.1 Physical examinations 44
8.3.2 Vital signs 44
8.3.3 Electrocardiograms and LVEF 44
8.3.4 Clinical safety laboratory tests 44
8.3.5 Pregnancy testing 45
8.3.6 Dose limiting toxicities 45
8.4 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING 46
8.4.1 Time period and frequency for collecting AE and SAE information 46
8.4.2 Method of detecting AEs and SAEs 46
8.4.3 Follow-up of AEs and SAEs 46
8.4.4 Regulatory reporting requirements for SAEs 47
8.4.5 Pregnancy 47
8.4.6 Cardiovascular and death events 48
8.4.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs 48
8.4.8 Adverse events of special interest 48
8.4.8.1 Cytokine release syndrome (CRS) 49
8.4.8.2 Immune effector cell-associated neurotoxicity syndrome (ICANS) 49
8.4.9 Medication errors or misuses of medicinal product 50
8.4.10 Guidelines for reporting product complaints 50
8.5 PHARMACOKINETICS 51
8.6 PHARMACODYNAMICS 51
8.7 GENETICS 51
8.8 BIOMARKERS 51
8.9 IMMUNOGENICITY ASSESSMENTS 52

8.10 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS 52
8.11 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH 53
9 STATISTICAL CONSIDERATIONS 54
9.1 POPULATIONS FOR ANALYSES 54
9.2 STATISTICAL ANALYSES 54
9.2.1 General considerations 54
9.2.2 Primary endpoint(s) analyses 55
9.2.2.1 Dose escalation/safety run-in 55
9.2.2.2 Dose optimization (when applicable) 55
9.2.2.3 Dose expansion 55
9.2.2.4 Main analytical approach 55
9.2.2.5 Sensitivity analysis 55
9.2.3 Secondary endpoint(s) analyses 55
9.2.3.1 Other secondary endpoints 55
9.2.4 Tertiary endpoints 56
9.2.5 Safety analyses 56
9.2.5.1 Adverse events 56
9.2.5.2 Clinical laboratory evaluations 57
9.2.6 Other analysis 58
9.3 INTERIM ANALYSES 58
9.3.1 Dose optimization (when applicable) and expansion stopping rule based on safety 58
9.3.2 Dose expansion stopping rule based on efficacy 58
9.4 SAMPLE SIZE DETERMINATION 59
10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 60
10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS 60
10.1.1 Regulatory and ethical considerations 60
10.1.2 Financial disclosure 62
10.1.3 Informed consent process 62
10.1.4 Data protection 63
10.1.5 Committees structure 65
10.1.6 Dissemination of clinical study data and results 65
10.1.7 Data quality assurance 66
10.1.8 Source documents 67
10.1.9 Study and site start and closure 67
10.1.10 Publication policy 68

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS 69

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING....70

10.3.1 Definition of AE 70

10.3.2 Definition of SAE 71

10.3.3 Recording and follow-up of AE/SAE and/or AESI....73

10.3.4 Reporting of SAEs....74

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE 75

10.4.1 Definitions 75

10.4.2 Contraception guidance 76

10.5 APPENDIX 5: GENETICS 78

10.6 APPENDIX 6: OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENT....78

10.7 APPENDIX 7: MEDICAL DEVICES AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES....78

10.8 APPENDIX 8: COUNTRY-SPECIFIC/REGION REQUIREMENTS....79

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY 79

10.10 APPENDIX 10: COLLECTION, STORAGE AND FUTURE USE OF DATA AND HUMAN BIOLOGICAL SAMPLES 79

10.10.1 Compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h) 79

10.10.2 Compliance with Member State applicable rules for the collection, storage and future use of (personal) data (Article 7 (1 d) of EU Regulation 536/2014) 79

10.11 APPENDIX 11: SAR443579 RISK....80

10.12 APPENDIX 12: LIST OF SENSITIVE CYP SUBSTRATED WITH NARROW THERAPEUTIC RANGE....82

10.13 APPENDIX 13: PROTOCOL AMENDMENT HISTORY 83

11 REFERENCES....84

LIST OF TABLES

Table 1 - Objectives and endpoints 26
Table 2 - Study intervention(s) administered 33
Table 3 - Auxiliary medicinal product administered 34
Table 4 - Populations for analyses 54
Table 5 - [redacted] 58
Table 6 - Protocol required laboratory tests 69
Table 7 - Contraception guidance 76
Table 8 - SAR443579 risk assessment 80

LIST OF FIGURES

Figure 1 - General graphical study design 19
Figure 2 - Schematic of SAR443579 22

LIST OF ABBREVIATIONS

ADA:	anti-drug antibody
ADCC:	antibody-dependent cellular cytotoxicity
AESI:	adverse event of special interest
AML:	acute myeloid leukemia
BPDCN:	blastic plasmacytoid dendritic neoplasm
BUN:	blood urea nitrogen
CRS:	cytokine release syndrome
DL:	dose level
DLT:	dose-limiting toxicity
FIH:	first in human
IAs:	interim analyses
IB:	investigator's brochure
ICAN:	immune effector cell associated neurotoxicity syndome
IL-3:	interleukin-3
IMPs:	investigational medicinal products
IRR:	infusion-related reaction
IV:	intravenous
MOA:	mechanism of action
NA:	not applicable
NHP:	nonhuman primate
NK:	natural killer
NKCE:	NK cell engager
NMPA:	National Medical Products Administration
NTR:	narrow therapeutic range
OR:	odds ratio
PDy:	pharmacodynamic
PK:	pharmacokinetic
PMM:	product management manual
PO:	oral
POC:	proof of concept
RDE:	recommended dose for expansion
SB:	study board
SC:	subcutaneous
SOC:	standard of care
SUSAR:	suspected unexpected serious adverse reaction
TCE:	T cell engagers
TLS:	tumor lysis syndrome

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A Phase 1/Phase 2, randomized, open-label, multi cohort, multi center, study assessing the safety, tolerability and preliminary efficacy of SAR443579 a natural killer cell engager (NKCE) targeting CD123, administered with different agents in participants with CD123 expressing Hematological malignancies - Master protocol

Brief title:

A study to investigate natural killer cell engager (SAR443579) with different agents in participants with hematological malignancies

Regulatory agency identifier number(s):

IND:	169765
NCT:	Not applicable
WHO:	Not applicable
EUDAMED:	Not applicable
EU trial number:	2023-509438-20
Other:	Not applicable

Rationale:

CD123, the alpha-subunit of the IL-3 receptor, is widely overexpressed in various hematological malignancies, including acute myeloid leukemia (AML), B-cell acute lymphoblastic leukemia, hairy cell leukemia, Hodgkin's lymphoma and particularly, blastic plasmacytoid dendritic neoplasm (BPDCN). CD123 has emerged in recent years as an attractive novel target of therapy as varying levels of evidence have shown that CD123-targeted therapy represents a promising therapeutic approach in several cancers.

SAR443579 is a bispecific IgG-like monoclonal antibody with a competent Fc domain. SAR443579 functions as an natural killer (NK) cell engager (NKCE) by binding NKp46 and CD16a on the surface of the NK cell and CD123 on the malignant cell. Co-engagement of NK cell and malignant cell by SAR443579 induces NK cell activation and results in killing of CD123 expressing malignant cells via both immune synapse formation and antibody-dependent cellular cytotoxicity (ADCC).

SAR443579, as an anti-CD123 NK cell engager (NKCE), is being developed as a potential safe and highly efficacious therapy against CD123-expressing hematologic malignancies, including AML.

In order to improve outcomes for pariticipants with hematological malignancies, this Phase 1/Phase 2 study will assess the potential of SAR443579 with different agents in adolescent and/or adult participants with different CD123-expressing hematological malignancies.

This study is developed as a master protocol where a series of exploratory sub-studies with approved standard of care (SOC) product(s) and investigational agent(s) will be explored. Subcutaneous administration may be explored for different combinations. The proposed combination partners rely on functional NKCE for their activity. Therefore, combining SAR443579 with different partners with potential synergistic mechanism of action (MOA) is expected to lead to deeper and/or more durable clinical responses.

Common protocol elements are contained in this document ("Master Protocol") and cohort-specific protocol elements are contained in separate sub-study protocols. This design has the flexibility to open new treatment cohorts as new treatments become available and close existing treatment cohorts that demonstrate minimal clinical activity or unacceptable toxicity, or due to internal strategic reasons.

Objectives and endpoints:

Control arm and several experimental arms will be evaluated in the trial. Details on arms are provided in substudy protocols.

The common objectives and endpoints are summarized below.

Objectives	Endpoints
Primary	
• To determine the RDE of SAR443579 in combination with other drugs in participants with CD123 expressing hematological malignancies.	• Overall safety including AEs, SAEs, AESIs, laboratory abnormalities and preliminary anti-tumor activity
Secondary	
• To assess overall safety and tolerability profile of SAR443579 in combination with other drugs in participants with CD123 expressing hematological malignancies (all parts).	• Incidence of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V 5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).
• To characterize the PK profile of SAR443579 in combination with other drugs if relevant (all parts).	• PK parameters of SAR443579 (C_{trough}).
• To evaluate the potential immunogenicity of SAR443579 in combination with other drugs if relevant (all parts).	• Incidence of anti-drug anti body (ADA) against SAR443579.
• To assess other indicators of antitumor activity of SAR443579 in combination with other drugs if relevant.	• Please refer to individual sub-study for details.

For country specific requirement, please see Section 10.8 of full protocol for details.

Overall design synopsis:

This protocol is structured as a master protocol (containing common protocol elements). SAR443579 with additional investigational medicinal products (IMPs) will be evaluated in separate experimental arms (substudies) and a control arm may be added in substudies. The study is designed with the flexibility to open new treatment arms as new treatments become available. Details on arms are provided in substudy protocols.

Brief summary:

This is a parallel, Phase 1/Phase 2, randomized, open-label, multi-cohort, multi-center study assessing the safety, tolerability and preliminary efficacy of SAR443579 with different agents for treatment in adolescent and/or adult participants with CD123 expressing hematological malignancies.

A graphical presentation of the study schema is shown in Figure 1.

Individual sub-studies will explore SAR443579 with combination partners, either approved or investigational, whose MOA is hypothesized to favor combined use with SAR443579 or for which nonclinical studies supports the putative safety and proof of concept (POC).

For the combination partners which are approved and marketed, the dose and schedule per the approved product information will be followed, Alternate schedules may be used as per local practices and evaluated when clinically indicated. For combinations proposed with investigational products, clinical and nonclinical data from the development program has been used to support the dose and schedule of each product (see Section 2.1).

Experimental substudies will be tested through 3 parts:

- Part 1: dose finding (such as dose escalation/safety run-in).
- Part 2: dose optimization (when applicable).
- Part 3: dose expansion.

In each sub-study, a dose escalation following the modified toxicity probability interval 2 (mTPI-2) design or other appropriate dose-finding designs will identify preliminary recommended dose for expansion (pRDE) of SAR443579 and its respective combination partner. At least 3-6 dose-limiting toxicity (DLT) evaluable participants will be treated at each dose level (DL) in the dose escalation or safety run-in, and safety data for these participants will be reviewed by the Study Board. The DLT-evaluable population and DLT observation period are defined in the individual sub-study.

Following the determination of the preliminary RDE, additional participants will be enrolled in the dose expansion part, or if dose optimization needs to be further evaluated, additional participants will be enrolled in the “dose optimization/expansion” part. Dose optimization and dose expansion part could involve randomization depending on specific sub-study design. Participants who are enrolled in the dose escalation/safety run-in and treated at the RDE will be included in the total number of participants for that specific cohort, if the inclusion/exclusion criteria are identical. Please refer to the individual sub-study for the specific design option.

[redacted].
Timing to initiate and dose schedule of such backfilling will be decided by the Sponsor based on totality of tolerability (both DLT and treatment emergent adverse event [TEAE] which occurred during and after completion of DLT observation period), pharmacodynamic (PDy), pharmacokinetic (PK), and preliminary anti-tumor activity as available. This backfilling may increase the total number of participants enrolled.

Overall safety monitoring will be performed throughout the study.

Following the determination of the RDE, additional participants will be enrolled in the dose expansion part.

Number of participants:

Please refer to the individual sub-study for the numbers of participants to be enrolled and treated.

Study arms and duration:

Study will consist of a screening period, treatment period, and follow-up period. Participants will receive study treatment until documented disease progression, unacceptable adverse events, participant's decision to stop study treatment, or completion of the maximum cycles allowed in the sub-studies, or the participant meets other criteria for discontinuation per study protocol (whichever occurs first). For specific details refer to individual sub-study protocols.

Study intervention(s)

Investigational medicinal product(s)

SAR443579

- **Formulation:** SAR443579 drug product is presented as a lyophilized powder for solution for infusion in vials.
- **Route(s) of administration:** Specific instructions on the preparation and administration of SAR443579 is provided in the Product Management Manual.
- **Dose regimen:** Please refer to the individual sub-study for dose level, timing and frequency of administration.

For detailed information on IMPs that will be combined with SAR443579, please refer to the individual sub-study protocol.

AxMP

To prevent or reduce the acute effect of infusion-related reaction (IRR) or cytokine release syndrome (CRS), participants should routinely receive premedication 30-60 minutes prior to SAR443579 administration (no longer than 60 minutes) for the first cycle, premedication may be optional during the subsequent cycles. Please refer to individual sub-study protocol for more details.

- N02BE01 (acetaminophen [paracetamol]) 650-1000 mg IV or oral route (or equivalent) is preferred.
- D04AA32 (diphenhydramine) 25-50 mg IV or PO (or equivalent, eg, R06AE07 [cetirizine], R06AD02 [promethazine], R06AB02 [dexchlorpheniramine], according to local approval and availability).

Additional premedication may be considered at the Investigator's discretion.

Devices: Not applicable.

Posttrial access to study medication: Not applicable.

Duration of study intervention

Please refer to protocol sub-studies for details.

Statistical considerations:

The statistical considerations for common endpoints are summarized below.

- **Analysis of primary endpoint:**
  - Please refer to sub-study for details.
- **Analysis of secondary endpoints:**
  - All parts: Number and percentage of participants experiencing treatment-emergent adverse events (TEAEs) by primary System Organ Class (SorC) and preferred Term (PT) will be summarized by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0 or American Society for Transplantation and Cellular Therapy (ASTCT) grade (all grades) for the exposed population. Similar summaries will be prepared for treatment related TEAEs, TEAEs leading to permanent partial intervention discontinuation (any of the IMP components), TEAEs leading to permanent full intervention discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, adverse events of special interests (AESIs), and AEs/SAEs occurring during the post-treatment period. In addition, the number (%) of participants with and Grade 5 AE (TEAE and post-treatment), participants who died by study period (treatment-emergent period, post-treatment period) and reasons for death will be summarized. Immune Cell-Associated Neurotoxicity Syndrome (ICANS) and cytokine release syndrome (CRS) events will be graded using ASTCT Consensus Grading and will be summarized separately. Hematology and clinical chemistry results will be graded according to the NCI-CTCAE v5.0, when applicable. Number and percentage of participants with laboratory abnormalities (all grades and by grade) using the worst grade during the on-treatment period will be provided for the exposed population.
  - All parts: Concentration of SAR443579 and its respective combination partners, incidence of antidrug anti body (ADA) will be summarized with descriptive statistics by each cohort.

Data Monitoring/Other committee: No

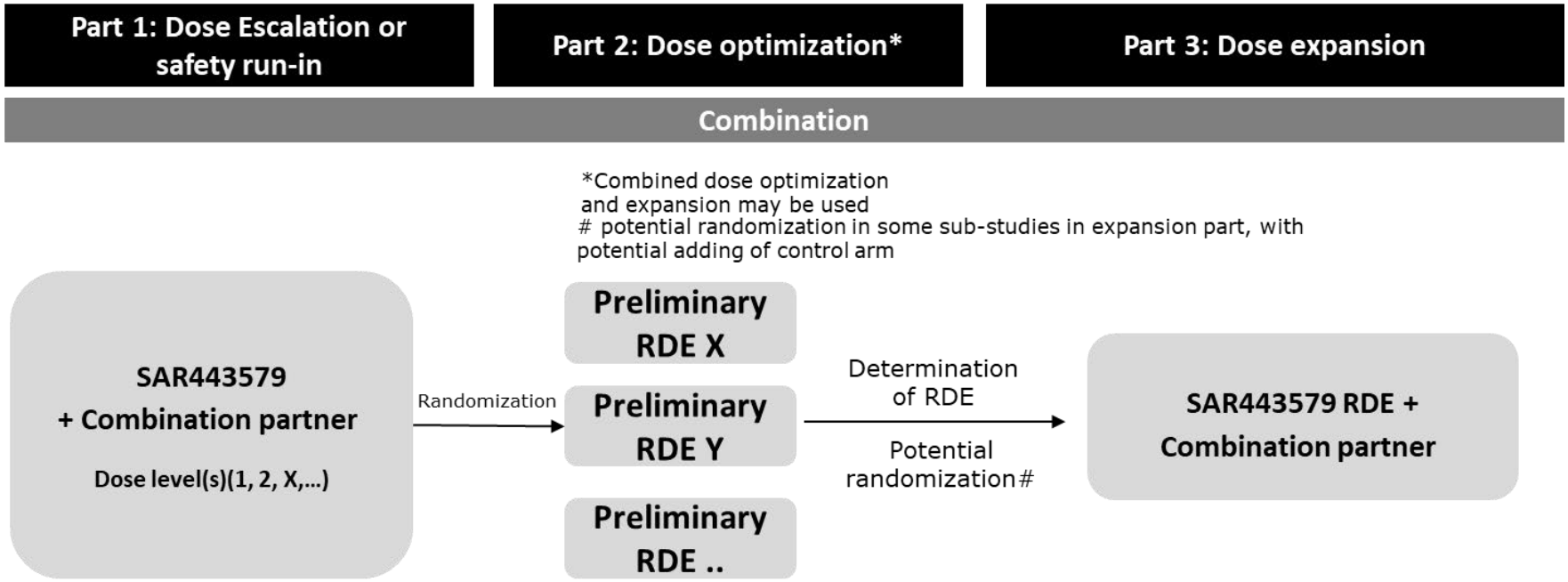
Study Board:

A Study Board (SB) will be set up for each sub-study, and will include the Investigators (or designee), Sponsor clinical team members and, when appropriate, ad hoc experts (eg, biostatisticians). The SB will meet first when the first few sites are open and can start screening of participants in the dose escalation/safety run-in part and will review clinical data on a regular basis in order to make decisions whether to escalate to the next dose level or proceed to the dose expansion on the basis of their knowledge of the safety data, tolerability, along with the mTPI-2 or other appropriate dose-finding designs' recommendations. The SB will decide on whether to escalate, de-escalate, stay at the current DL, or to add alternative dose levels. Decision regarding final dose selection will be documented in the meeting minutes.

Evaluation of an intermediate IMP dose level may be considered necessary by the Study Board upon review of available data.

1.2 SCHEMA

Figure 1 - General graphical study design



Abbreviations: RDE, recommended dose for expansion

1.3 SCHEDULE OF ACTIVITIES (SOA)

Please refer to each sub-studies for details.

2 INTRODUCTION

Globally, incident cases of hematologic malignancies have been increasing since 1990, reaching over 1.3 million in 2019, but the age-standardized death rate (ASDR) for all types of hematologic malignancies has been declining. The ASDR for leukemia, multiple myeloma, non-Hodgkin lymphoma, and Hodgkin lymphoma were 4.26, 1.42, 3.19, and 0.34 per 100 000 population in 2019, respectively, with Hodgkin lymphoma showing the most significant decline. However, the trend varies by gender, age, region, and the country's economic situation (1).

Significant advances in the treatment of hematological malignancies, including the development of new targeted therapies, immunotherapies, and more effective chemotherapy regimens have been made. However, hematologic malignancies remain a major public health concern globally, and while ASDR is declining globally, they are still on the rise in many countries (1).

2.1 STUDY RATIONALE

CD123 has emerged in recent years as an attractive novel target of therapy. CD123, the alpha-subunit of the interleukin-3 (IL-3) receptor, is widely overexpressed in various hematological malignancies, including acute myeloid leukemia (AML), HR-MDS, B-cell acute lymphoblastic leukemia, hairy cell leukemia, Hodgkin lymphoma and particularly, blastic plasmacytoid dendritic neoplasm (BPDCN). CD123 is expressed at both the level of leukemic stem cells (LSCs) and more differentiated leukemic blasts (2). The upregulation of CD123 expression in leukemic stem cells relative to non-neoplastic hematopoietic stem cells, makes it a useful diagnostic and therapeutic biomarker in hematologic malignancies. Varying levels of evidence have shown that CD123-targeted therapy represents a promising therapeutic approach in several cancers (3).

Various drugs targeting CD123 have been developed and evaluated at clinical level: IL-3 conjugated with diphtheria toxin; naked neutralizing anti-CD123 antibodies; drug-antibody conjugates; bispecific antibodies targeting both CD123 and CD3; and chimeric antigen receptor (CAR) T cells engineered to target CD123. Some of these agents have shown promising results at the clinical level, including tagraxofusp (CD123 conjugated with diphtheria toxin) for the treatment of BPDCN and IMGN632 (anti-CD123 drug-conjugate), and flotetuzumab (bispecific anti-CD123 and anti-CD3 monoclonal antibody) for the treatment of AML. However, the therapeutic efficacy of CD123-targeting treatments is still unsatisfactory and must be improved through new therapeutic strategies and combined treatments with other antileukemic drugs (4).

SAR443579 is a bispecific IgG-like monoclonal antibody with a competent Fc domain designed as an NKCE to treat CD123-expressing hematologic malignancies, including AML.

Treatment with SAR443579, in combination with additional agents, may improve outcomes for participants with CD123-expressing hematological malignancies.

2.2 BACKGROUND

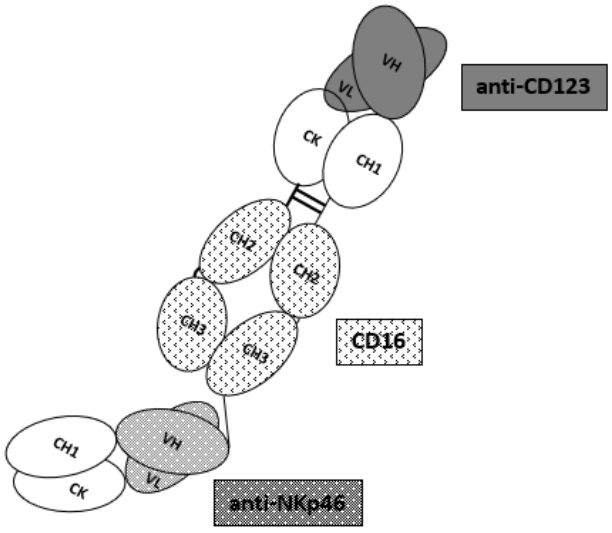
SAR443579 functions as an NKCE by binding NKp46 and CD16 on the surface of the NK cell and CD123 on the malignant cell. Co-engagement of NK cell and malignant cell by SAR443579 induces NK cell activation and results in killing of CD123 expressing malignant cells via both immune synapse formation and ADCC. SAR443579, as an anti-CD123 NKCE, is being developed as a potential safe and highly efficacious therapy against CD123-expressing hematologic malignancies, including AML.

In order to improve outcomes for people with hematological malignancies, this Phase 1/Phase 2 study will assess the potential of SAR443579 with additional combination agents on participants with different CD123-expressing hematological malignancies.

2.2.1 SAR443579

SAR443579 is a bispecific IgG-like monoclonal antibody with a competent Fc domain that binds selectively the tumor antigen CD123 and the NK cell activating receptor NKp46, via its variable region, and CD16a (FcγRIIIa) via its Fc domain (see Figure 2). SAR443579 is designed as an NK cell engager to act in two ways (1) to facilitate formation of a cytolytic synapse between NK cells and CD123 positive tumor cells leading to direct tumor cell killing; (2) to activate ADCC via its interaction with CD16.

Figure 2 - Schematic of SAR443579



CD123, the alpha-subunit of the IL-3 receptor, is overexpressed on leukemic blasts and LSCs in the majority of patients with AML, regardless of prognostic risk group, based on cytogenetic and molecular analysis (5). Additionally, CD123 is over-expressed on CD34-positive/CD38-negative AML leukemic stem cells, while other hematological malignancies (including MDS and B-ALL) have also been shown to be CD123 positive. In normal peripheral blood, CD123 exhibits a varying level of expression, with the highest density on plasmacytoid dendritic cells (pDCs) and

basophils, and intermediate levels on myeloid dendritic cells, monocytes, eosinophils and naive B cells (6). CD123 demonstrates limited expression outside the hematopoietic system and is a promising target for immune cell redirected therapies.

The immune cell engager field initially focused on redirecting T cells to mediate tumor cell killing and this approach was clinically validated with registration of blinatumomab, Blincyto®, a CD19-CD3 T cell engager for the treatment of B-ALL. Novel NK cell immune engagers are under active clinical investigation and are being utilized to target multiple different tumor antigens across a range of hematopoietic malignancies (CD30, NCT04101331; BCMA, NCT04434469; CD33, NCT03214666).

A detailed description of the chemistry, pharmacology, efficacy, and safety and PK of SAR443579 is provided in the Investigator's brochure (IB).

2.2.2 Benefit assessment

In nonclinical studies, SAR443579 mediates potent killing of primary AML blasts in an ex vivo, co-culture assay in the presence of healthy donor NK cells. A single administration of SAR443579 significantly improved the overall survival of mice engrafted with the human MOLM-13 AML model. Preliminary clinical data for the NK cell engager GTB-3550 TriKE™, an anti-CD16 and anti-CD33 antibody with a modified form of IL-15 indicates that engaging NK cells are able to provide clinical benefit in difficult to treat R/R-AML and HR-MDS cancer patients significantly reducing blasts levels and, in some cases, stopping transfusion dependency with patients becoming eligible for bone marrow transplantation.

Limited human clinical data in adults are available for SAR443579 from the currently ongoing first in Human (FIH) study. Treatment with SAR443579 at 1000 µg/kg has shown preliminary clinical benefit in study participants to date.

For further detail please refer to information provided in the Investigator’s brochure.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of SAR443579 may be found in the IB.

2.3.1 Risk assessment

Safety data from clinical studies conducted with SAR443579 in humans is currently limited to data available from TCD17197, the FIH/Phase 1/Phase 2 study of SAR443579 in participants with AML, MDS and B-ALL. Consequently, the assessment of the risks associated with SAR443579 is based on existing pre-clinical safety data and the ongoing Phase 1/Phase 2 study. As of 12 October 2023, 56 adult participants total have been treated with SAR443579 monotherapy in TCD17197 study at 11 different dosing levels which range from 10 µg/kg to 6 mg/kg. For a summary of SAR443579 risks assessment, see Section 10.11, Table 8.

In ex vivo experiments on human PBMC samples, SAR443579 partially depleted basophils with a maximum percentage of depletion of 37% and a concentration-dependent cytotoxicity activity. This effect was associated with minimal cytokine release when compared to that induced by T cell engagers (TCE). In vitro cytokine release assay in whole blood-aqueous phase confirmed the minimal cytokine release. In nonclinical toxicology studies in nonhuman primate (NHP), no SAR443579-related effects were noted on ECG, blood pressure, respiratory rate, body temperature, and on neuro-behavior up to the highest dose tested (3000 µg/kg/administration), which, in a context of very low induction of cytokine release in the animals, was consistent with the minimal cytokine release induced in ex vivo or in vitro experiments. No CRS was reported from preliminary clinical data for the NK cell engager GTB-3550 TriKE™, which indicates NKCE may not have the same propensity to induce CRS than TCE (7, 8).

No SAR443579-related microscopic findings in tissues and/or organs were observed with SAR443579 twice weekly intravenous (IV) and/or subcutaneous (SC) dosing in NHP up to the highest doses tested of 3 mg/kg/administration. Note that there was no evidence of hematology findings and no bone marrow suppression induced by SAR443579 in NHP.

Preliminary safety data (data cut-off; 12 October 2023) (9) from 56 adult participants in TCD17197, the FIH/ Phase 1/Phase 2 study of SAR443579 in participants with AML, MDS and B-ALL showed that 54 of 56 exposed participants (96.4%) experienced at least 1 TEAE. Of these, 33 of 56 exposed participants (58.9%) experienced a Grade ≥3 TEAE. The most frequently reported TEAEs (all grades) by Preferred Terms (PTs), occurring in more than 10% of participants, were the following: Infusion related reaction (IRR) (57.1%), constipation (21.4%), febrile neutropenia (16.1%), arthralgia (14.3%), nausea (14.3%), stomatitis (14.3%), vomiting (14.3%), epistaxis (12.5%), decreased appetite (12.5%), dyspnoea (10.7%), non-cardiac chest pain (10.7%), oedema peripheral (10.7%) and pneumonia (10.7%).

- 32 of 56 (57.1%) participants have experienced adverse events of IRR, low grade (Grade <3) across all dose levels. There is only one serious adverse event of infusion-related reaction, Grade 2, which occurred in one of 56 participants (1.8%) at dose level (DL) 3 (1 mg/kg target dose).
- 3 of 56 (5.4%) participants experienced adverse events of cytokine release syndrome, all Grade 1, all non-serious. One event each was reported at DL 4 (1 mg/kg target dose), DL 1.5 mg and DL 5 (3 mg/kg target dose). There were no events of high grade (Grade 3-5) CRS.
- In Study TCD17197, 29 of 56 exposed participants (51.8%) had at least one SAE. Of these, all 29 participants (51.8%) experienced a Grade ≥3 SAE. The SAEs, occurring in more than 2 participants, by PT were the following: febrile neutropenia (12.5%), pneumonia (8.9%) sepsis (5.4%) and anemia (3.6%).
    - 7 of 56 participants (12.5%) experienced a serious adverse event of febrile neutropenia, all Grade ≥3. Three events occurred at DL 6 (target dose 3 mg/kg) and 1 event each occurred at DL 4 (1 mg/kg target dose), DL 1 mg, DL 1.5 mg and DL 2 mg. 2 of 56 participants (3.6%) experienced a serious adverse event of anemia, both Grade ≥3. The events occurred at DL 2 mg and DL 6 (target dose 3 mg/kg).

- 1 of 56 participants (1.8%) experienced a SAE of thrombocytopenia, Grade ≥3, which occurred at DL 6. 1 of 56 participants (1.8%) experienced a serious adverse event of platelet count decreased, Grade ≥3, which occurred at DL 7 (target dose 6 mg/kg).

- No reports to ICANS or TLS
- No DLTs reported

Currently, there are no identified risks for SAR443579.

Based upon the ongoing clinical study, TCD17197, ex vivo experiments on human peripheral blood mononuclear cells (PBMCs), toxicology studies in cynomolgus monkeys with SAR443579, class effects of biologicals, and safety information from CD123 immune cell engagers, such as T cell engaging antibodies or Chimeric antigen receptor (CAR)-T cell therapy, the following risks are considered to be the important potential risks for SAR443579:

- Infusion related reaction
- Tumor lysis syndrome
- Myelosuppression
- Cytokine release syndrome
- Immune effector cell-associated neurotoxicity syndrome
- Immunogenicity

For the most up-to-date safety information, please refer to the SAR443579 IB.

2.3.2 Overall benefit/risk conclusion

While the benefits of SAR443579 are not yet proven, it is anticipated to benefit trial participants by causing NK cells to kill CD123-expressing malignant cells via both immune synapse and ADCC mechanisms. The eradication of CD123-expressing malignant cells is expected to be beneficial, and the hematologic malignancies investigated in this study have a high frequency (at least 80%) of CD123 expression.

Taking into account the measures taken to minimize risks to participants in this study, the potential risks identified in association with SAR443579 combined with other anticancer therapies are justified by the anticipated benefits that may be afforded to participants with hematological malignancies.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 1 - Objectives and endpoints

Control arm and several experimental arms will be evaluated in the trial. Details on arms are provided in substudy protocols.

The common objectives and endpoints are summarized below.

Objectives	Endpoints
Primary	
• To determine the RDE of SAR443579 in combination with other drugs in participants with CD123 expressing hematological malignancies.	• Overall safety including AEs, SAEs, AESIs, laboratory abnormalities and preliminary anti-tumor activity
Secondary	
• To assess overall safety and tolerability profile of SAR443579 in combination with other drugs in participants with CD123 expressing hematological malignancies (all parts).	• Incidence of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) V 5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).
• To characterize the PK profile of SAR443579 in combination with other drugs if relevant (all parts).	• PK parameters of SAR443579 (C_{trough}).
• To evaluate the potential immunogenicity of SAR443579 in combination with other drugs if relevant (all parts).	• Incidence of anti-drug anti body (ADA) against SAR443579.
• To assess other indicators of antitumor activity of SAR443579 in combination with other drugs if relevant.	• Please refer to individual sub-study for details.
Tertiary	
• For Tertiary objectives and endpoints please refer to individual substudies	

For country specific requirements, please see Section 10.8 for details.

3.1 APPROPRIATENESS OF MEASUREMENTS

The efficacy and safety assessments chosen for use in this study are considered well established and relevant in the setting of each sub-study.

In addition, suitable steps have been built into each of these assessments to ensure their reliability and accuracy and to minimize any risks to participant safety.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a parallel, Phase 1/Phase 2 open-label, randomized, multi-cohort, multi-center study assessing the safety, tolerability and preliminary efficacy of a natural killer cell engager molecule (SAR443579) with additional agents in participants with CD123-expressing hematological malignancies.

A schematic representation of the general study design is shown in Figure 1. Detailed study design and intervention information are described in each individual sub-study protocol.

This study is developed as a Master Protocol in order to accelerate the investigation of SAR443579 in different clinical settings by identifying early signals. This design provides flexibility to open new substudies as new treatments become available and close existing substudies that show little clinical activity or unacceptable toxicity.

Individual substudies will explore SAR443579 with combination partners, which may include approved or investigational agents, for which combination with SAR443579 is supported by the hypothesized MOA and available nonclinical data. For combination partners that are approved and marketed, the dose and schedule will be based on the approved product information. For combination partners that are investigational, available clinical and nonclinical data will be used to support the tested dose and schedule of each product.

Each substudy may include three parts: a dose finding part (such as safety run-in or dose escalation), a randomized dose optimization part (when applicable), and an expansion part. Combined dose optimization and expansion may be used in some substudies. In some substudies, the expansion phase may be randomized and include a control group for comparison.

For each substudy, the dose finding part may follow the mTPI-2 design to identify a pRDE of SAR443579 and a combination partner. At least 3 to 6 DLT evaluable participants may be treated at each DL and safety data for these participants may be reviewed by a Study Board. Details regarding the DLT-evaluable population and the DLT observation period are outlined in the substudy protocol. Backfilling may be proposed by the Sponsor based on the totality of tolerability, PDy, PK and preliminary anti-tumor activity as available.

Following identification of a pRDE, additional participants may be enrolled in the dose optimization part, if applicable, or dose expansion part. Design of the dose optimization and expansion parts is dependent on the specific substudy design and outlined in each substudy protocol.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study aims to establish SAR443579, with additional anticancer therapies, as a safe and effective therapy for treatment of participants with CD123-expressing hematological malignancies.

The design of this study includes a dose finding stage (safety run-in or dose escalation) followed by a randomized dose optimization stage (if applicable) and dose expansion phase, to demonstrate safety and tolerability of SAR443579 with additional anticancer therapies.

Please refer to sub-study protocols for details.

4.3 JUSTIFICATION FOR DOSE

Please refer to sub-studies for more details.

In the ongoing FIH study, SAR443579 is administered by IV infusion either weekly (induction cycles) or every 4 weeks (maintenance/continued therapy cycles). As of 12 October 2023, 56 adult participants have been treated with SAR443579 at 11 different dose levels ranging from 10 ug/kg to 6 mg/kg. SAR443579 was well tolerated and no dose-limiting toxicities were observed. The most common treatment-related adverse event was infusion-related reactions, which were observed in 32 of 56 participants (57.1%). Antileukemic disease response was assessed using the AML modified International Working Group response criteria. Best overall response (BOR) of CR/CRi was observed in 5 out of 54 evaluable participants treated across 11 dose levels. All 5 participants with BOR of CR/CRi were treated at a maximal target dose of 1 mg/kg. Based on the available data, a dose level of 1 mg/kg appears to be safe. A target dose of 1 mg/kg will be further evaluated in this study. Additional dose levels may be tested in order to fully characterize the risk-benefit profile for this patient population. The Study Board will decide whether an alternative dose should be tested prior to proceeding to the dose optimization part of the study based on their knowledge of the safety data, tolerability.

4.4 END-OF-STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all period of the study including the last visit/last contact or the last scheduled procedure shown in the Schedule of Activities (SOA), whichever occurs later.

The end of each sub-study is defined as the date of the last visit of the last participant in the sub-study or last scheduled procedure shown in the Schedule of Activities in the sub-study for the last participant, whichever occurs first.

The end of study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA for the last participant in the trial globally.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

The inclusions/exclusion criteria listed in the Master Protocol are only those applicable to all the participants common to all sub-studies. For additional sub-study specific criteria, refer to the particular sub-study protocol.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

Please check details in individual sub-studies.

Type of participant and disease characteristics

I 01. Participants with CD123-expressing hematological neoplasm per the 5th edition of the WHO Classification of Hematolymphoid Tumors (10).

Please check additional details in individual sub-studies.

Weight

Please check details in individual sub-studies.

Sex, contraceptive/barrier method and pregnancy testing requirements/breastfeeding

All

a) Male participants

   Please check details in individual sub-studies.

b) Female participants

   Please check details in individual sub-studies.

Informed Consent

I 02. Capable of giving signed informed consent as described in Appendix 1 of the full protocol which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. In countries where legal age of majority is above 18 years and for participants ≥12 and <18 years of age: the parent(s)/legal guardian(s) must provide written informed consent and adolescents must provide assent prior to any study-related procedures being performed. If the participant is also considered able by local regulation, consent from the participant will also be obtained before any study-related procedures are performed.

Please check for additional details in individual sub-studies.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply. For additional individual sub-study specific criteria, refer to the particular sub-study:

Medical conditions

E 01. Any clinically significant, uncontrolled medical conditions (including any serious active systemic infection that is not controlled) that, in the Investigator's opinion, would expose excessive risk to the participant or may interfere with compliance or interpretation of the study results.

E 02. Known second malignancy either progressing or requiring active treatment within the last 3 years prior to first IMP administration. Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (eg, breast carcinoma, cervical cancer in situ) that have undergone potentially curative therapy are not excluded. Hormonal therapy as a part of long-term maintenance post-malignancy is allowed.

E 03. Known acquired immunodeficiency syndrome (AIDS-related illnesses) or HIV disease requiring antiretroviral treatment, or having active hepatitis B or C infection, or SARS-CoV-2 infection. With exception for:

- HBV as determined by positive test for hepatitis B surface antigen (HBsAg) and/or HBV DNA. Participant who tests positive for anti-hepatitis B core (HBc) antigen IgG (with or without testing positive for anti-HBs), but tests negative for HBsAg and HBV DNA, is eligible.
- A participant who tests positive for anti-HCV antibodies and has undetectable HCV RNA without receiving antiviral treatment for HCV is eligible.

E 04. Active, known, or suspected clinically significant autoimmune disease that has required systemic treatment in the past 2 years prior to first IMP administration (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs), except controlled by replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc). The following are not exclusionary: vitiligo, childhood asthma that has resolved, psoriasis that does not require systemic treatment.

E 05. Predicted life expectancy ≤3 months.

E 06. Live vaccines within 28 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, seasonal flu (seasonal flu or covid vaccines that do not contain live virus are permitted), nasal H1N1 flu, rabies, Bacillus Calmette-Guérin (BCG), and typhoid.

Prior/concomitant therapy

E 07. Known hypersensitivity to or contraindication for the use of any of the study interventions, or components thereof including the AxMP to be administered in the study.

E 08. Receiving at the time of first IMP administration corticosteroid as a concomitant medication with corticosteroid dose >10 mg/day of oral prednisone or the equivalent, except steroid inhaler, nasal spray, or ophthalmic solution.

E 09. Any major surgery within 28 days prior to first study intervention administration. Note: If the participant had major surgery, the participant must have recovered adequately from the procedure and/or any complications from the surgery prior to starting study intervention.

E 10. Medical conditions requiring treatment with medications with narrow therapeutic index that are substrates of CYP enzymes and that cannot be closely monitored to allow for dose adjustment.

E 11. Ongoing adverse event of NCI CTCAE [Version 5.0] Grade 2 or greater severity cause by any prior anti-cancer therapy.

Prior/concurrent clinical study experience

E 12. Participation in any other clinical study involving an investigational study treatment or any other type of medical research within 28 days or 5 half-lives of the investigational treatment, whichever is longer prior to first IMP administration.

Diagnostic assessments

Please check details in individual sub-studies.

Other exclusion criteria

E 13. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 14. Participant not suitable for participation, whatever the reason, as judged by the Investigator, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 15. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals (in conjunction with Section 1.61 of the ICH-GCP Ordinance E6).

E 16. History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject’s participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.

Please check for additional details in individual sub-studies.

5.3 LIFESTYLE CONSIDERATIONS

Please refer to sub-studies for details.

5.4 SCREEN FAILURES

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently enrolled/randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once only. Participants who are rescreened are required to sign a new informed consent form, and should be assigned a new study participant number, and all the screening procedures should be repeated and entered in the screening visit pages. In case the participant is a temporary screen failure, there is no need to have participant reconsent (ie, new ICF signed) if the participant finally participates in the trial. However, if the reason for temporary screen failure is a reason that might have altered the initial given agreement of the participant to participate, the Investigator should ensure the willingness of the participant to continue or redo some screening procedures and his/her participation to the trial. This oral agreement should be documented in the participant's chart. All the tests out of protocol window should be repeated and entered in the additional pages.

5.5 CRITERIA FOR TEMPORARILY DELAYING SCREENING, ENROLLMENT AND ADMINISTRATION OF STUDY INTERVENTION

During a regional or national emergency declared by a governmental agency, if the site is unable to adequately follow protocol mandated procedures, contingency measures are proposed in Appendix 9: (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency) should be considered for screening, enrollment, and administration of study intervention.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified IMPs and AxMPs, medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Participants may receive study treatment until disease progression, unacceptable toxicity, other permanent discontinuation criteria as described in Section 7.1, or completion of the maximum cycles allowed in the sub-studies.

6.1.1 Investigational medicinal product(s)

Except for SAR443579 IMP (Table 2), the combination IMPs differ between sub-study. Please refer to individual sub-study for information regarding the combination IMP.

SAR443579 drug product is presented as a powder for solution in vials containing 100 mg/vial.

Prior to administration, the powder is to be reconstituted as a solution with sterile water (commercially available) and further prepared in NaCl solution for infusion without delay after removal of the drug from the refrigerator. The infusate volume for IV administration is 100 ml for the planned doses. The prepared infusate should be administered intravenously over 1 hour (+/- 10 minutes).

Before their use, the SAR443579 drug products must be stored at 2 to 8°C, protected from light and vials kept in the box until use. The prepared infusate should be used within **12h at room temperature**, from the end of bag preparation to the end of the dose infusion.

Each preparation step is described in detail in the Product Management Manual (PMM). Details on the materials, dilution method, final infusion volumes, recommended infusion rate, and IMP storage are also provided in the PMM.

Table 2 - Study intervention(s) administered

Intervention label	SAR443579 100 mg/vial
Intervention name	SAR443579 100 mg/vial
Intervention description	100 mg/vial, single use vial
Type	Drug
Dose formulation	Powder for solution for infusion
Unit dose strength(s)	100 mg
Dosage level(s)	Please refer to individual substudies
Route of administration	IV infusion

Use	Experimental
IMP and AxMP	IMP
Packaging and labeling	Study intervention will be provided in single-use 100 mg/vial. Each vial will be labeled as required per country requirement.
[Current/former name(s) or alias(es)]	Not applicable

6.1.2 Auxiliary medicinal product(s)

All participants will receive premedication (acetaminophen and diphenhydramine, see Table 3) to prevent or reduce the acute effect of infusion-related reactions (IRR) , 30 to 60 minutes prior to SAR443579 infusion (no longer than 60 minutes) for the first cycle. premedication may be optional during the subsequent cycles. Please refer to each substudy for further details.

Table 3 - Auxiliary medicinal product administered

Intervention label	Acetaminophen	Diphenhydramine
Intervention name	ATC code: N02BE01	ATC code: D04AA32
Intervention description	Oral or single use vial	oral or single use vial
Type	Drug	Drug
Dose formulation	Tablet or solution for IV administration	Tablet or solution for IV administration
Unit dose strength(s)	**IV:** 10 mg/mL **Oral:** 325 mg tablet	**IV:** 50 mg/mL in a 1 mL prefilled single-use syringe **Oral:** 50 mg tablet
Dosage level(s)	650 to 1000 mg IV or PO	25 to 50 mg IV or PO
Route of administration	IV or PO	IV or PO
Use	As per label	As per label
Packaging and labeling	As per label	As per label
Current/former name(s) or alias(es)	As per label	As per label

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate conditions (eg, temperature) have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply, prepare, or administer study intervention.
3. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

4. The Investigator, institution, or authorized site staff is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
5. Further guidance and information for the final disposition of unused study interventions are provided in the product management manual.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.4.10).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, or allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

Any dispensed and unused IMP will be destroyed on site per institutional practices and documented on the study accountability logs. At the end of the study, any IMP remaining on site will be destroyed as outlined in the Product Management Manual and will be recorded on the drug accountability form.

Refer to individual sub-study for potential additional details about the combination product preparation, handling, storage and accountability.

6.3 ASSIGNMENT TO STUDY INTERVENTION

- After each participant has completed the necessary screening visit procedures, the corresponding baseline eCRFs have been completed and the participant is deemed eligible for the study by the Investigator or designee, the study site will contact the IRT. All eligible participants will be assigned to a treatment cohort or randomized using IRT.
- The randomized intervention kit number list is generated centrally by Sanofi for the dose optimization and expansion parts of the study. Before the study is initiated, the login information and directions for the interactive response technology (IRT) will be provided to each site.
- The IMPs are packaged in accordance with above list.
- The randomization (if applicable) and IMP allocation are performed centrally by an IRT. The IRT generates the participant randomization list and allocates the intervention number and the corresponding intervention kits to the participants according to it.
- Randomized Participants will receive the first study treatment within 3 working days of IMP assignment or randomization.

- During the trial, administration of IMP will be open-label, and no attempts will be made to blind administration. An IRT centralized randomization system will be used to prevent the Investigators from knowing in advance the study intervention assignment, as the randomization is the best method to avoid bias.
- A participant cannot be randomized more than once in the study.

6.4 BLINDING

Although this is an open-label study, the IMP to be administered to a participant will be assigned using an IRT. The site will contact the IRT prior to the start of study intervention administration for each participant. The site will record the intervention assignment on the applicable case report form. Potential bias will be reduced by using central randomization during the dose optimization and expansion parts of the study.

6.5 STUDY INTERVENTION COMPLIANCE

When participants are dosed at the site, they will receive study intervention directly from the Investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention. The date, time and quantity of each dose administered, will be recorded in the source documents and in the eCRF.

When participants self-administer study intervention(s) at home (for oral administration), compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets/capsules during the site visits and documented in the source documents and relevant form. Deviations from the prescribed dosage regimen have to be recorded.

A record of the quantity of IMP dispensed to and administered by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded.

6.6 DOSE MODIFICATION

6.6.1 General rules

Please refer to sub-study protocol for general rules on dose modifications.

6.6.2 Cycle delay and dose omission

Please refer to sub-study protocol for general rules on dose modifications.

6.6.3 Guidelines for the management of treatment-related adverse events

See individual sub-study protocols for details.

6.6.4 Guidelines for the management of specific adverse events

See individual sub-study protocols for details.

6.6.5 Retreatment criteria

Not applicable.

6.7 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

There will be no post-trial access to IMP(s).

6.8 TREATMENT OF OVERDOSE

SAR443579 overdose is defined in Section 8.4.8.

There is no specific antidote for overdose with SAR443579 and the Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

- Closely monitor the participant for any AE/SAE/AESI and laboratory abnormalities for at least 3 days.
- Evaluate the participant to determine, if possible, whether study intervention should be interrupted or whether the dose should be reduced.
- Document appropriately in the CRF.
- Contact the study medical monitor immediately.
- Obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study intervention and as soon as the overdose is identified.
- Decision regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor based on the clinical evaluation of the participant.

For definition of overdose and recommended specific treatments in the case of overdose for other IMP agents, please refer to Section 8.4.8 and the individual sub-study protocols for details.

In the event of an AxMP overdose, the Sponsor does not recommend specific treatment for and AxMP overdose, the Investigator should follow local standards for monitoring and management. Signs, symptoms, or the clinical sequelae of an AxMP overdose should be documented in the CRF and reported as an AE per Section 8.4.

6.9 PRIOR AND CONCOMITANT THERAPY

For details, refer to individual sub-study.

Any medication (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Route of concomitant medication administration

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the treatment and maintenance period. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy may be required. The Investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the participant's primary physician. However, the decision to continue the participant on trial therapy schedule requires the mutual agreement of the Investigator, the Sponsor, and the participant.

6.9.1 Acceptable concomitant medication

See individual sub-studies for details.

6.9.2 Prohibited concomitant medication

See individual sub-studies for details.

6.9.3 Concomitant therapy requiring careful monitoring

The cytokines release after SAR443579 administration is anticipated to be limited and transient. However, since cytokines release may lead to CYP450 mediated drug interactions, caution should be taken with sensitive CYP substrates with narrow therapeutic range (NTR) (eg, including but not limited to cyclosporine or theophylline) for which circulating exposure may increase. (Please see Section 10.12).

6.9.4 Rescue medicine

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1 (Section 10.1).

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Permanent discontinuation

The study treatment should be continued whenever possible but it may be necessary for a participant to permanently discontinue study intervention. Any study treatment discontinuation must be fully documented in the eCRF. In any case, the participant should remain in the study for as long as possible.

Participants should permanently discontinue study intervention for following reasons:

- At the participant's request, at any time and irrespective of the reason (withdrawal of consent for treatment) or at the request of their legally authorized representative (if allowed by local regulations). A "legally authorized representative" is considered to be an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective participant to engage in the procedure(s) involved in the research. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical records check. The value of all of their study data collected during their continued involvement will be emphasized as important to the public health value of the study. Participants who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented. The participant should preferably withdraw consent in writing and if the participant or the participant's representative refuses or is physically unavailable, the site should document any case of withdrawal of consent.
- If in the Investigator's opinion, continuation of the study treatment would be detrimental to the participant's wellbeing, such as due to:
  - Unacceptable AE
  - Disease progression
  - Poor compliance to the study protocol
  - Other reasons eg, concurrent illness, that prevents further administration of study intervention, or that in the Investigator's opinion, in the best interest of the participant.
- A participant does not achieve a partial remission after 6 induction cycles (approximately 6 months) and in the Investigator opinion further administration of study treatment is not likely to benefit the participant.
- Occurrence of pregnancy

If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for tumor assessment if permanent discontinuation is not due to PD, for safety assessment as per SoA in the individual sub-study and until resolution or stabilization of AE, and any other assessment as per SoA. Data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed are reported in the SoA.

At the time of discontinuing an EOT visit should be conducted, as defined in each individual sub-study SoA, if possible.

Handling of participants after permanent intervention discontinuation

Participants will be followed-up according to the study procedures specified in the individual sub-study protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in the individual sub-study protocol, whichever comes last.

If possible, and after the permanent discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP including a pharmacokinetics sample, if appropriate.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

7.1.2 Liver chemistry stopping criteria

Discontinuation of study intervention for abnormal liver tests is required by the Investigator in the presence of abnormal liver chemistries not meeting protocol-specified stopping rules if the Investigator believes that it is in best interest of the participant.

7.1.3 QTc stopping criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline in QT interval corrected using Fridericia's formula [QTcF] after enrollment, the Investigator or qualified designee will determine if the participant can continue on the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

7.1.4 Temporary discontinuation

Temporary intervention discontinuation may be considered by the Investigator and Sponsor because of a regional or national emergency declared by a governmental agency (Appendix 9 [Section 10.9/Contingency measures for a regional or national emergency that is declared by a governmental agency]).

For all temporary intervention discontinuations, reason and duration should be recorded by the Investigator in the appropriate pages of the eCRF.

7.1.5 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical and/or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned adverse event was unlikely and if the selection criteria for the study are still met (refer to Sections 5 of each sub-study).

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at the participant's own request for any reason (or without providing any reason).
- A participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or compliance reasons.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the individual sub-study SoA. See individual sub-study SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed.
- If the participant withdraws consent from the study, the Sponsor will retain and continue to use any data collected before such a withdrawal of consent, as per applicable clinical regulation(s).
- If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be rerandomized/reallocated (treated) in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if the participant repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule, and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, telephone calls, and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.
- The last known information for all assessments required at the EOT visit including disease and survival status will be collected and reported in the medical record and eCRF.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA of each individual sub-study. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in each individual substudy SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count, urine tests) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the individual substudy SoA.
- In the event of a significant study-continuity issue (eg, caused by a pandemic), alternate strategies for participant visits, assessments, medication distribution and monitoring may be implemented by the Sponsor or the Investigator, as per local Health Authority/ethics requirements [see Appendix 9 (Section 10.9) Contingency measures for a regional or national emergency that is declared by a governmental agency].
- Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 (Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency).

8.1 ADMINISTRATIVE PROCEDURES

Not applicable.

8.2 EFFICACY ASSESSMENTS

Planned timepoints for all efficacy assessments are provided in each of the individual substudy SoA.

8.3 SAFETY ASSESSMENTS

This section presents safety assessments other than adverse events which are presented in Section 8.4.

Planned timepoints for all safety assessments are provided in each of the individual substudy SoAs.

8.3.1 Physical examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, skin and neurological systems. Height and weight will also be measured and recorded.
- A directed physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses. Abnormal findings at screening will be considered medical history. New or worsening physical examination findings identified after the participant has been enrolled will be considered as AE.

8.3.2 Vital signs

- Vital signs including temperature (one of the following methods: oral, tympanic or temporal artery), pulse rate, respiratory rate, blood pressure, and oxygen saturation will be recorded. When feasible, the selected method of temperature assessment should remain consistent during the course of the study.
- Blood pressure and pulse measurements will be assessed in a semi-supine position with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones). Whenever possible, vital signs should be recorded before blood collection for laboratory tests.

For specific details on vital sign assessments, please refer to the individual sub-study protocol.

8.3.3 Electrocardiograms and LVEF

- 12-lead ECG will be performed at screening and then as clinically indicated using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and QT intervals corrected using Fridericia's formula [QTcF].
- Left ventricular ejection fraction (LVEF) evaluation will be done by echocardiography or multigated acquisition (MUGA) scan, and any repeated assessment should be done with the same technology used at screening.
- Additional evaluations such as unscheduled ECG, LVEF, Holter monitoring, cardiac enzymes and consultation with a cardiologist should be done when clinically indicated.

For specific details on vital sign assessments, please refer to the individual sub-study protocol.

8.3.4 Clinical safety laboratory tests

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the individual substudy SoA (Section 1.3) for the timing and frequency.

- The Investigator must review the laboratory results, document this review, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents. See Appendix 3 (Section 10.3) for abnormal laboratory results reporting. Abnormal laboratory findings associated with the underlying disease are not considered clinically significant, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.
  - If clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.
  - All protocol-required laboratory tests, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
  - If laboratory values from non-protocol specified laboratory tests performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded.

8.3.5 Pregnancy testing

Refer to Section 5.1 Inclusion criteria for pregnancy testing criteria in each individual sub-study; the Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female participant with an early undetected pregnancy.

For females of childbearing potential (FOCBP), a serum beta-human chorionic gonadotropin (β-HCG) test (serum or urine test as required by local regulations) must be performed as detailed in the individual sub-study SOAs. Pregnancy tests must be obtained in girls who are post-menarchal.

Males or females of reproductive potential may not participate unless they have agreed to use an effective contraceptive method for the duration of study therapy. Please refer to individual sub-study for duration of contraception following last administration of IMP.

Additional serum or urine pregnancy tests may be performed, as determined necessary by the Investigator or required by local regulation, to establish the absence of pregnancy at any time during the participant's participation in the study.

8.3.6 Dose limiting toxicities

Please refer to protocol sub-studies.

8.4 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.4.8.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) that meet the definition of an AE or SAE and remain responsible for following up (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.4.1 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious), including adverse events of new onset, ASE and AESIs and worsening of baseline signs and symptoms, will be collected throughout the study period from the signing of the informed consent form (ICF) until 30 days following the last administration of study treatment.

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE or AESI data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.4.2 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs and AEs of special interest (as defined in Section 8.4.8), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Stabilization is defined as an AE ongoing without any change for at least 3 months. Participants with an AE of grade >1 will be followed until the resolution of the AE to grade 0-1or starting of a new antineoplastic therapy, which occurs first.

Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

8.4.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Serious adverse events that are considered expected will be specified in the reference safety information (IB for SAR443579).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB/IDFU/package insert and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.4.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until completion (child birth or pregnancy termination).
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner) pregnancy.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such.
- The participant/pregnant female partner will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant/pregnant female partner and the neonate and the information will be forwarded to the Sponsor.
- Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.4.4 While the Investigator is not obligated to actively seek this information in former participant/pregnant female partner, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

8.4.6 Cardiovascular and death events

Not applicable.

8.4.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable.

8.4.8 Adverse events of special interest

An adverse event of special interest (AESI) is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

The following AESIs will be monitored continuously throughout the treatment part of the study:

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP;
  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Section 10.4).
- Symptomatic overdose (serious or nonserious) with IMP:
  - An overdose (accidental or intentional) with the IMP/AxMP is an event suspected by the Investigator or spontaneously notified by the participant or legally authorized representative and defined as below:
    - An overdose of IMP is defined as an increase of at least 30% of the dose to be administered in the specified duration or if the dose is administered in less than half the recommended duration of administration.
    - An overdose of the AxMP is defined as at least twice the intended dose within the intended therapeutic interval, adjusted to the tested drug.
- Other project specific AESI(s)
  - IRR Grade ≥3
  - CRS Grade ≥2 (please refer to Section 8.4.8.1 below)

- ICANS of any grade (please refer to Section 8.4.8.2 below)
- TLS

Note: comprehensive instructions for the recommended management of IRR, CRS and ICANS are provided in Section 6 of each Sub-Study protocol

8.4.8.1 Cytokine release syndrome (CRS)

ASTCT CONSENSUS GRADING FOR CRS (11)

CRS Parameter	1. Grade 1	2. Grade 2	3. Grade 3	4. Grade 4
Fever[a]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		with		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		and/or[b]		
Hypoxia	None	Requiring low-flow nasal cannula[c] or blow-by	Requiring high-flow nasal cannula[c], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

a Fever is defined as temperature ≥38°C not attributable to any other cause. In participants who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

b CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a participant with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

c Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute

8.4.8.2 Immune effector cell-associated neurotoxicity syndrome (ICANS)

ASTCT CONSENSUS GRADING FOR ICANS (ADULTS)

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (participant is unarousable and unable to perform ICE)
Depressed level of consciousness[a]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
			on EEG that resolve with intervention	seizures without return to baseline in between
Motor findings[b]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[c]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Abbreviations: ICAN = Immune effector cell-associated neurotoxicity syndrome; N/A= not applicable.

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a participant with an ICE score of 3 who has a generalized seizure is classified as Grade 3 ICANS.

* A participant with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a participant with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable.

a Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

b Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

c Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

8.4.9 Medication errors or misuses of medicinal product

All reports of medication error or misuse in relation to the IMP with or without an AE must be recorded on the corresponding page(s) of the CRF and transmitted to the Sponsor's representative following standard processes.

A medication error is an unintended failure in the drug treatment process (ie, mistake in the process of prescribing, storing, dispensing, preparing, or administering medicinal products in clinical practice) that leads to, or has the potential to lead to harm to the participant. This includes situations in which a participant was involved or not (eg, even if the error was recognized and intercepted before the participant received or used the product), and whether it resulted in harm to the participant or not.

A misuse refers to situations where the medicinal product is intentionally and inappropriately used, ie, not in accordance with the terms of the marketing authorization or outside what is foreseen in the protocol, by the participant for a therapeutic purpose.

Of note, if a medication error or misuse meets the protocol definition of an overdose, it will be recorded in the overdose page of the CRF.

8.4.10 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines. Please see Product Management Manual for guidelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.5 PHARMACOKINETICS

- Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate document. The actual date and time of each sample will be recorded. Pharmacokinetic samples will be tested by the Sponsor or Sponsor's designee.
- The pharmacokinetic parameters will be calculated from plasma SAR443579 concentrations obtained after SAR443579 administration with combination agent. The parameters will include but may not be limited to C_{trough} (predose).
- Population PK approaches will be used for SAR443579.
- Pharmacokinetic samples could also be used for testing analytical method performance such as comparability and incurred sample reproducibility, and for possible exploratory analysis of drug metabolites. The exploratory data may not be included in the study report but will be kept on file.
- Please refer to individual sub-study protocol for more pharmacokinetic information.

8.6 PHARMACODYNAMICS

Potential PDy assessments are included in the biomarker assessments, Section 8.8 and in Biomarker section of individual sub-studies.

8.7 GENETICS

Genetics will be evaluated in this study as described in Appendix 5 (Section 10.5).

For country specific requirement please refer to Section 10.8.

8.8 BIOMARKERS

- This study will evaluate exploratory biomarkers in whole blood (including derivatives such as serum and plasma) and either bone marrow (aspirates- liquid, and/or biopsy-solid) or tumor tissue (biopsy), depending on the sub-study to evaluate the impact of SAR443579 treatment with the combination agent.
- Collection of biological samples for biomarker studies is an important part of this study and will be collected from all participants of this study as specified in the individual sub-study Biomarkers SoA.
- Please refer to the Laboratory Manual(s) of specific sub-studies for details regarding sample collection handling and shipping logistics.

[redacted]

8.9 IMMUNOGENICITY ASSESSMENTS

Antibodies to SAR443579 will be evaluated in plasma samples collected from all participants according to the SoA. Additionally, plasma samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

Instructions for the collection and handling of these samples will be provided by the Sponsor in a separate document. These samples will be tested by the Sponsor or Sponsor's designee using a qualified assay method.

A 3-tiered approach will be employed to assess the immunogenicity of SAR443579 when applicable. Samples will be screened and then confirmed for antibodies binding to SAR443579 and the titer of confirmed positive samples will be reported. Other analyses may be performed to further characterize the immunogenicity of SAR443579.

All samples collected for detection of antibodies to study intervention may also be evaluated for SAR443579 plasma concentration to enable interpretation of the immunogenicity data.

The impact of positive immune response, including pre-existing, treatment-induced or treatment-boosted ADA, will be evaluated on efficacy, pharmacokinetic, and safety endpoints when relevant.

8.10 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Medical resource utilization and health economics parameters are not evaluated in this study.

8.11 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease and the development of new medicines. Reuse of coded data and biological samples (leftover and additional) will be limited to future scientific research conducted under a research plan for the purpose of diagnosing, preventing or treating diseases. The future research projects will be conducted under the Sponsor's and/or its affiliates' and/or, if applicable, the partner of the Sponsor which has licensed the study drug to the Sponsor or which is co-developing the study drug with the Sponsor's control, acting alone or in collaboration with research partners such as universities, research institutions or industrial partners with whom the coded data may be shared.

Data and biological samples will be stored and used for future research only when consented to by participants (see Section 10.1.3) and, when applicable, further information on the future research has been provided to the study participant, unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of data/sample will not be included in the local ICF). The conditions for reuse will be adapted locally with the appropriate language in the ICF.

In any case, a specific consent will be collected for the performance of genetic analyses on leftover and/or additional samples.

Data protection - Processing of coded clinical data

The study participant will be provided will all mandatory details of the data processing in the Core ICF.

The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Use of leftover samples and additional samples for future research

Remaining leftover samples will be used only after the study ends, ie, end of study as defined in the study protocol. Additional/extra samples can be collected and used during the study conduct at a given timepoint (eg, at randomization visit) as defined in the study protocol.

The study participant will be provided with all mandatory details of the use of the human biological samples (leftover and additional) in the Core ICF.

Study participant data will be stored for up to 25 years for regulatory purposes and future research. Biological samples for future use will be stored for up to 25 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

9 STATISTICAL CONSIDERATIONS

Please refer to individual sub-study protocol for additional statistical considerations. No pooled data analysis across sub-studies is planned in the master protocol.

9.1 POPULATIONS FOR ANALYSES

The following populations for analyses are defined.

Table 4 - Populations for analyses

Population	Description
Screened	All participants who signed the ICF.
Exposed/safety	All screened participants who have taken at least 1 dose of study intervention regardless of the amount of study intervention administered. Participants will be analyzed according to the intervention they actually received.
Efficacy population	See sub-study protocols for definition
DLT-evaluable	See sub-study protocols for definition
Pharmacokinetic	All participants from the exposed population with at least one post-baseline PK result with adequate documentation of dosing and sampling dates and times.
Pharmacodynamics	See sub-study protocols for definition
ADA	See sub-study protocols for definition

Abbreviations: ICF = informed consent form, IRT = Interactive Response Technology, DLT = dose limiting toxicity, PK = pharmacokinetics, PDy = pharmacodynamics, ADA = anti-drug antibody

9.2 STATISTICAL ANALYSES

The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.2.1 General considerations

The baseline value is defined as the last assessment prior to the first dose of the IMP unless specified otherwise. Unless specified otherwise, analyses will be performed based on the populations defined in Table 4.

The observation period will be divided into 3 segments:

- The **pre-treatment period** screening period prior to starting study treatment.
- The **treatment period** (ie, treatment-emergent (TE) period) is defined as the period from the first IMP administration to the last IMP administration + 30 days.
- The **post-treatment period** is defined as the period from the end of the on-treatment period.

9.2.2 Primary endpoint(s) analyses

9.2.2.1 Dose escalation/safety run-in

Please refer to individual sub-studies for detailed specification of primary endpoints.

9.2.2.2 Dose optimization (when applicable)

Please refer to individual sub-studies for detailed specification of primary endpoints.

9.2.2.3 Dose expansion

Please refer to individual sub-studies for detailed specification of primary endpoints. Descriptive statistics will be used to summarize binary, categorical and continuous variables. The 90% two-sided CI computed using Clopper-Pearson method will be provided. The Kaplan-Meier method will be used to summarize time-to-event variables.

9.2.2.4 Main analytical approach

The primary safety endpoint (Dose Escalation or safety run-in part) is the incidence of DLTs during the DLT observation period, and it will be analyzed based on the DLT-evaluable population using the mTPI-2 design or other appropriate dose-finding designs on a cohort-by-cohort basis. If no excessive toxicity is observed, the candidate dose(s) will be determined when at least 6 participants had been treated at the highest dose.

Please refer to individual sub-studies for detailed main analytical approach of the optimization and expansion part.

9.2.2.5 Sensitivity analysis

Please refer to individual sub-studies for details.

9.2.3 Secondary endpoint(s) analyses

The key secondary safety endpoints include treatment-emergent AEs/SAEs including those from clinically significant laboratory abnormalities during the on-treatment period, and severity, frequency and type of infections.

Please refer to the sub-study protocol for the key secondary efficacy endpoints analyses.

9.2.3.1 Other secondary endpoints

[redacted]

9.2.4 Tertiary endpoints

[redacted]

9.2.5 Safety analyses

All DLT modeling will be performed on the DLT-evaluable population or those who experienced a DLT. All other safety analyses will be performed on the safety population using descriptive statistics.

9.2.5.1 Adverse events

General common rules for adverse events

All AEs will be categorized according to NCI-CTCAE v5.0 and classified by SOC and PTs according to the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA), with the exception of ICANS and CRS. ICANS and CRS events will be graded using ASTCT Consensus Grading and will be summarized separately.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- TEAEs: AEs that developed, worsened or became serious during the treatment-emergent period.
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period.

For participants with multiple occurrences of the same PT, the maximum grade will be used.

The primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be descripted separately.

Treatment-emergent adverse events:

An overall summary of TEAEs will be provided. The number and percentage of participants who experience any of the following will be provided:

- TEAEs
- TEAEs of Grade ≥3
- Grade 5 TEAE (any TEAE with a fatal outcome during the on-treatment period)
- Serious TEAEs
- Serous treatment-related TEAEs
- TEAE leading to partial intervention discontinuation

- TEAE leading to full intervention discontinuation
- Treatment-related TEAEs
- Treatment- related TEAEs of Grade ≥3

Number and percentage of participants experiencing TEAEs by primary SOC and PT will be summarized by NCI-CTCAE v5.0 grade (all grades and Grade ≥3). Missing grades, if any, will be included in the "all grades" category. Similar summaries will be prepared for treatment-related TEAEs, TEAEs leading to partial intervention discontinuation, TEAEs leading to full intervention discontinuation, TEAEs leading to dose modification, serious TEAEs, TEAEs with fatal outcome, AESIs, and AEs/SAEs occurring during the post-treatment period. In addition, the number (%) of participants with any Grade 5 AE (TEAE and post-treatment) will be summarized.

The following deaths summaries will be generated:

- Number and percentage of participants who died by study period (treatment-emergent period, pot-treatment period) and reasons for death (disease progression, AE, or other reason).
- All TEAEs leading to death by primary SOC and PT showing number and percentage (%) of participants.

9.2.5.2 Clinical laboratory evaluations

Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

When relevant, for laboratory variables, descriptive statistics for results and changes from baseline will be provided for the last value and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period.

Hematology and clinical chemistry results will be graded according to the NCI-CTCAE v5.0, when applicable. Number and percentage of participants with laboratory abnormalities (all grades and by grade) using the worst grade during the treatment period will be provided.

When the NCI-CTCAE v5.0 grading scale is not applicable, the number of participants with laboratory abnormality out-of-normal laboratory range value will be displayed.

For laboratory variables graded by NCI-CTCAE:

- The number (%) of participants with abnormal laboratory tests at baseline will be presented by grade.
- The number (%) of participants with abnormal laboratory tests during the treatment-emergent period will be summarized by grade. When appropriate, the number (%) of participants with abnormality of any grade with Grade 3-4 abnormalities will be provided. All safety analyses will be made on the exposed population. When relevant, the summary statistics (including mean, median, standard error, minimum and maximum) for all vital signs (raw data and changes from baseline) will be calculated for baseline, last on treatment and/or worst value.

9.2.6 Other analysis

For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.9.

9.3 INTERIM ANALYSES

9.3.1 Dose optimization (when applicable) and expansion stopping rule based on safety

Continuous evaluation of toxicity events will be performed throughout enrollment for each dose optimization (when applicable) and expansion cohort. Bayesian toxicity monitoring analysis will be conducted to determine the stopping rule based on excessive toxicities, which are defined as deaths (other than death related to PD) within 30 days of last IMP administration or Grade 4 and above TEAEs.

The stopping boundary is the number of participants with excessive toxicities observed associated with a >80% posterior probability of true excessive toxicity rate >20% under the corresponding number of participants being evaluated.

If a stopping boundary is met, the patient enrollment will be paused. An appropriate evaluation of the cause of death and toxicity will be conducted by the Study Board, and a correction plan will be established and submitted to FDA for review prior to enrolling any new participants.

The stopping boundaries (Table 5) are determined based on the following assumptions:

- maximum probability of true excessive toxicities allowed = 0.2,
- prior distribution for excessive toxicity rate: Beta (1,1),
- minimum number of participants before early stopping rule applies = 6,
- posterior probability of excessive toxicity rate >0.2 is at least 80%.
- cohort size = 1.

Table 5 - [redacted]

9.3.2 Dose expansion stopping rule based on efficacy

No formal interim analyses (IAs) are planned. However, in order to support project strategic planning and design of future studies, informal interim analysis(es) may be conducted during the dose expansion part of the study, eg, after 10 participants have been treated and completed the induction period or have discontinued the study intervention, whichever is earlier. Such continuous assessments will be performed for cohort(s) with clinical benefits until the planned sample size per cohort is reached. Early futility decisions by cohort may be made at any of the informal interim analysis based on the totality of data.

9.4 SAMPLE SIZE DETERMINATION

Please refer to the different sub-study protocol for corresponding sample size determination.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) international ethical guidelines
  - Applicable ICH Good Clinical Practice (GCP) guidelines
  - The Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014 on clinical trials on medicinal products for human use, as applicable
  - The General Data Protection Regulation (GDPR) and any other applicable data protection laws
  - Any other applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following, as applicable:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, Regulation No 536/2014 of the European Parliament and the Council of the European Union for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.
  - Determining whether an incidental finding (as per Sanofi policy) should be returned to a participant and, if it meets the appropriate criteria, to ensure the finding is returned (an incidental finding is a previously undiagnosed medical condition that is discovered

unintentionally and is unrelated to the aims of the study for which the tests are being performed). The following should be considered when determining the return of an incidental finding:

- The return of such information to the study participant (and/or his/her designated healthcare professional, if so designated by the participant) is consistent with all applicable national, state, or regional laws and regulations in the country where the study is being conducted, and
- The finding reveals a substantial risk of a serious health condition or has concerned reproductive importance, AND has analytical validity, AND has clinical validity.
- The participant in a clinical study has the right to opt out of being notified by the Investigator of such incidental findings. In the event that the participant has opted out of being notified and the finding has consequences for other individuals, eg, the finding relates to a communicable disease, Investigators should seek independent ethical advice before determining next steps.
- In case the participant has decided to opt out, the Investigator must record in the site medical files that she/he does not want to know about such findings.

As applicable, according to requirements of the Regulation No536/2014 of the European Parliament and the Council of the European Union, the Sponsor will be responsible for obtaining approval from the Competent Authorities of the EU Member States and/or Ethics Committees, as appropriate, for any amendments to the clinical trial that are deemed as “substantial” (ie, changes which are likely to have a significant impact on the safety or physical or mental integrity of the clinical trial participants or on the scientific value of the trial) prior to their implementation.

According to the Regulation No 536/2014 of the European Parliament and the Council of the European Union and as specified by the applicable regulatory requirements in non-EU/EEA countries, Sanofi, as the clinical trial Sponsor, needs to report to the concerned regulatory agency/ies serious breaches without undue delay but not later than 7 calendar days of becoming aware of that breach. A serious breach is defined as a deviation of the version of the protocol applicable at the time of the breach or the applicable clinical trial regulation that is likely to affect to a significant degree the safety and rights of a subject or the reliability and robustness of the data generated in the clinical trial.

The Sponsor shall ensure that all parties involved in the conduct of the clinical trial promptly report any events that might meet the definition of a serious breach.

Therefore, Investigators shall within 48h after being aware of a deviation that might meet the definition of a serious breach, report to the Sponsor any suspected serious breach to enable the Sponsor to carry out the required assessment and notify the regulatory agency/ies in the event of a confirmed serious breach. To that extent, the principal Investigator must have a process in place to ensure that the site staff or service providers engaged by the principal Investigator/institution are able to identify the occurrence of a (suspected) serious breach and that a (suspected) serious breach is promptly reported to the Sponsor through the contacts (e-mail address or telephone number) provided by the Sponsor.

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

The ICF will be provided to the study participant in paper version.

- The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participants or their legally authorized representative , and answer all questions regarding the study, including what happens to the participants when their participation ends.
- Potential participants must be informed that their participation is voluntary. Participant their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Privacy and Data Protection requirements including those of the General Data Protection Regulation (GDPR) and of the French law, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- In case of ICF amendment while the participants are still included in the study, they must be re-consented to the most current version of the ICF(s).Where participants are not in the study anymore, teams in charge of the amendment must define if those participants must or not re-consent or be informed of the amendment (eg, if the processing of personal data is modified, if the Sponsor changes, etc).
- A copy of the ICF(s) must be provided to the participant or their legally authorized representative, where applicable.

Participants who are rescreened are required to sign a new ICF.

The ICF contains 2 separate sections that address the use for future research of participants' data and/or samples (remaining mandatory ones or new extra samples collected for optional research). Optional exploratory research must be detailed in the section "Optional tests/procedures" and future research is to be defined in Core Study Informed Consent Form (CSICF) Part 2. Each option is subject to an independent consent and must be confirmed by ticking checkboxes in CSICF Part 3, each checkbox corresponding to a specific use: consent for the performance of an optional exploratory research; consent for storage and use of coded data for future research; consent for use of leftover samples and associated coded data for future research; consent for collection of additional biological samples for storage and use for future research, and consent for performance of genetic analyses on biological samples. The Investigator or authorized designee

will explain to each participant the objectives of the exploratory research and why data and samples are important for future research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

For a regional or national emergency declared by a governmental agency, contingency measures are included in Appendix 9 in Section 10.9: Contingency measures for a regional or national emergency that is declared by a governmental agency.

10.1.4 Data protection

All personal data collected and/or processed in relation to this study will be handled in compliance with all applicable Privacy & Data Protection laws and regulations, including the GDPR (General Data Protection Regulation). The study Sponsor is the Sanofi company responsible for ensuring compliance with this matter, when processing data from any individual who may be included in the Sanofi databases, including trial participants, Investigators, nurses, experts, service providers, Ethics Committee members, etc.

When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor takes all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Protection of participant personal data

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

"Participant race and ethnicity will be collected in this study because they are expected to modify the drug response/because they are required by regulatory agencies (eg, on African American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan)". They will not be collected in the countries where this is prohibited by local regulation.

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor or its service providers, when applicable, will be identifiable only by the unique identifier; participant names or any information which would make the participant identifiable will not be transferred to the Sponsor.
- Participants must be informed that their personal study-related data will be used by the Sponsor in accordance with applicable data protection laws. The level of disclosure must also be explained to the participant as described in the informed consent.
- Participants must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

- The contract between Sponsor, Investigators, and study sites specifies responsibilities of the parties related data protection, including handling of data security breaches and respective communication and cooperation of the parties. Accordingly, the Investigator and the institution will promptly notify the Sponsor about any data security breaches and detail in the notification the nature of the breach, the categories (eg, Sponsor's personnel, study participants or their relatives, healthcare professionals, etc), the approximate number of subjects concerned, the type and approximate number of data records concerned and the likely consequences of the breach. The institution and/or Investigator will investigate the causes of the data security breach and take actions to minimize the effects of said breach. The institution and/or Investigator will record all information relating to the breach, including the results of their own investigations and investigations by authorities, as applicable, and will take all measures as necessary to prevent future data security breaches.
- Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.
- Participants must be informed that their study-related data will be used for the whole "drug development program", ie, for this trial as well as for the following steps necessary for the development of the investigational product, including to support negotiations with payers and publication of results.

Protection of personal data related to professionals involved in the study

- Personal data (eg, contact details, affiliation(s) details, job title and related professional information, role in the study, professional resume, training records) are necessary to allow Sanofi to manage involvement in the study and/or the related contractual or pre-contractual relationship. They may be communicated to any company of the Sanofi group ("Sanofi") or to Sanofi service providers, where needed.
- Personal data can be processed for other studies and projects. At any time, objection to processing can be made by contacting the Sanofi Data Protection Officer (link available at Sanofi.com).
- In case of refusal to the processing of personal data by or on behalf of Sanofi, it will be impossible to involve the professionals in any Sanofi study. In case the professionals have already been involved in a Sanofi study, they will not be able to object to the processing of their personal data as long as they are required to be processed by applicable regulations. The same rule applies in case the professionals are listed on a regulatory agencies disqualification list.
- Personal data can be communicated to the following recipients:
  - Personnel within Sanofi or partners or service providers involved in the study.
  - Judicial, administrative and regulatory authorities, in order to comply with legal or regulatory requirements and/or to respond to specific requests or orders in the framework of judicial or administrative procedures. Contact details and identity may also be published on public websites in the interest of scientific research transparency.

- Personal data may be transferred towards entities located outside the Economic European Area, in countries where the legislation does not necessarily offer the same level of data protection or in countries not recognized by the European Commission as offering an adequate level of protection. Those transfers are safeguarded by Sanofi in accordance with the requirement of European law including, notably:
  - The standard contractual clauses of the European Commission for transfers towards our partners and service providers,
  - Sanofi's Binding Corporate Rules for intra-group transfers.
- Professionals have the possibility to lodge a complaint with Sanofi leading Supervisory Authority, the "Commission Nationale de l'Informatique et des Libertés" (CNIL) or with any competent local regulatory authority.
- Personal data of professionals will be retained by Sanofi for up to thirty (30) years, unless further retention is required by applicable regulations.
- In order to facilitate the maintenance of Investigators personal data, especially if they contribute to studies sponsored by several pharmaceuticals companies, Sanofi participates in the Shared Investigator Platform (SIP) and in the TransCelerate Investigator Registry (IR) project (https://transceleratebiopharmainc.com/initiatives/investigator-registry) Therefore, personal data will be securely shared by Sanofi with other pharmaceutical company members of the TransCelerate project. This sharing allows Investigators to keep their data up-to-date once for all across pharmaceutical companies participating in the project, with the right to object to the transfer of the data to the TransCelerate project.
- Professionals have the right to request the access to and the rectification of their personal data, as well as their erasure (where applicable) by contacting the Sanofi Data Protection Officer: Sanofi DPO - 54 rue La Boétie - 75008 PARIS - France (to contact Sanofi by email, visit https://www.sanofi.com/en/our-responsibility/sanofi-global-privacy-policy/contact).

10.1.5 Committees structure

Not applicable.

10.1.6 Dissemination of clinical study data and results

Study participants

At the end of the clinical study, the Sponsor may publish the study results in scientific journal(s). As part of the review for publication, independent scientists may need to use "coded" data of all the study participants to independently verify the study's results.

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include ClinicalTrials.gov, euclinicaltrials.eu, and sanofi.com, as well as some national

registries. For pediatric and adult trials, the results will generally be submitted/released 6 and 12 months respectively, after the end of the clinical trial worldwide (ie, the last active, participating country).

In addition, results from clinical trials in participants are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to vivli.org.

Individual anonymized participant data and supporting clinical documents are available for request at vivli.org. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: vivli.org.

Professionals involved in the study or in the drug development program

Sanofi undertakes the legal obligation to disclose the full name of the Investigator and his/her affiliated institute/ hospital's name and location on the China Trial Disclosure website as required by the National Medical Products Administration (NMPA) in its guidance "Drug Clinical Trial Registration and Information Disclosure Management Practice (Trial Implementation)", requesting name disclosure of Chinese and foreign investigational sites and Investigators in any eligible clinical trial

Sanofi may publicly disclose, and communicate to relevant authorities/institutions, the funding, including payments and transfers of value, direct or indirect, made to healthcare organizations and professionals and/or any direct or indirect advantages and/or any related information or document if required by applicable law, by regulation or by a code of conduct such as the "EFPIA Code on Disclosure of Transfers of Value from Pharmaceutical Companies to Healthcare Professionals and Healthcare Organisations".

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- Guidance on completion of CRFs will be provided in the relevant Sponsor data management study document.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy, including definition of study critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.

- The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, contract research organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a different retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Sponsor or designee will perform monitoring to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

10.1.9 Study and site start and closure

First act of recruitment

The first act of recruitment is the first participant screened and will be the study start date.

Study/Site termination

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for study termination by the Sponsor, as well as reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- For study termination:
  - Information on the product leads to doubt as to the benefit/risk ratio
  - Discontinuation of further study intervention development
- For site termination:
  - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
  - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator
  - Total number of participants included earlier than expected

If the study, sub-study or cohort is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up. He/she should also stop all screening activities pertaining to the study or the relevant cohort(s). Should the Sponsor decide to pause recruitment in a cohort to allow decision making, the Investigator should pause all screening activities until further notice.

If the study is early terminated the participants who are receiving and benefitting from study treatment as per Investigator judgement may continue study treatment until protocol defined treatment discontinuation criteria are met. The participants who continue study treatment after early study termination should be followed for safety (ie. Study treatment administrations, ongoing SAE/related AE, new related AE, AESI or SAE and their associated concomitant medications and laboratory results if any) and end of treatment reason during the time period.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 6 will be performed by the local laboratory.
- Local laboratory/central laboratory results, please refer to individual sub-study.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 6 - Protocol required laboratory tests

Laboratory tests	Parameters
Hematology	Platelet count Red blood cell (RBC) count White blood cell (WBC) count with differential: Neutrophils - Lymphocytes - Monocytes - Eosinophils - Basophils - Hemoglobin Hematocrit
Clinical chemistry	Blood urea nitrogen (BUN) or total urea depending on local standards Albumin Potassium Creatinine with eGFR estimation using MDRD formula[a] Glucose [should be fasting condition] Chloride Magnesium Phosphate Sodium Calcium (corrected calcium) Amylase Aspartate aminotransferase (AST)/ Serum glutamic-oxaloacetic transaminase (SGOT) Alanine aminotransferase (ALT)/ Serum glutamic-pyruvic transaminase (SGPT) Alkaline phosphatase[b] Total and direct bilirubin Total protein GGT
Pregnancy testing	[Serum or highly sensitive urine] human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[c]
Coagulation	International normalized ratio (INR) or Prothrombin Time (PT) (or Activated Partial Thromboplastin Time [aPTT])
Endocrine function tests	Thyroid-stimulating hormone (TSH)

Laboratory tests	Parameters
Endocrine function tests (continued)	Tri-iodothyronine (T3) Free thyroxine (FT4)
Routine Urinalysis	Specific gravity, pH, glucose, protein, blood, ketones, [bilirubin, urobilinogen, nitrite, leukocyte esterase] by dipstick, Microscopic examination (if blood or protein is abnormal)
Other screening tests	Follicle-stimulating hormone and estradiol (as needed in women of nonchildbearing potential only) [Serology (HIV antibody, hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody or specify other tests)]

Notes:
a Modification of Diet in Renal Disease (MDRD) equation: Glomerular filtration rate (mL/min/1.73 m2) = 175 × (Serum Creatinine)-1.154 × (Age)-0.203 × (0.742 if Female) × (1.212 if African American).
b If alkaline phosphatase is elevated, consider fractionating.
c Local urine testing will be standard for the protocol unless serum testing is required by local regulation or IRB/IEC.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

10.3.1 Definition of AE

AE definition

- An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>meeting</u> the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease, or more severe than expected for the participant's condition), eg:
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.

- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- Signs, symptoms, or the clinical sequelae of any medication errors, misuse and abuse with the IMP.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

- Any abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets one or more of the criteria listed:

a) Results in death

b) Is life-threatening

The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c) Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the

physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d) Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:
        - Intensive treatment in an emergency room or at home for:
            - Allergic bronchospasm
            - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
            - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
        - Development of drug dependence or drug abuse
        - Suicide attempt or any event suggestive of suicidality
        - Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
        - Bullous cutaneous eruptions

10.3.3 Recording and follow-up of AE/SAE and/or AESI

AE/SAE and AESI recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the required form.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE/AESI.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories as per NCI CTCAE V5.0 definitions (except for ICANS and CRS that will be graded using ASTCT 2019 consensus grading):

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL). Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL; Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- The Investigator will use clinical judgment to determine the relationship.
- A reasonable possibility of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- For causality assessment, the Investigator will also consult the IB and/or product information, for marketed products.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor's representative with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally submitted documents.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE reporting to the Sponsor via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.

- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
- Contacts for SAE reporting can be found in the Investigator study file.

SAE reporting to the Sponsor via paper data collection tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the Sponsor's representative.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting timeframes].
- Contacts for SAE reporting can be found in Investigator study file.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

A Woman is considered WOCBP (fertile) from the time of menarche until becoming postmenopausal (see below) unless permanently sterile (see below). A postmenopausal state is defined as the period of time after a woman has experienced no menses for 12 consecutive months without an alternative medical cause.

- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT).
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods include:

- Documented hysterectomy.
- Documented bilateral salpingectomy.
- Documented bilateral oophorectomy.

- For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity, gonadal dysgenesis), Investigator discretion should be applied to determining study entry eligibility.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first administration of study intervention, additional evaluation should be considered.

10.4.2 Contraception guidance

Participant should be given advice about donation and cryopreservation of germs cells prior to the start of the study intervention, in line with the fact that study intervention may affect ova and sperm for up to the number of days specified respectively for each sub-studies in the inclusion criteria. Contraception guidance is presented in Table 7 below.

Table 7 - Contraception guidance

CONTRACEPTIVES[a] ALLOWED DURING THE STUDY INCLUDE:
Highly effective methods[b] that have low user dependency (Failure rate of <1% per year when used consistently and correctly) - Implantable progestogen-only hormone contraception associated with inhibition of ovulation - Intrauterine device (IUD) - Intrauterine hormone-releasing system (IUS) - Bilateral tubal occlusion - Vasectomized partner (Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.)
Highly effective method[b] that are user dependent (Failure rate of <1% per year when used consistently and correctly). - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[c] a) Oral b) Intravaginal c) Transdermal d) Injectable - Progestogen-only hormone contraception associated with inhibition of ovulation[c] a) Oral b) Injectable - Sexual abstinence (Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant)

a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

b Failure rate of <1% per year when used consistently and correctly. Typical use failure rates differ from those when used consistently and correctly.

c If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Note: Periodic abstinence (calendar, symptothermal, post ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure with friction).

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <22 weeks gestational age) or still birth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.4.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

- Any female participant who becomes pregnant while participating in the study will discontinue study intervention

10.5 APPENDIX 5: GENETICS

Use/Analysis of DNA



10.6 APPENDIX 6: OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENT

Not Applicable.

10.7 APPENDIX 7: MEDICAL DEVICES AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC/REGION REQUIREMENTS

Please refer to protocol sub-studies.

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

Continuation of the study in the event of a regional or national emergency declared by a governmental agency:

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack, COVID-19) may prevent access to the clinical trial site. Contingency procedures are suggested below and in sections (Section 6.1, Section 7.1.4, Section 8, and Section 10.1.3 Appendix 1) for an emergency that prevents access to the study site, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

During the emergency, if the site will be unable to adequately follow protocol mandated procedures, alternative treatment outside the clinical trial should be proposed, and screening/enrollment/randomization/administration of study intervention may be temporarily delayed/halted (see also Section 7).

For European countries contingency measures are currently only applicable for the COVID-19 pandemic.

10.10 APPENDIX 10: COLLECTION, STORAGE AND FUTURE USE OF DATA AND HUMAN BIOLOGICAL SAMPLES

10.10.1 Compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h)

This appendix is provided separately.

10.10.2 Compliance with Member State applicable rules for the collection, storage and future use of (personal) data (Article 7 (1 d) of EU Regulation 536/2014)

This appendix is provided separately.

10.11 APPENDIX 11: SAR443579 RISK

Table 8 - SAR443579 risk assessment

Risk	Preclinical data	Clinical data	Actions
Important identified risks for SAR443579			
None	N/A	N/A	N/A
Important potential risks for SAR443579			
Infusion-related reactions	In non-clinical toxicology cynomolgus monkey studies SAR443579 was clinically well tolerated, no compound-related histopathological (macroscopic or microscopic) findings at the IV and/or SC injection sites were seen.	As of 12-Oct-2023, there is only one SAE of IRR, Grade <3, which occurred in one of 56 participants (1.8%) at DL 3. In study TCD17197, 32 of 56 (57.1%) participants have experienced AEs of IRRs, Grade <3, across all DLs. The majority of the events are non-serious. Dose Level 1 - one participant Dose Level 2 - three participants Dose Level 0.75 mg - one participant Dose Level 3 - two participants Dose Level 4 - four participants Dose Level 1 mg - seven participants Dose Level 1.5 mg - one participant Dose Level 2 mg - one participant Dose Level 5 - two participants Dose Level 6 - four participants Dose Level 7 - six participants	Mitigation Strategy: Premedication with acetaminophen and diphenhydramine, for the first cycle and optionally thereafter, 30-60 minutes prior to administration of SAR443579. Instructions for dose interruptions, dose reductions and additional premedication instructions for further treatments detailed in individual protocols.
Tumor lysis syndrome	None	As of 12-Oct-2023, there are no events of TLS reported across the SAR443579 program.	Protocol Exclusion Criteria: Participants with white blood cell count ≥15 000/mm^3; Estimated creatinine clearance <30 mL/min (using Cockcroft-Gault formula) OR estimated creatinine clearance <30 mL/min/1.73 m^2 (for adolescent and pediatric participants [one to 17 years] Schwartz formula will be used). Mitigation Strategy: Monitoring of participants blood levels of urea nitrogen or BUN, Creatinine, corrected Calcium, Potassium, Magnesium, Phosphorous, and uric acid are detailed in the individual protocols. Metabolic abnormalities and hyperuricemia will be corrected, as needed following standard

Risk	Preclinical data	Clinical data	Actions
			guidelines, including use of rasburicase, if needed, for severe hyperuricemia.
Myelosuppression	In non-clinical toxicology studies of SAR443579, no hematological findings and no bone marrow suppression were observed in monkeys up to 3 mg/kg/ administration when given twice weekly for five weeks suggesting a low risk for myelosuppression with SAR443579.	As of 12-Oct-2023, in study TCD17197: Seven of 56 participants (12.5%) experienced SAEs of febrile neutropenia, all Grade ≥3. Three events occurred at DL-6 and one event each occurred at DL 4, DL 1 mg, DL 1.5 mg and DL 2 mg. Two of 56 participants (3.6%) experienced SAEs of anemia, both Grade ≥3. The events occurred at DL 2 mg and DL 6. One of 56 participants (1.8%) experienced a SAE of thrombocytopenia, Grade ≥3, which occurred at DL 6. In addition, one of 56 participants (1.8%) experienced a SAE of platelet count decreased, Grade ≥3, which occurred at DL 7.	Protocol exclusion criteria: Grade 4 hematologic toxicity: bone marrow hypocellularity, anemia, thrombotic thrombo-cytopenic purpura. Mitigation: Participant will be monitored for signs or symptoms of infection. Potential infections will be investigated with cultures and/or radiologic evaluation or other tests, as needed, to determine the etiology. Infections will be managed with appropriate antimicrobial therapies and supportive care. Participant will be monitored for signs or symptoms of bleeding. Platelet and red blood cell transfusions will be performed when indicated.
Cytokine release syndrome	Preclinical data suggest low risk as SAR443579 exhibits some cytokine release in vitro in human whole blood, and negligible cytokine release after SAR443579 weekly or twice weekly IV and/or SC dosing in cynomolgus monkey up to 3 mg/kg/ administration.	As of 12-Oct-2023, in TCD17197, three of 56 (5.4%) participants experienced AEs of cytokine release syndrome, all Grade <3, all non-serious. One event each was reported at DL 4, DL 1.5 mg and DL 5. There were no events of high grade (Grade 3-5) CRS.	Mitigation strategy: Close monitoring of participants vital signs. Premedication as detailed above in IRR. Guidelines for management of CRS included is included in the clinical trial protocol, including dose interruptions, discontinuations, use of dexamethasone and tocilizumab as needed for the treatment of Grade ≥2 CRS, per institutional recommended guidelines; supportive care with supplemental oxygen, IV fluids, vasopressors, and/or mechanical ventilation if needed.

Risk	Preclinical data	Clinical data	Actions
Immune Effector Cell-Associated Neurotoxicity Syndrome	No neurotoxicity was observed in monkeys up to 3 mg/kg administration when given twice weekly for five weeks.	As of 12-Oct-2023, there are no events of immune effector cell-associated neurotoxicity syndrome reported across the SAR443579 program.	Protocol Exclusion Criteria: Adult participants with evidence of active central nervous system leukemia. Mitigation: Close monitoring of participants neurologic system by physical exam. Guidelines for management of ICANS included in the clinical trial protocol, including the dose interruptions, discontinuations, use of IV corticosteroids and IV tocilizumab.
Immunogenicity	In non-clinical toxicology cynomolgus monkeys studies ADAs response was observed, impacting the PK profile leading to dramatic exposure decrease without any associated signs of toxicity.	No data available yet.	The occurrence of ADAs against SAR443579 will be measured. Potential ADAs-associated toxicities will be monitored through standard clinical and laboratory measures.

Abbreviations: IV: Intravenous; SC: Subcutaneous; ADA: Anti-Drug Antibody; SAE: Serious Adverse Event; IRR: Infusion-Related Reaction; TLS: Tumor Lysis Syndrome; PK: Pharmacokinetic; CRS: Cytokine Release Syndrome, DL: Dose Level, AE: Adverse event, ICANS: Immune effector Cell Associated Neurotoxicity Syndome, BUN:Blood Urea Nitrogen, OR: Odds Ratio, SAE: Serious Adverse Event, NA: Not Applicable.

10.12 APPENDIX 12: LIST OF SENSITIVE CYP SUBSTRATED WITH NARROW THERAPEUTIC RANGE

The following table was extracted in October 2023 from the Drug Interaction Database from the University of Washington (www.druginteractionsolution.org).

Drug	Drug therapeutic class
(S)-mephenytoin	Anticonvulsants
(S)-warfarin	Anticoagulants and Antiplatelets
acenocoumarol	Anticoagulants and Antiplatelets
astemizole	H-1 Receptor Antagonists
cisapride	Gastrointestinal Prokinetic Agents
colchicine	Antigout and Uricosuric Agents
cyclosporine	Immunosuppressants
digoxin	Antiarrhythmics
everolimus	Immunosuppressants
fentanyl	Opioids
flecainide	Antiarrhythmics

gliclazide	Sulfonylureas
glyburide (glibenclamide)	Sulfonylureas
mexiletine	Antiarrhythmics
paclitaxel	Taxanes
phenprocoumon	Anticoagulants and Antiplatelets
phenytoin	Anticonvulsants
pimozide	Antipsychotics
quinidine	Antiarrhythmics
quinine	Antimalarials
sirolimus	Immunosuppressants
tacrolimus	Immunosuppressants
terfenadine	H-1 Receptor Antagonists
theophylline (1,3-DMX)	Methylxanthines
thioridazine	Antipsychotics
tizanidine	Muscle Relaxants
tolbutamide	Sulfonylureas
warfarin	Anticoagulants and Antiplatelets

Compounds were classified as NTR drugs if they were listed by at least one of the following agencies: European Medicines Agency, US Food and Drug Administration, Japan National Institute of Health Sciences, Health Canada.

10.13 APPENDIX 13: PROTOCOL AMENDMENT HISTORY

Not applicable.

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tcd17796-16-1-1-amended-protocol01-master

Approve & eSign	[redacted] Clinical [redacted]

Approve & eSign	[redacted] Clinical [redacted]

AMENDED CLINICAL TRIAL PROTOCOL 02 (SUBSTUDY 01)

Protocol title:	**A Phase 1/Phase 2, open-label, multi-center study, assessing the safety, tolerability and the preliminary efficacy of SAR443579 administered in combination with azacitidine + venetoclax in adult participants with CD123 expressing newly diagnosed Acute Myeloid Leukemia (ND-AML) that are ineligible for intensive chemotherapy - Substudy 01**
Protocol number:	**TCD17796-01**
Amendment number:	**02**
Compound number (INN/Trademark):	**SAR443579** **Not applicable**
Brief title:	**A study to investigate natural killer cell engager (SAR443579) in combination with azacitidine + venetoclax in adult participants with newly diagnosed acute myeloid leukemia - Substudy 01**
Acronym:	**Not applicable**
Study phase:	**Phase 1/ Phase 2**
Sponsor name:	**Sanofi-Aventis Research & Development**
Legal registered address:	**82 Avenue Raspail** **94250 Gentilly**
Monitoring team's representative name and contact information	

Regulatory agency identifier number(s):

IND:	169765
NCT:	Not applicable
WHO:	Not applicable
EUDAMED:	Not applicable
EU trial number:	2023-509438-20
Other:	Not applicable

Date: 17-May-2024 Total number of pages: 126

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PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 02 (Sub-study01)		17 May 2024, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 01 (Sub-study01)		06 May 2024, version 4 (electronic 4.0)
Original Protocol		05 February 2024, version 1 (electronic 1.0)

Amended protocol 02 (17 May 2024)

This amended protocol 01 (Amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment is to align with health authorities' recommendations to remove the plan for the dose optimization and dose expansion parts at this stage of development and to submit the details in a future amendment when the data is available.

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

Section # and Name	Description of Change	Brief Rationale
Cover page, Protocol amendment summary of changes and headers throughout the document	The description of the protocol was updated to Amended Clinical Trial Protocol (Substudy 01).	Administrative change.
Throughout the document	The description of dose optimization/dose expansion has been removed in the document and reference to future protocol amendment for further details on optimization and expansion has been added The tables and schemes have been updated accordingly and some sections have been removed (see below in summary of changes table)	In alignment with HA's recommendation to not already include the plan for dose optimization and dose expansion parts but wait for available data before going to optimization and expansion part
Throughout the document	Randomized has been removed from title and study design description	For correction
Section 1.1-Brief summary	In dose escalation part some text was added/modified on SAR443579 administration	For better clarity and readability
Section1.3 Schedule of activities	Footnote s for hospitalization has been updated and following text has been added "for cycle 2 and beyond."	For clarification on hospitalization time.
Section 4.3.2 Dose optimization and	As per quoted before description of dose optimization and dose expansion has been removed therefore this corresponding section was removed	In alignment with HA's recommendation to not already include the plan for dose

Section # and Name	Description of Change	Brief Rationale
recommended dose for expansion (RDE)		optimization and dose expansion parts but wait for available data before going to optimization and expansion part
Section 9.1 Populations for analyses	Randomized population has been removed from Table 12 - Populations for analyses	In alignment with HA's recommendation to not already include the plan for dose optimization and dose expansion parts but wait for available data before going to optimization and expansion part
Section 9.3 Interim analysis	Section 9.3.2 Dose expansion stopping rule based on efficacy has been removed as per ne amendment requirement to remove dose optimization/ dose expansion description within the protocol	In alignment with HA's recommendation to not already include the plan for dose optimization and dose expansion parts but wait for available data before going to optimization and expansion part
Section 9.4 Sample size determination	Section has been updated and reference to expansion part removed	In alignment with HA's recommendation to not already include the plan for dose optimization and dose expansion parts but wait for available data before going to optimization and expansion part
Appendix 16: Statistical details about BAC+3ODM	Section has been removed as it refers to expansion part	In alignment with HA's recommendation to not already include the plan for dose optimization and dose expansion parts but wait for available data before going to optimization and expansion part

In addition, minor typographical error/editorial corrections were implemented throughout the protocol.

TABLE OF CONTENTS

AMENDED CLINICAL TRIAL PROTOCOL 02 (SUBSTUDY 01) 1

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE 2

TABLE OF CONTENTS 4

LIST OF TABLES 10

LIST OF FIGURES 10

LIST OF ABBREVIATIONS 11

1 PROTOCOL SUMMARY 12

1.1 SYNOPSIS 12

1.2 SCHEMA 22

1.3 SCHEDULE OF ACTIVITIES (SOA) 24

1.3.1 All parts: PK and ADA flowchart (Cycle 1) 29

1.3.2 All parts: PK and ADA flowchart (Cycle 2 and beyond) 31

1.3.3 All parts PDy flowchart (Cycle 1) 32

1.3.4 All parts PDy flowchart (Cycle 2 and beyond) 34

2 INTRODUCTION 37

2.1 STUDY RATIONALE 37

2.2 BACKGROUND 38

2.2.1 Venetoclax + azacitidine 38

2.2.2 SAR443579 39

2.3 BENEFIT/RISK ASSESSMENT 39

2.3.1 Risk assessment 39

2.3.1.1 SAR443579 39

2.3.1.2 Venetoclax 39

2.3.1.3 Azacitidine 40

2.3.1.4 SAR443579 combined with venetoclax and azacitidine 41

2.3.2 Benefit assessment 41

2.3.3 Overall benefit/risk conclusion 41

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS 42

3.1 APPROPRIATENESS OF MEASUREMENTS 45

4 STUDY DESIGN 46

4.1 OVERALL DESIGN 46
4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN 47
4.3 JUSTIFICATION FOR DOSE 47
4.3.1 Rationale for dose escalation 47
4.4 END-OF-STUDY DEFINITION 49
5 STUDY POPULATION 50
5.1 INCLUSION CRITERIA 50
5.2 EXCLUSION CRITERIA 52
5.3 LIFESTYLE CONSIDERATIONS 53
5.3.1 Meals and dietary restrictions 53
5.4 SCREEN FAILURES 53
5.5 CRITERIA FOR TEMPORARILY DELAYING SCREENING, ENROLLMENT AND ADMINISTRATION OF STUDY INTERVENTION 53
6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY 54
6.1 STUDY INTERVENTION(S) ADMINISTERED 54
6.1.1 Investigational medicinal product(s) 54
6.1.2 Auxilliary medicinal product(s) 55
6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY 56
6.3 ASSIGNMENT TO STUDY INTERVENTION 56
6.4 BLINDING 56
6.5 STUDY INTERVENTION COMPLIANCE 56
6.6 DOSE MODIFICATION 57
6.6.1 General rules 57
6.6.2 Venetoclax/azacitidine dose reduction, delay and omission 57
6.6.3 SAR443579 dose reduction, interruption, delay and omission 57
6.6.4 Guidelines for the management of treatment-related adverse events 58
6.6.5 Guidelines for the management of specific adverse events. 59
6.6.5.1 Infusion-related reactions (IRR) 59
6.6.5.2 Anaphylaxis 60
6.6.5.3 Fever, flu-like symptoms and cytokine release syndrome (CRS) 60
6.6.5.4 Immune cell-associated neurotoxicity syndrome (ICANS) 64
6.6.5.5 Tumor lysis syndrome 65
6.6.5.6 Management of hematological toxicities 65

6.6.5.7 Management of non-hematological toxicities: 66
6.6.6 Retreatment criteria 66
6.7 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY 66
6.8 TREATMENT OF OVERDOSE 66
6.9 PRIOR AND CONCOMITANT THERAPY 67
6.9.1 Acceptable concomitant medications 67
6.9.2 Concomitant therapy requiring careful monitoring 68
6.9.3 Prohibited concomitant medications 68
6.9.4 Rescue medicine 69
7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL 70
7.1 DISCONTINUATION OF STUDY INTERVENTION 70
7.1.1 Permanent discontinuation 70
7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY 70
7.3 LOST TO FOLLOW UP 70
8 STUDY ASSESSMENTS AND PROCEDURES 71
8.1 ADMINISTRATIVE PROCEDURES 71
8.2 EFFICACY ASSESSMENTS 71
8.3 SAFETY ASSESSMENTS 71
8.3.1 Physical examinations 71
8.3.2 Vital signs 71
8.3.3 Electrocardiograms and LVEF 72
8.3.4 Clinical safety laboratory tests 72
8.3.5 Pregnancy testing 72
8.3.6 Dose limiting toxicities 72
8.4 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING 73
8.4.1 Time period and frequency for collecting AE and SAE information 73
8.4.2 Method of detecting AEs and SAEs 74
8.4.3 Follow-up of AEs and SAEs 74
8.4.4 Regulatory reporting requirements for SAEs 74
8.4.5 Pregnancy 74
8.4.6 Cardiovascular and death events 75

8.4.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs 75
8.4.8 Adverse events of special interest 75
8.4.9 Medication errors or misuses of medicinal product 75
8.4.10 Guidelines for reporting product complaints 75
8.5 PHARMACOKINETICS 75
8.6 PHARMACODYNAMICS 76
8.7 GENETICS 77
8.8 BIOMARKERS 77
8.9 IMMUNOGENICITY ASSESSMENTS 78
8.10 CLINICAL OUTCOMES ASSESSMETS 78
8.11 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS 79
8.12 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH 79
9 STATISTICAL CONSIDERATIONS 80
9.1 POPULATIONS FOR ANALYSES 80
9.2 STATISTICAL ANALYSES 80
9.2.1 General considerations 80
9.2.2 Primary endpoint(s) analyses 81
9.2.2.1 Dose escalation 81
9.2.2.2 Dose optimization 81
9.2.2.3 Dose expansion 81
9.2.2.4 Main analytical approach 81
9.2.2.5 Sensitivity analysis 81
9.2.2.6 Supplementary analyses 81
9.2.3 Secondary endpoint(s) analyses 81
9.2.4 Tertiary/exploratory endpoints 84
9.2.5 Safety analyses 84
9.2.6 Pharmacokinetics 84
9.2.7 Pharmacodynamics 84
9.2.8 Other analysis 85
9.2.9 Timing of planned analysis 85
9.3 INTERIM ANALYSES 85
9.3.1 Dose expansion stopping rule based on safety 85
9.4 SAMPLE SIZE DETERMINATION 85

9.5 DOSE ESCALATION DECISION RULES 86

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS 88

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS 88

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS 88

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTINGS 88

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE 88

10.4.1 Definitions 88

10.4.2 Contraception guidance 88

10.5 APPENDIX 5: GENETICS 88

10.6 APPENDIX 6: OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS 89

10.6.1 Cytokine release syndrome (CRS) 89

10.6.2 Immune effector cell-associated neurotoxicity syndrome (ICANS) 89

10.6.3 Child-Pugh Scoring System 90

10.7 APPENDIX 7: MEDICAL DEVICES AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES 90

10.8 APPENDIX 8: COUNTRY-SPECIFIC/REGION REQUIREMENTS 91

10.8.1 China specific requirements 91

10.8.2 Germany 91

10.8.3 France 91

10.8.4 European Union 92

10.8.4.1 Safety reporting to the agency 92

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY 92

10.10 APPENDIX 10: COLLECTION, STORAGE AND FUTURE USE OF DATA AND HUMAN BIOLOGICAL SAMPLES 92

10.10.1 Compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h) 92

10.10.2 Compliance with Member State applicable rules for the collection, storage and future use of (personal) data (Article 7 (1 d) of EU Regulation 536/2014) 92

10.11 APPENDIX 11: AZACITIDINE RISK ASSESSMENT 92

10.12 APPENDIX 12: VENETOCLAX RISK ASSESSMENT 94

10.13 APPENDIX 13: DRUG-DRUG INTERACTIONS VENETOCLAX 96

10.14 APPENDIX 14: MODIFIED ELN 2022 CRITERIA 104
10.15 APPENDIX 15: CYTOGENETIC RISK 106
10.16 APPENDIX 16: CLINICAL OUTCOME ASSESSMENT (COA) 107
10.16.1 Quality of life in acute myeloid leukemia (AML-QoL) 107
10.16.2 Patient global impression of severity (PGIS) 110
10.16.3 Patient global impression of change (PGIC) 111
10.16.4 Patients' qualitative assessment of treatment version 2 112
10.17 APPENDIX 17: PROTOCOL AMENDMENT HISTORY 114
11 REFERENCES 124

LIST OF TABLES

Table 1 - Venetoclax day ramp-up dosing schedule 18
Table 2 - Management of venetoclax co-administration with CYP3A inhibitors 18
Table 3 - Objectives and endpoints 42
Table 4 - Dose: induction and maintenance/continued therapy (all doses in mg/kg) 48
Table 5 - Investigational medicinal product(s) administered 55
Table 6 - Guidelines for the treatment of infusion-related reactions (IRRs) 59
Table 7 - Guidelines for management of cytokine release syndrome (CRS) 61
Table 8 - Guidelines for the management of ICANS 64
Table 9 - Dose adjustment instructions for hematological toxicity 65
Table 10 - Dose adjustments instructions for non-hematological toxicity 66
Table 11 - List of pharmacokinetic parameters and definitions 76
Table 12 - Populations for analyses 80
Table 13 - Dose escalation rule of the modified toxicity probability interval-2 method 87
Table 14 - Risk assessment of azacitidine 93
Table 15 - Risk assessment of venetoclax 94
Table 16 - 2022 ELN risk classification by genetics at initial diagnosis 106

LIST OF FIGURES

Figure 1 - Graphical study design 22
Figure 2 - Study scheme 23

LIST OF ABBREVIATIONS

ADCC:	antibody-dependent cellular cytotoxicity
AEs:	adverse events
AML:	acute myeloid leukemia
Aza:	azacitidine
B/R:	benefits and disadvantages
BOR:	best overall response
CR:	complete remission
CRh:	CR with partial hematologic recovery
CRi:	CR with incomplete hematologic recovery
DLs:	dose levels
EFS:	event free survival
HMA:	hypomethylating agent
HRQL:	health related quality of life
IC:	induction chemotherapy
ICU:	intensive care unit
IL:	interleukin
IV:	intravenous
LoDAC:	low dose of cytarabine
LSCs:	leukemia stem cells
MOA:	mechanism of action
mOS:	median overall survival
MRD:	minimal residual disease
ND-AML:	newly diagnosed acute myeloid leukemia
NTR:	narrow therapeutic range
OS:	overall survival
PDy:	pharmacodynamic
PGIC:	patient global impression of change
PGIS:	patient global impression of severity
PK:	pharmacokinetic
PQAT-v2:	patient’s qualitative assessment of treatment version 2
QOL:	quality of life
QW:	once weekly
R/R AML:	relapsed/refractory acute myeloid leukemia
SAEs:	serious adverse events
SOP:	standard of practices
SUSAR:	suspected unexpected serious adverse reaction
TTF:	time to treatment failure
Ven:	venetoclax
VS:	versus

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A Phase 1/Phase 2, open-label, multi-center study, assessing the safety, tolerability and the preliminary efficacy of SAR443579 administered in combination with azacitidine + venetoclax in adult participants with CD123 expressing newly diagnosed Acute Myeloid Leukemia (ND-AML) that are ineligible for intensive chemotherapy - Substudy 01

Brief title:

A study to investigate natural killer cell engager (SAR443579) in combination with azacitidine + venetoclax in adult participants with newly diagnosed acute myeloid leukemia - Substudy 01

Regulatory agency identifier number(s):

IND:	169765
NCT:	Not applicable
WHO:	Not applicable
EUDAMED:	Not applicable
EU trial number:	2023-509438-20
Other:	Not applicable

Rationale:

Currently patients with newly diagnosed acute myeloid leukemia (ND-AML) who have comorbidities that preclude use of intensive induction chemotherapy receive venetoclax (Ven) (BCL-2 inhibitor) combined with a hypomethylating Agent (HMA), azacitidine (Aza) or decitabine; or venetoclax (Ven) combined with a low dose of cytarabine (LoDAC). Both combinations have shown to improve CR/CRi rates and median overall survival (mOS) versus (vs) HMA (1) or LoDAC (2) alone.

There is growing evidence to suggest that acute myeloid leukemia (AML) derives from leukemia stem cells (LSCs) that give rise to leukemic blasts in vitro and in vivo models. It is hypothesized that the persistence of LSCs causes relapse after an initial remission. Thus, the eradication of LSCs may be a requirement for cure and is an important therapeutic goal. One potential therapeutic target in AML is the surface receptor CD123, the interleukin (IL)-3 receptor alpha chain (IL-3R α) that is expressed at high levels on LSCs. CD123 is strongly expressed in LSCs and blasts in most pediatric, young adolescent, and adult participants with AML, regardless of the prognostic risk group based on cytogenetic and molecular analyses. Based on the safety and tolerability data generated from the adult participants, SAR443579 will be further investigated combined with venetoclax and azacitidine in participants with CD123 expressing ND-AML ineligible for intensive chemotherapy (IC).

SAR443579 is a bispecific IgG-like monoclonal antibody with a competent Fc domain. SAR443579 functions as an NK cell engager (NKCE) by binding NKp46 and CD16 on the surface of the NK cell and CD123 on the malignant cell. Co-engagement of NK cell and malignant cell by SAR443579 induces NK cell activation and results in killing of CD123-expressing malignant cells via both immune synapse formation and antibody-dependent cellular cytotoxicity (ADCC). This results in potent cytotoxicity activity against the human AML cell lines expressing various densities of CD123. The co-engagement of NK and CD123-positive cells by SAR443579 against human MOLM-13 AML cells leads to NK activation, degranulation and expression of effector molecules. This leads to significant increase in survival of mice engrafted with MOLM-13. SAR443579 also induces dose-dependent blast cell killing when primary blasts from participants with AML are co-cultured with healthy donor NK cells.

Literature supports the combination of venetoclax with NK cell based therapies due to the upregulation NKG2D ligand and synergistic antileukemic effects in vitro (3, 4).

In vitro data show no effect of venetoclax and azacitidine on NK cell viability; and the triplet combination of azacitidine + venetoclax + SAR443579 shows some increase in tumor cell line killing vs venetoclax and azacitidine (MOLM-13) (unpublished data).

The proposed sub-study is a Phase 1/Phase 2, dose escalation and expansion to determine the safety, pharmacokinetics (PK), pharmacodynamics (PDy) and preliminary efficacy of SAR443579 administered IV (intravenous) combined with venetoclax and azacitidine in participants with CD123 expressing ND-AML ineligible for IC.

Objectives and endpoints:

Objectives	Endpoints
Primary	
• Escalation part: To determine the preliminary recommended dose(s) for optimization of SAR443579 when combined with venetoclax and azacitidine in participants with CD123 expressing ND-AML ineligible for intensive chemotherapy.	• Incidence of dose limiting toxicities (DLTs).
• Optimization part: To determine the RDE of SAR443579 with venetoclax and azacitidine in participants with CD123 expressing ND-AML ineligible for intensive chemotherapy (IC).	• Overall safety including AEs, SAEs, AESIs, laboratory abnormalities and preliminary anti-tumor activity.
• Expansion part: To assess the anti-tumor activity of SAR443579 at the identified RDE combined with venetoclax and azacitidine in participants with CD123 expressing ND-AML ineligible for intensive chemotherapy.	• Complete Remission (CR) rate: proportion of participants who have a CR (Complete Remission) determined by the Investigator according to 2022 European Leukemia Net (ELN) recommendations for diagnosis and management of AML.

Objectives	Endpoints
Secondary	
• To assess overall safety and tolerability profile of SAR443579 when combined with venetoclax and azacitidine in participants with CD123 expressing ND-AML ineligible for IC (all parts).	• Incidence of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), clinically significant laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).
• To assess minimal residual disease (MRD) in participants achieving a CR, CRh or CRi (expansion part).	• Percentage of participants with Minimal residual disease as defined by 2022 ELN recommendations for AML.
• To characterize the PK of SAR443579, venetoclax and azacitidine (all parts).	• PK parameters of SAR443579 (C_{trough}), venetoclax and azacitidine (C_{max} and AUC).
• To evaluate the potential immunogenicity of SAR443579 (all parts).	• Incidence anti-drug antibody (ADA) against SAR443579.
• To assess additional parameters of anticancer activity of SAR443579 at the RDE in combination with venetoclax and azacitidine (expansion part).	• Composite Complete Remission (CRc) rate: proportion of participants who have a CR (Complete Remission) + CRh (complete remission with partial hematologic recovery) + CRi (Complete Remission with Incomplete Hematologic Recovery) determined by the Investigator according to 2022 European Leukemia Net (ELN) recommendations for diagnosis and management of AML. (CRc = CR + CRh + CRi)
	• Overall response rate: Proportion of participants who have a CR or CRi or CRh or PR or MLFS (morphological leukemia-free state) according to the 2022 ELN criteria.
	• Duration of CR defined as the time interval from the first documented evidence of CR until disease relapse as per 2022 ELN recommendations or death due to any cause, whichever comes first.
	• Duration of CR+CRh+CRi (Duration of CRc) defined as the time interval from first documented evidence of CRc (CR, CRh or CRi) until disease relapse as per 2022 ELN recommendations or death due to any cause, whichever comes first.
	• Duration of CR+CRi+CRh+PR+MLFS (Duration of overall response rate) defined as the time from the first documented evidence of CR or CRi or CRh or PR or MLFS until disease relapse as per 2022 ELN recommendations or death due to any cause, whichever comes first.

Objectives	Endpoints
	• Alternative CR rate defined as proportion of participants with CR+CRh (complete remission with partial hematological recovery). • Duration of CR+CRh (Duration of alternative CR) defined as the time from the first documented evidence of CR or CRh until disease relapse as per 2022 ELN recommendations or death due to any cause, whichever comes first. • Event-free survival (EFS) defined as the time interval from the first day of treatment assignment to the date of earliest evidence of relapse, treatment failure, or death. • Overall survival (OS) defined as time interval from the day of treatment assignment to death from any cause. • Rate of hematopoietic stem cell transplantation (HSCT) procedures immediately following study treatment administration but prior to subsequent therapy for treatment of AML. • Time to treatment failure (TTF) defined as the time from first day of treatment assignment to discontinuation for any reason excluding remission, eg, relapsed disease, refractory disease, unacceptable AE, participant preference or death.
• To assess transfusion independence rate (TI) after treatment with SAR443579 in combination with venetoclax and azacitidine (all parts).	• Rate of conversion from transfusion dependence to transfusion independence and rate of participants who are transfusion independent at baseline and remain independent during 56-day post-baseline period.

For country specific requirement, please see Section 10.7 details.

Overall design synopsis:

A graphical representation of the study schema is shown in Figure 1. The study design, number of participants, intervention group and duration are described below.

Brief summary:

This is a parallel, Phase 1/2, 2-arms, open-label, controlled, dose-escalation and expansion study to determine the safety, pharmacokinetic (PK), pharmacodynamic (PDy) and preliminary efficacy of SAR443579 administered IV combined to venetoclax and azacitidine treatment in adult participants with CD123 expressing ND-AML ineligible for IC.

Study treatment consists of 3 cycles of 28 days in the Induction period, followed by up to 21 cycles of 28 days in the Maintenance/continued therapy period.

Dose-escalation part: During the dose-escalation, it is planned for approximately 3 dose levels to be tested (see Table 4). Participants with adverse risk cytogenetics per ELN 2022 criteria will be enrolled in dose escalation. Escalation will start at a dose of 0.6 mg/kg SAR443579 in combination with venetoclax and azacitidine and and will escalate to 1 mg/kg and 1.5 mg/kg according to the incidence of dose limiting toxicities (DLTs) occurring within the DLT observation period using a modified toxicity probability interval 2 (mTPI-2) approach. Lower dose levels (DLs) may be investigated in case of excessive toxicity. The final decision will be determined by the Study Board based on evaluation of available safety data (including DLTs, adverse events [AEs] and serious adverse events [SAEs]), clinical PK and PDy. SAR443579 will be administered IV once-weekly during induction period from C1-C3 (Days 1, 8, 15, and 22) that may be extended up to 6 cycles in case the patient didn't reach complete remission (CR)/CR with incomplete hematologic recovery (CRi)/CR with partial hematologic recovery (CRh) withing the first 3 induction cycles after discussion and agreement between the Investigator and the Sponsor. Participants achieving a CR, CRi or CRh will then be transition to SAR443579 administration every 4 weeks during maintenance/continued therapy period combined with venetoclax and azacitidine up to 21 maintenance/continued therapy cycles. When supported by PK data, alternative schedules may be tested. The DLT observation period is from the first administration of study treatment until the end of the 28th day. A participant in the escalation will be considered evaluable for DLT assessment if he/she complete the DLT observation period and receive at least 75% of the planned dose of SAR443579 and 75% of the adjusted dose of venetoclax and azacitidine during that period, or if a DLT occurs during the DLT observation period. Participants who discontinued early before the end of DLT observation period due to an adverse reaction will also be considered evaluable for DLT assessment.

A minimum of 3 DLT-evaluable participants will be treated per each DL for escalation-part. De-escalation to DL(-1) occurs if excessive toxicity observed at DL1. Recommendations for the dose level at which the next cohort of participants may be treated will be provided by mTPI-2. However, the final decision whether to move to the next DL, or stay at the current DL, or to evaluate alternative lower dose level will be determined by the Study Board based on evaluation of available safety data (including DLTs, AEs and SAEs), PK and PDy. If an alternative DL is chosen, a minimum of 3 participants will be enrolled in the chosen DL. Within the escalation part there will be at least 7 days between dosing of the first participant and all subsequent participants in each dose level. [redacted] Timing to initiate and dose schedule of such backfilling will be decided by the Sponsor based on totality of tolerability (both DLT and treatment emergent adverse events (TEAE) which occurred during and after completion of DLT observation period, PDy, PK, and preliminary anti-tumor activity as available. This backfilling may increase the total number of participants enrolled in escalation part.

At the end of escalation, a preliminary Recommended Dose(s) for Expansion (RDE) will be based on all available data including PK, PDy, preliminary efficacy, safety and tolerability of SAR443579 when combined with venetoclax and azacitidine.

Enrollment will be paused upon completion of Part 1: Dose Escalation. The available data including but not limited to safety, PK, PDy, and preliminary efficacy will be reviewed and the recommended doses and schedule for optimization will be selected by the study board. Enrollment in the Part 2: Dose optimization and Part 3: Dose expansion will be provided in a future protocol amendment.

Optimization/Expansion part: further details will be provided in future protocol amendment.

Participants will receive study treatment until documented disease progression, unacceptable adverse events, participant's decision to stop study treatment, or the participant meets other criteria for discontinuation per study protocol (whichever occurs first). Treatment duration will be up to approximately 27 cycles. The study treatment duration by participant will be approximately up to 2.5 years. The entire study duration is approximately close to 5 years.

Number of participants:

Escalation part: There is no formal sample size calculation in the escalation part. SAR443579 combined with venetoclax and azacitidine will be administered to participants with CD123 expressing ND-AML ineligible for IC. It is anticipated that approximately 3-6 DLT-evaluable participants per each DL may be enrolled in the escalation part with expected assessment of about [redacted] while intermediate DLs may be investigated in case of dose or schedule modifications. The actual sample size will vary depending on dose limiting toxicities (DLTs) observed, number of DLs actually explored and the number of participants enrolled that are not DLT-evaluable.

Optimization/Expansion part: further details will be provided in future amendment.

Note: Enrolled participants are all participants from screened participants who have been allocated to an intervention regardless of whether the intervention was received or not.

Study arms and duration:

Please refer to Figure 1.

Study intervention(s)

Investigational medicinal product(s)

SAR443579

- **For formulation and route of administration details, please refer to master protocol.**
- **Dose regimen:**
  - Induction: SAR443579 will be administered once weekly, ie, on D1, D8, D15, D22 of a 28-day cycle. Participants will receive at minimum 3 induction cycles prior to switching to maintenance/continued treatment. If CR/CRi/CRh is not achieved within 3 induction cycles, induction therapy may continue for three additional cycles (Cycle 3.1, 3.2, and 3.3) after discussion and agreement between the Investigator and the Sponsor.

- Maintenance/continued therapy: Once a participant achieves CR or CRi or CRh, and after a minimum of 3 induction cycles are completed SAR443579 will be administered IV on D1 of a 28-day cycle for up to 21 cycles. As additional clinical data emerges, the dosing schedule within the maintenance/continued therapy cycle may be further adjusted to potentially include more or less frequent dosing within the cycle.
- The IV dosing regimen will be weight-based; however, if a participant weight >133 kg, the participant's weight will be capped at 133 kg for dose calculations.

Venetoclax

- **Formulation:** Film-coated tablets containing 10, 50, 100 mg of venetoclax
- **Route(s) of administration:** Oral
- **Dose regimen:** The recommended dosage is 400 mg once daily after completion of the 4-day ramp-up dosing schedule (see Table 1 and Table 2).
- See venetoclax package insert for initial ramp-up phase in case of concomitant administration with CYP3A including P-gp Inhibitors (5).

Table 1 - Venetoclax day ramp-up dosing schedule

	venetoclax oral daily dose
Day 1	100 mg
Day 2	200 mg
Day 3 and beyond	400 mg orally once daily of each 28-day cycle

Table 2 - Management of venetoclax co-administration with CYP3A inhibitors

Inhibitor	Phase	Dose
Strong CYP3A inhibitor	Initiation and ramp-up dosing	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg or less
	Steady daily dose (After ramp-up dosing phase).	Reduce the Venetoclax dose to 100 mg or less (or by at least 75% if already modified for other reasons).
Moderate CYP3A inhibitor	All	Reduce the Venetoclax dose by at least 50%

Note: Please also refer to latest labelling information available and local standard of practices for management.

Azacitidine

- **Formulation:** Lyophilized powder for suspension for injection
- **Route(s) of administration:** IV or SC
- **Dose regimen:** 75 mg/m^2 intravenously or subcutaneously once daily on Days 1-7 of each 28-day cycle. A full 7 days of azacitidine is required, but as per institutional practice, a schedule of 5 days of daily dosing, followed by no dose received on the weekend, and

2 daily doses given again at the start of the next week, is allowed. The same schedule and route of administration should be used for each participant throughout the duration of treatment, when possible.

Auxiliary medicinal products (AxMP)

Please refer to the Section 6.1.2 Auxilliary medicinal products in Master protocol for common details and each Section 6.1.2 in substudy for details on SAR443579 premedication and auxiliary medicinal products (AxMP).

Devices: Not applicable.

Posttrial access to study medication: Not applicable.

Duration of study intervention

Study duration: The expected duration of the study treatment for a participant is approximately 2.5 years, provided the participant does not meet the criteria for stopping treatment with the study treatment. The study duration includes a screening period of up to 3 weeks (21 days), an induction treatment duration of 12 weeks (3 cycles of 28 days each) that may be extended to 24 weeks (6 induction cycles as maximum), a maintenance/continued therapy duration of 84 weeks (21 cycles of 28 days each), and an end of treatment (EOT) visit (30 days ±5 days) after the last study treatment administration or prior to initiation of further therapy, whichever comes first.

A trial participant will receive 3 induction cycles even if CR (complete remission), CRh (CR with partial hematologic recovery) and CRi (CR with incomplete hematologic recovery) is achieved prior to completion of 3 cycles (28 days per cycle). An increase or a decrease in the number of induction cycles may be recommended by the Study Board based on evaluation of available safety data including DLTs, AEs, SAE, clinical PK and PDy. If CR or CRi or CRh is not achieved within 3 induction cycles, induction therapy may continue for 3 additional cycles (Cycle 3.1, 3.2 and 3.3 - maximum of 6 inductions cycles is allowed) upon agreement between the Investigator and the Sponsor. Once a trial participant has achieved CR or CRi or CRh, the trial participant continues with maintenance/continued therapy cycles (28 days per cycle) up to a total of 21 cycles.

EOT visit: will occur at 30 days (+/-5 days) of the last study treatment administration or prior to initiation of future therapy. After the EoT participants will enter the follow-up period.

Follow- up: All ongoing related AEs or newly reported related AEs, and all SAEs regardless of causal relationship are to be followed at least every 30 days until resolution or stabilization.

Survival status of each participant will also be collected during the follow-up period that will occur every 3 months ±14 days to assess survival status. However, an updated survival status may be requested by the Sponsor at any time during the course of the study. Survival follow-up will continue until death, or the participant's request to discontinue from follow-up, or until the last participant to enter survival follow-up has been followed for 2 years from the last study treatment administration, or upon cancellation of survival follow-up at the discretion of the Sponsor at any timepoint.

Cut-off dates:

The first cut-off date will be at the end of the first cycle of the last participant treated and evaluable for DLT in the escalation part, in order to evaluate data from at least the first cycle for all participants when identifying the MTD, MAD, and preliminary RDE.

The second cut-off date will be when the last participant in the "optimization" part has completed 3 cycles of induction (or the required allowed additional induction cycles), has early discontinuation, or has reached CR, CRh or CRi, whichever occurs first, in order to assess malignancy response.

The third cut-off date will be when the last participant in the "expansion" part has completed 3 cycles of induction (or the required allowed additional induction cycles), has early discontinuation, or has reached CR, CRh or CRi, whichever occurs first, in order to assess malignancy response.

Different data extraction dates may apply depending on the timing of enrollments and data maturity.

The study completion date will be when the last participant in the "optimization/expansion" part has been followed for 24 months or until death (whichever occurs first), to document prolonged remission and survival rate at 2 years.

All primary analysis and key secondary analysis will be conducted at the third cut-off date. Safety results and efficacy results including but not limited to overall survival (OS), time to treatment failure (TTF) and event-free survival (EFS) will be updated at the study completion date. After the third cut-off date, participants can continue to receive IMP, if clinical benefit is observed, until permanent discontinuation criteria described in Section 7 are met, and will continue to undergo all assessments as per the study schedule of activities unless otherwise specified in the protocol. The reduction of some assessments including but not limited to PK, ADA and PDy may be considered based on the updated knowledge of IMPs and upon notification from the sponsor.

Statistical considerations:

Please refer to the master protocol for description of common statistical considerations.

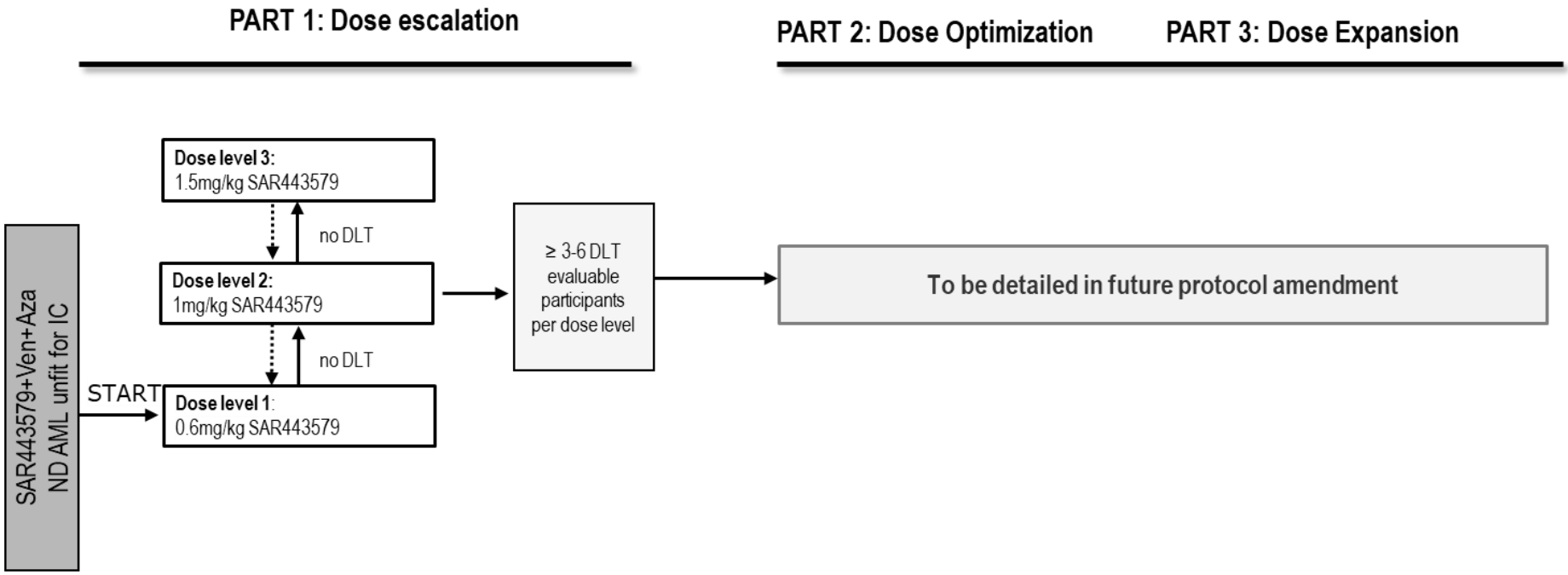
- Primary endpoint for dose escalation part: The primary endpoint is incidence of dose limiting toxicity (DLTs). All DLT modeling will be performed on the DLT evaluable population or those who experienced a DLT (dose escalation part). Statistical descriptive analysis will be used to summarize the incidence of DLT by dose level and overall.
- Primary endpoint for optimization part: CR rate per 2022 European Leukemia Net (ELN) criteria will be summarized with descriptive statistics. A 90% two-sided confidence interval will be computed using Clopper-Pearson method. Type, frequency, severity, seriousness, and relationship to the study treatment AEs according to the National Cancer Institute Common Terminology for Adverse Events (NCI-CTCAE) Version 5.0 and the American society for transplantation and cellular therapy (ASTCT) consensus grading will be summarized with descriptive statistics. Laboratory abnormality and AESI will be summarized by descriptive statistics.

- Primary endpoint for expansion part: CR rate per 2022 European Leukemia Net (ELN) criteria will be summarized with descriptive statistics. A 90% two-sided confidence interval will be computed using Clopper-Pearson method.
- Main secondary endpoints: Overall response rate (ORR), CRc rate, alternative CR rate, rate of HSCTs and minimal residual disease (MRD) rate will be summarized by using descriptive statistics. Time-to-event endpoints such as duration of CR, duration of CRc, duration of alternative CR, duration of overall response rate, EFS, TTF, OS will be summarized with Kaplan-Meier method. In case of the presence of competing risks, appropriate statistical methods (eg, the cumulative incidence function) will be used for some time-to-event endpoints. Selected efficacy analysis from above will also be provided for the escalation part. Rate of conversion from transfusion dependence to transfusion independence and rate of participants who are transfusion independent at baseline and remain independent during 56-day post-baseline period will be summarized by using descriptive statistics.

Data Monitoring/Other committee: No

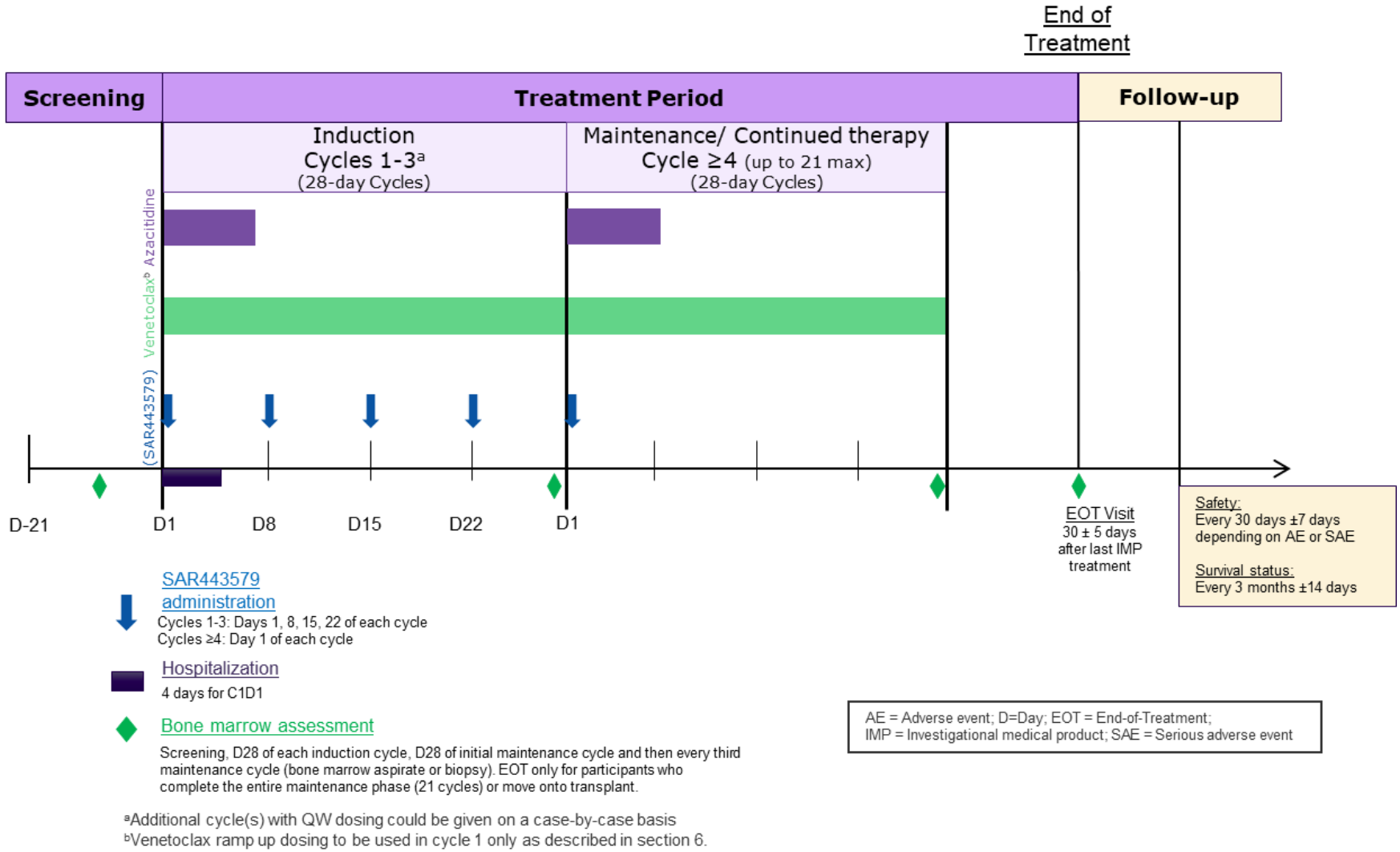
1.2 SCHEMA

Figure 1 - Graphical study design



Abbreviations: DLT, dose limiting toxicity; IC, intensive chemotherapy; ND AML, newly diagnosed acute myeloide leukemia; Aza, azacitidine; Ven, venetoclax

Figure 2 - Study scheme



1.3 SCHEDULE OF ACTIVITIES (SOA)

Evaluation	Screening[c]	Treatment												Follow up[g]
		Induction Cycles 1 to 3 (up to 6 induction cycles to achieve remission)[d]									Maintenance/continued therapy Cycles ≥4 (up to 21 maintenance/continued therapy cycles)[e]		EOT[f]	
	D-21 to D-1	D1[h]	D2	D3	D4	D5	D6	D7	D8; D15; D22[h]	D28	D1[h]	D28	30 days after last study treatment	Every 3 months
Visit window (days)		(±3)							(±1)	(±1)	(±3)	(±1)	(±5 days)	(±14 days)
CD123 Status [a]	X													
IRT contact[b]	X	X							X		X		X	
Informed consent[c]	X													
Inclusion/Exclusion Criteria	X													
Demography and Medical/Disease History[i]	X													
Performance status (ECOG)[j]	X	X									X		X	
Body weight[k]	X	X									X		X	
Height	X													
Full physical examination	X													
Directed physical examination[l]		X							X		X		X	
Vital signs[m]	X	X							X		X		X	
Treatment														
Bone marrow biopsy and/or aspirate[n]	X									X		X	X	
Azacitidine[o]		X	X	X	X	X	X	X			X			
Venetoclax[o]		X	X	X	X	X	X	X	X	X	X	X		

Evaluation	Screening[c]	Treatment												Follow up[g]
		Induction Cycles 1 to 3 (up to 6 induction cycles to achieve remission)[d]									Maintenance/continued therapy Cycles ≥4 (up to 21 maintenance/continued therapy cycles)[e]		EOT[f]	
	D-21 to D-1	D1[h]	D2	D3	D4	D5	D6	D7	D8; D15; D22[h]	D28	D1[h]	D28	30 days after last study treatment	Every 3 months
Visit window (days)		(±3)							(±1)	(±1)	(±3)	(±1)	(±5 days)	(±14 days)
SAR443579 administration[p]		X							X		X[q]			
Tumor lysis syndrome prophylaxis[r]	X	X	X	X	X	X								
Hospitalization[s]		X	X	X	X									
Biomarkers		See biomarkers table Section 1.3.3 and Section 1.3.4												
Laboratory and other investigations														
LVEF[t] using MUGA (preferred)/2D Echocardiogram w/Doppler	X	As clinically indicated												
12-lead ECG	X	As clinically indicated												
Pulmonary function test[u]	X													
Serum or urine pregnancy test[v]	X	X									X			
Blood Hematology/CBC[w]	X	X	X	X	X	X			X	X[y]	X	X[y]	X	
Blood chemistry[x]	X	X	X	X	X	X			X	X[y]	X	X[y]	X	
Coagulation[z]	X	As clinically indicated												
Urinalysis[aa]	X	As clinically indicated											X	
HIV and Hepatitis B and C screening[bb]	X													
CRP, ferritin[cc]	X	As clinically indicated												
PK/Immunogenicity		See PK and ADA flowcharts Section 1.3.1 and Section 1.3.2												

Evaluation	Screening[c]	Treatment												Follow up[g]
		Induction Cycles 1 to 3 (up to 6 induction cycles to achieve remission)[d]									Maintenance/continued therapy Cycles ≥4 (up to 21 maintenance/continued therapy cycles)[e]		EOT[f]	
	D-21 to D-1	D1[h]	D2	D3	D4	D5	D6	D7	D8; D15; D22[h]	D28	D1[h]	D28	30 days after last study treatment	Every 3 months
Visit window (days)		(±3)							(±1)	(±1)	(±3)	(±1)	(±5 days)	(±14 days)
Extramedullary leukemic localizations[dd]	X									X		X	X	
Other clinical assessments														
Concomitant medication[ee]	X	Continuous throughout the treatment period											X	
AE assessment[ff]	X	Continuous throughout the treatment period											X	X
First subsequent anti-cancer therapy[gg]													X	X
Survival status														X
Subject calendar/diary[hh]		X									X			
AML-QoL[ii]		X									X		X	
PGIS[ii]		X									X		X	
PGIC[ii]		X (except C1)									X		X	
PQATv2[ii]		X (C3 only)									X (C6 only)		X	

Abbreviations: AE = Adverse event; ADA = anti-drug antibodies AML = acute myeloid leukemia; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BM = bone marrow; CBC = complete blood count; CRP = c-reactive protein; CRS = cytokine release syndrome; CMV = cytomegalovirus; DLCo = diffusing capacity of carbon monoxide; ECOG = eastern cooperative oncology group; EOT = end of treatment; FU = follow-up; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GVHD = graft-versus-host disease; IgG = immunoglobulin G; IHC = immunohistochemistry; ICF = informed consent form; IRT = Interactive response technology ; LDL = low-density lipoprotein; NK = natural killer; MRD = minimal residual disease; NGS = next generation sequencing; PCR = polymerase chain reaction; PRO = patient reported outcome; SoC = standard of care.

a CD123 expression at screening, please refer to inclusion criteria 09.

b For all parts, one IRT call will be performed for each visit.. All efforts should be made to start study treatment within 3 days of randomization.

c Screening: ICF must be signed before any study-specific procedures are performed.

d Induction: If CR, CRh or CRi is not achieved within 3 induction cycles, induction therapy may continue for an additional 3 cycles (called cycle 3.1, 3.2, 3.3. Maximum total of 6 induction cycles) until CR, CRh or CRi is achieved. Once a trial participant has achieved CR, CRh or CRi, the trial participant must continue with maintenance/continued therapy cycles (28 days per cycle) up to a total of 21 cycles.

e Maintenance/continued therapy: Participant eligible for maintenance/continued therapy may receive SAR443579 on Day 1 every 28 days for up to 21 maintenance/continued therapy cycles.

f EOT: EOT is 30 days (+/-5 days) of the last study treatment administration or prior to initiation of further therapy, whichever comes first. EOT visit must be performed before initiation of new therapy.

g Follow up: Survival follow-up: Beyond 30 days after last study treatment all ongoing related AEs or new related AEs, and all the SAEs regardless of causal relationship are to be followed at least every 30 days (±7 days) until resolution or stabilization. In addition, survival status assessment of each participant will also be performed every 3 months ±14 days until death or the participant's request to discontinue from follow-up, or until the last participant to enter Survival Follow-up has been followed for 2 years from last study treatment administration, or upon cancellation of survival follow-up at the discretion of the Sponsor at any timepoint.

h Assessments on day of study treatment administration: Assessments can be done the day of study treatment administration or the day before, unless otherwise specified in the protocol. During the study treatment period, all assessments must be performed, and results should be reviewed by the Investigator prior to study treatment administration. Vital signs must be taken on the day of study treatment is administered. CBC and blood chemistry can be done the day before study treatment administered.

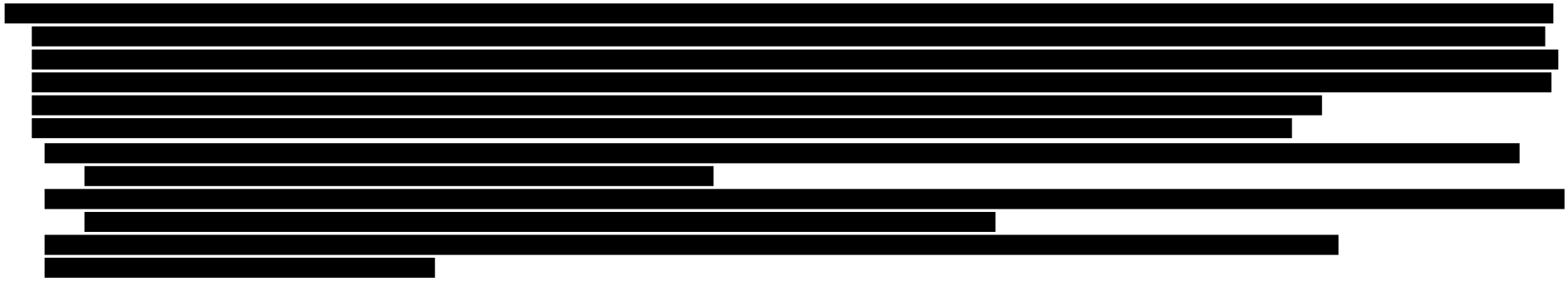
i Cytogenetic risk category per ELN 2022 should be recorded in the disease history, please refer to Table 16 in Appendix 15. For expansion part, this cytogenetic risk is considered as stratification factor, so it's mandatory to collect it for patients before their enrollment.

j Will be performed on day one of each cycle during treatment period.

k Weight: Weight is required at Screening, D1 of each cycle, and EOT. The total dose will be calculated based on the most recent weight available the day of the infusion preparation: the weight on the day of the infusion or the most recent weight assuming it was assessed in a reasonable time frame according to Investigator assessment. If the infusion is prepared with the most recent weight assessed in a reasonable time frame, this will not prevent to assess the weight on D1 of each cycle, which has to be recorded in the eCRF.

l Physical examination: Examination of major body systems, including cardiovascular, respiratory, neurologic, skin and digestive systems.

m Vital signs & Pulse Oximetry: Participants' vital signs (blood pressure, heart rate, respiratory rate, oxygen saturation and temperature) will be monitored. For SAR443579, vital signs will be taken 5 min (+/-5 min) before starting infusion, during infusion every 30 minutes (+/-15 minutes) during administration, end of infusion time, and 1 and 2 (+/-30 minutes) hours following completion of SAR443579 administration. Vital signs monitoring shall be made continuously if CRS Grade ≥2 develops.



o Azacitidine + venetoclax: Azacitidine will be administered at a dose of 75 mg/m^2 on days 1 through 7 days of each cycle. In Cycle 1, a full 7 days of azacitidine is required, but as per institutional practice, a schedule of 5 days of daily dosing, followed by no dose received on the weekend, and 2 daily doses given again at the start of the next week, is allowed. The same schedule and route of administration should be used for each participant throughout the duration of treatment, when possible. Alternate schedules of azacitidine administration may be evaluated when clinically indicated or as per institutional practice. Venetoclax will be administered at a dose of 100 mg on C1D1, 200 mg on C1D2, 400 mg on C1D3 and all subsequent days; 400 mg of venetoclax will be administered on all subsequent days and cycles. Venetoclax dose is adjusted due to interaction with azole antifungal prophylaxis. Venetoclax dosing will need to be adjusted if participant is also taking other drugs with potential for interactions. See dose modifications, drug interactions and concurrent medication sections below (Section 6.6; Section 6.9).

p SAR443579 administration: Specific instructions for the preparation and administration of SAR443579 are provided in the Product Management Manual. Max duration of treatment 108 weeks (27 cycles total, including induction and maintenance/continued therapy). For premedication, please refer to Section 6.1.2 of the Master protocol and substudy.

q D1 only for "Maintenance/continued therapy ".

r Tumor lysis syndrome prophylaxis: Prophylaxis for tumor lysis syndrome, including adequate hydration and anti-hyperuricaemic agents, should be initiated prior to C1D1 and continue through C1D4 and is left to Investigator judgment for further administration. Blood chemistry (potassium, uric acid, phosphorus, corrected calcium, and creatine) should be assessed and corrected prior to C1D1. Blood chemistries should be reassessed 6 to 8 hours after C1D1, C1D2, C1D3 and C1D4, and 24 hours after C1D4 for SAR443579, venetoclax and azacitidine. For participants with risk factors for tumor lysis syndrome, consider increased monitoring and/or reducing venetoclax starting dose.

s Hospitalization: Participants will be monitored inpatient for 4 days after the first SAR443579 administration on Cycle 1 Day 1. Hospitalization may be extended at the Investigator's discretion, during cycle 1, for cycle 2 and beyond.

t Echocardiogram: Echocardiogram done in the previous 2 months from first study treatment administration is acceptable.

u Pulmonary function test: Pulmonary function test is only required if LVEF, DLCO or FEV1 are used to confirm patient's eligibility >/= 18 to 74 years of age.

v Serum or urine pregnancy test: Women of childbearing potential must have a negative serum or urine pregnancy test result within 7 days prior to starting SAR443579 dosing.

w Hematology: To be performed at screening and repeated within 1 day prior to first study treatment administration if screening test >7 days of first study treatment administration. On days of SAR443579 infusion, sample must be obtained prior to infusion (D1, D8, D15 and D22) and prior to each new dose during ramp-up phase on Day 1 through 5 (hemoglobin, hematocrit, white blood cell count with differential, percentage of blasts, platelet count, RBC count and indices). At screening and EOT, hematology assessments need to be synchronized and performed on the same day (if feasible) with bone marrow and whole blood assessments and indices. Assessment of blasts by morphology on days of disease assessments or suspected disease relapse (ie, Screening, D28 of induction and maintenance/continued therapy cycles, respectively), for all other timepoints as per local standards. Assessment of blasts by morphology may be performed up to 3 days after bone marrow assessment, but prior to next study treatment administration. Monitor CBC of Grade 3-4 neutropenia through resolution as per Investigator's discretion.

x Blood chemistry: To be performed at screening and repeated within 1 day prior to first study treatment administration if screening test >7 days of first study treatment administration. Liver tests: SGOT (AST), SGPT (ALT), GGT, total bilirubin, direct bilirubin, alkaline phosphatase (ALP). Renal function tests and electrolytes: Sodium, potassium, corrected calcium, magnesium, phosphorus (phosphate), bicarbonate, total urea or blood urea nitrogen depending on local practice, creatinine, and estimated creatinine clearance (MDRD), uric acid, glucose (should be fasting condition). Others: LDH, albumin, and total protein. For Cycle 1, blood chemistry will be evaluated on Days 1 through 5 and Days 8, 15 and 22; for subsequent cycles, blood chemistry will be evaluated on the day of SAR443579 dosing. Blood chemistry will also be monitored for signs of tumor lysis syndrome from C1D1 to C1D4 and 24hours after C1D4 as outlined in footnote [r]. A scheduled blood chemistry assessment can serve as part of the TLS monitoring if performed within the required time period per protocol.

y If the blood assessment has been performed Day 28, it does not need to be redone on Day 1 of the next cycle.

z Coagulation: Coagulation includes international normalized ratio (INR), prothrombin time (PT) and activated partial thromboplastin time (aPTT).

aa Urinalysis: Dipstick for pH, protein, glucose, blood, ketones, bilirubin, urobilinogen, nitrite, and leukocyte esterase at baseline, then as clinically indicated and at EOT.

bb Hepatitis viral and HIV serologies: Screening with serological tests for hepatitis B, and C to be done prior to enrollment (HBsAg, anti-HBs, anti-HBc [total and IgM], anti-HCV, HCV RNA level) if not performed within 1 year. Participants with anti-HBc positive (HBsAg positive participants being not eligible), HBV DNA testing by PCR will also be done at Screening. In case HBV vaccination will be started before first study treatment administration, anti-HBs should be monitored at 1, 2, and 3 months after end of vaccination. HIV serology will be tested at Screening only for participants of countries where required as per local regulations.

cc CRP and ferritin: Will be collected at screening and then as clinically indicated, particularly it should collect locally in case of CRS events as per institutional procedures.

dd Extramedullary leukemic localizations at physical examination: Evaluation for hepatomegaly, splenomegaly, lymphadenopathy, dermal involvement, gingival infiltration, at screening, for disease assessment and as clinically indicated.

ee Generally, the period of collection of concomitant medications extends from the signature of the ICF until EOT, and post EOT if associated with ongoing SAEs or ongoing treatment related. Receipt of any transfusions (platelet or red blood cell) which should be recorded 28 days prior to the receipt of study treatment.

ff AE assessment: Severity will be graded according to NCI-CTCAE v 5. ICANS and CRS will be graded using ASTCT criteria. All AEs, including adverse events of new onset, as well as worsening of baseline signs and symptoms will be collected throughout study treatment period, from the signing of the informed consent form (ICF) until 30 days following last administration of study treatment. SAEs, AESIs, pregnancy, and overdose reports should be assessed and reported as described in the protocol. Beyond 30 days of last study treatment, all ongoing related AEs or new related AEs, and all ongoing SAEs regardless of causal relationship, are to be followed until resolution or stabilization.

gg For participants for whom the first subsequent anticancer therapy is HSCT, limited additional data (relapse and MRD status) will be collected.

hh Diaries will be dispensed upon discharge from the hospital.

ii Questionnaires will be administered during expansion part only. Questionnaires will be administered on day 1 of the corresponding cycle and will be completed by the participants prior to discussing their heath/disease status, and prior to study treatment administration, or other study-related procedures. AML-QoL and PGIS will be provided on Day 1 of every cycle and at EOT. PGIC: Questionnaire will be provided on Day 1 of every cycle (except for Cycle 1) and at EOT. PQATv2: Questionnaire will be provided on Day 1 of Cycles 3, 6 and at EOT. Estimated time to complete AML-QoL is 2-3 minutes, for PGIS and PGIC is one minute each and for PQATv2 is 4 minutes.

1.3.1 All parts: PK and ADA flowchart (Cycle 1)

Cycle		Cycle 1																			
Day Within Cycle		**D1**							**D2**	**D4**	**D8**								**D9**	**D15**	**D22**	**D28**
Indicative clock time (hh:mm 24h clock)		**08:00**	**09:30**	**10:00**	**11:00**	**12:00**	**14:00**	**19:00**	**08:00**	**08:00**	**08:00**	**09:30**	**10:00**	**11:00**	**12:00**	**14:00**	**17:00**	**19:00**	**08:00**	**08:00**	**08:00**	**08:00**
Treatment administration																						
Venetoclax	PO administration (daily)	X							X	X	X								**X**	X	X	X
Azacitidine	SC or IV administration		X—X (30min)						X	X		X—X (30min)							-	-	-	-
SAR443579	IV administration			X---	---X				-	-			X---	---X					-	X	X	-
Pharmacokinetics and Immunogenicity																						
Venetoclax PK (plasma)	**Sample Theoretical Time (Ref Drug intake)**	**0H**		**2H**	**3H**	**4H**	**6H**	**11H**	**24H**	**0H**	**0H**		**2H**	**3H**	**4H**	**6H**	**9H**	**11H**	**24H**	**0H**	**0H**	**0H**
	Time window	Within 48h before dosing		±10min	±30min	±30min	±1h	±1h	-3h[b]	-3h[b]	-3h[b]		±10min	±30min	±30min	±1h	±30 min	±1h	-3h[b]	-3h[b]	-3h[b]	-3h[b]
	PK venetoclax	PV00[a,b]		PV01	PV02	PV03	PV04	PV05	PV06[b]	PV07[b]	PV08[a,b]		PV09	PV10	PV11	PV12	PV13	PV14	PV15[b]	PV16[b]	PV17[b]	PV18[b]
Azacitidine PK (plasma)	**Sample Theoretical Time (Ref SOI or SC start)**		**0H (SC) or SOI (IV)**	**0H30 (SC) or EOI (IV)**	**1H30**	**2H30**	**4H30**	**9H30**	-	-		**0H (SC) or SOI (IV)**	**0H30 (SC) or EOI (IV)**	**1H30**	**2H30**	**4H30**	**7H30**	**9H30**	-	-	-	-
	Time window		Within 48h before dosing	+/-5 min	±30 min	±30 min	±30 min	±30 min	-	-			+/-5 min	±30 min	±30 min	±30 min	±30 min	±30 min	-	-	-	-
	PK azacitidine[c]		PZ00[a,b]	PZ01[d]	PZ02	PZ03	PZ04	PZ05	-	-		PZ06[a,b]	PZ07[d]	PZ08	PZ09	PZ10	**PZ11**	**PZ12**	-	-	-	-

Cycle		Cycle 1																			
Day Within Cycle		**D1**							**D2**	**D4**	**D8**								**D9**	**D15**	**D22**	**D28**
SAR443579 PK/ADA (plasma)	**Sample Theoretical Time (Ref. SOI)**			**SOI**	**EOI**	**EOI +1H**	**EOI +3H**	**EOI +8H**	**24H**	**72H**			**SOI**	**EOI**	**EOI+1H**	**EOI+3H**	**EOI+6H**	**EOI+8H**	**24H**	**0H**	**0H**	**0H**
	Time window (Ref.: Theoretical sampling time)			Within 48h before SOI	±10min	±10min	±30min	±1h	±8h	48-96h[b]			±8h	±10min	±10min	±30min	±1h	±1h	±8h	±8h	±8h	±8h
	PK SAR443579			P00[a,b]	P01[e]	P02	P03	P04	P05[b]	P06[b]			P07[a,b]	P08	P09	P10	P11	P12	P13[b]	P14[b]	P15[b]	P16[b]
	ADA			AB00																AB01		AB02
Tocilizumab (serum)	PK	In case of administration of tocilizumab, PK samples of tocilizumab will be collected as described in Section 6.6.5.3																				

a Predose samples for azacitidine and the SAR443579 can be collected at the same time as predose sample for venetoclax.

b Predose sample must be collected before next administration and even if the next administration is not done or delayed. No additional/ repeat samples are needed prior to recommencing treatment if treatment is delayed. D28 samples may be drawn on D1 of the subsequent cycle before the start of the infusion.

c D8 PK sample for azacitidine only if participants received azacitidine on Day 8.

d EOI sample should be collected at the actual end of infusion if IV administration or 30min post dose if SC administration.

e EOI sample should be taken at the actual end of infusion.

Note: PK sampling for SAR443579, venetoclax, azacitidine may be reduced or removed during the study based on the knowledge of the PK of SAR443579 and/or drug-drug interaction profiles with azacitidine and venetoclax upon notification of the Sponsor.

1.3.2 All parts: PK and ADA flowchart (Cycle 2 and beyond)

Cycle	Cycle 2						From Cycle 3 and subsequent additional induction cycles if any(C3.1, C3.2, C3.3)	From 1st Maintenance/continued therapy cycle and every 3rd cycle thereafter	EOT (±5 days)
Day Within Cycle	**D1**		**D8**	**D15**	**D22**	**D28**	**D28**	**D28**	
Study treatment administration (IV infusion)									
SAR443579	--X		X	X	X	X	X	X	
Time (decimal hours, Ref. SOI)	**EOI**	**EOI +6h**	**SOI**	**SOI**	**SOI**	**168H**	**168H**	**648H**	
Time window (Ref.: Theoretical sampling time)	±10min	±1h	-8h	-8h	-8h	-8h	-8h	-72h	
PK SAR443579 (plasma)	P01 *a*	P02	P03	P04	P05	P06 *b*	P00*b*	P00*b*	
PK tociluzumab	In case of administration of tocilizumab, PK samples of tocilizumab will be collected as described in Section 6.6.5.3								
Immunogenicity									
ADA (plasma)						AB00 *b*	AB00 *b*	AB00 *b*	AB00

Abbreviations: AB= antibody, ADA = anti-drug antibody, C = Cycle, D = day; EOI = end of infusion, EOT = end of treatment, IV = intravenous, PK = pharmacokinetic, P = Plasma.

a SAR443579: EOI sample should be taken at the actual end of infusion.

b Predose sample must be collected before next administration and even if the next administration is not done or delayed. No additional/ repeat samples are needed prior to recommencing treatment if treatment is delayed. D28 samples may be drawn on D1 of the subsequent cycle (eg. Cycle 3 Day 28 P00 PK sample must be collected before administration of Cycle 4 Day 1).

Note: PK sampling for SAR443579, may be reduced or removed during the study based on the knowledge of the PK of SAR443579 upon notification of the Sponsor.

1.3.3 All parts PDy flowchart (Cycle 1)

Cycle		Cycle 1 (Induction)														
Day Within Cycle	**Screening**	**D1**				**D2**	**D4**	**D8**			**D09**	**D15**			**D22**	**D28**
Study treatment administration (IV infusion)																
SAR443579		X----X						X				X			X	
Time (decimal hours, Ref. SOI)	**D-21 to D-1**	**SOI**	**EOI**	**EOI+1H**	**EOI+3H**	**24H**	**72H**	**168H**	**EOI+1H**	**EOI+3H**	**24H**	**168H**	**EOI+1H**	**EOI+3H**	**168H**	**SOI**
Time window (Ref.: Theoretical sampling time)		Within 48h before SOI	±10min	±10min	±30min	±8h	±24h	±48h	±10min	±30min	±8h	±8h	±10min	±30min	±8h	±168h
Baseline																
[redacted]																
Pharmacodynamics																
[redacted]																

Cycle		Cycle 1 (Induction)							
Day Within Cycle	Screening	D1	D2	D4	D8	D09	D15	D22	D28
[redacted]									

Abbreviations: AB = antibody, ADA = anti-drug antibody, BM = bone marrow, C = cytokine, CRS = cytokine release syndrome, D = day; DL = dose level, EOI = end of infusion, FISH = fluorescent in situ hybridization, IHC = Immunohistochemistry, study treatment = investigational medicinal product, IV = intravenous, MD = myelodysplasia, P = Plasma, PDy = pharmacodynamic, PK = pharmacokinetic MRD = Minimal residual disease, P = Plasma, SOI = start of infusion, WB = whole blood.

a Baseline IgG sample should be taken at any time between screening and D1 but prior to first dosing, but not in subsequent cycles.

b Pre-dose sample must be collected before next administration and even if the next infusion is not done or delayed. No additional/ repeat samples are needed prior to recommencing treatment if treatment is delayed.

[redacted]

1.3.4 All parts PDy flowchart (Cycle 2 and beyond)

Cycle	Cycle 2 (Induction)						From Cycle 3 and subsequent additional induction cycles if any (C3.1, C3.2, C3.3)[d]	From 1st Maintenance/continued therapy cycle and every 3rd cycle thereafter (Maintenance/continued therapy)[e]	EOT (±5 days)
Day Within Cycle	**D1**		**D8**	**D15**	**D22**	**D28 (C3D1)**	**D28**	**D28**	
Study treatment administration (IV infusion)									
SAR443579	--X		X	X	X	X	X	X	
Time (decimal hours, Ref. SOI)	**EOI**	**EOI +6h**	**SOI**	**SOI**	**SOI**	**168H**	**168H**	**648H**	
Time window (Ref.: Theoretical sampling time)	±10min	±1h	±8h	±8h	±8h	±168h	±168h	±168h	
[redacted]									

Cycle	Cycle 2 (Induction)					From Cycle 3 and subsequent additional induction cycles if any (C3.1, C3.2, C3.3)[d]	From 1st Maintenance/continued therapy cycle and every 3rd cycle thereafter (Maintenance/continued therapy)[e]	EOT (±5 days)
Day Within Cycle	**D1**	**D8**	**D15**	**D22**	**D28 (C3D1)**	**D28**	**D28**	
[redacted]								

Abbreviations: AB = antibody, ADA = anti-drug antibody, BM = bone marrow, C=cytokine, CRS = cytokine release syndrome, D = day; DL = dose level, EOI = end of infusion, EOT = end of treatment, FISH = fluorescent in situ hybridization, IHC = Immunohistochemistry, study treatment = investigational medicinal product, IV= intravenous, MD = myelodysplasia, P = Plasma, PDy = pharmacodynamic, PK = pharmacokinetic, MRD = Minimal residual disease, P = Plasma, SOI = start of infusion, WB = whole blood.

a Pre-dose sample must be collected before next administration and even if the next infusion is not done or delayed. No additional/ repeat samples are needed prior to recommencing treatment if treatment is delayed.

[redacted]

[redacted]

transplant. Sample collection of bone marrow (including solid biopsy for morphology & % Blasts (local assessment); IHC (central assessment, expansion only) and aspiration for morphology & % Blasts; Blast/Immuno-phenotyping (central assessment); Genomics including MRD & Transcriptomics (central assessment) and whole blood (for local hematology and Blast/Immuno-phenotyping (central assessment); Genomics including MRD &Transcriptomics (central assessment) can be done within 60 days +/-7 days after last study treatment in maintenance/continued therapy or before transplant.

g MRD sample for flow cytometry will be collected from all patients at screening, and further on only from patients with confirmed CR, CRh or CRi during subsequent bone marrow aspirations.

Note 1: The sampling time-points for PDy including Cytokines may be reduced during the course of the study based on the updated knowledge of drug behavior, upon notification from the Sponsor.

2 INTRODUCTION

AML is a hematological malignancy characterized by clonal expansion of immature blast cells in the bone marrow, peripheral blood and extramedullary tissue (6). It is the most common form of acute leukemia in adults with 20 380 new cases estimated in the United States in 2023. It is a heterogenous disease and prognosis varies widely among different clinical subtypes. AML primarily affects the elderly population, with an average age of diagnosis of 69 years and roughly one third of patients being diagnosed at over 75 years of age (7).

Standard of care treatment for ND-AML patients who are medically fit is intensive induction chemotherapy typically involving cytarabine in combination with an anthracycline agent such as daunorubicin (known as 7 + 3 regimen), followed by consolidation therapy with high dose cytarabine. Disease in elderly patients is biologically distinct from other disease subtypes, exhibiting reduced responsiveness to chemotherapy, low remission rates and lower overall survival. Higher prevalence of unfavorable cytogenetics, prior treatment for other malignancies and multidrug resistance all contribute to the poorer outcomes observed in older patients. Further, elderly AML patients often present with a significant number of comorbidities and compromised organ function that reduce the patient's capacity to tolerate intensive chemotherapy.

ND-AML patients who cannot tolerate intensive chemotherapy are treated with lower intensity chemotherapy regimens such as single agent azacitidine or low intensity decitabine. More recently, clinical studies have demonstrated improved treatment outcomes when azacitidine or low dose decitabine is combined with the BCL-2 inhibitor venetoclax, and these combination therapies have emerged as the new standard of care in this patient population.

2.1 STUDY RATIONALE

The goal of developing SAR443579 is to provide a safe and efficacious therapy for the treatment of CD123-expressing hematological malignancies. Combination of SAR443579 with standard-of-care treatment with venetoclax and azacitidine may result in improved outcomes for patients with CD123 expressing ND-AML who are ineligible for intensive chemotherapy.

In patients with previously untreated AML who were not eligible for intensive chemotherapy, treatment with azacitidine plus venetoclax was efficacious and achieved complete remission in 36.7% of patients (1). Despite this favorable response rate, a substantial proportion of patients do not derive therapeutic benefit as a result of refractory disease or relapse after initial response. Patients with relapsed or refractory disease tend to harbor disease with adverse risk cytogenetic profile or co-occurring mutations in genes such as TP53, N/KRAS, FLT3, and/or KIT (8). Combining standard of care treatment with novel agents that are safe and effective can improve front-line outcomes and improve quality of life, particularly for older patients less likely to tolerate intensive chemotherapy.

Combination of azacitidine and venetoclax with immune cell engagers may improve clinical outcomes for AML patients and is supported by available preclinical data. In vitro studies underscore the potential for venetoclax to enhance NK-mediated killing of AML by modulating the NKG2D pathway (3). The human AML cell lines THP-1 and HL60 upregulated NKG2D ligands ULBP1, ULBP2 and ULBP3 following treatment venetoclax. Further, venetoclax treatment increased expression of the receptor NKG2D on human primary NK cells without inducing NK cell apoptosis or growth inhibition. Consistent with activation of NKG2D pathway, treatment with venetoclax increased NK cell degranulation, IFNγ and granzyme B production, and ultimately resulted in increased cytotoxicity against human AML cells in vitro. In addition, in vitro data show no effect of venetoclax and azacitidine on NK cell viability; and the triplet combination of azacitidine + venetoclax + SAR443579 shows some increase in tumor cell line killing vs venetoclax and azacitidine (MOLM-13) (unpublished data). The improved antileukemic activity observed upon combination of NK cells with azacitidine and venetoclax in vitro support further investigation of their combination with NK cell engaging immunotherapies.

The ability of NKCE to mediate their therapeutic effects may rely on a sufficient pool of functional immune cells to clear malignant cells. Importantly, no changes in the abundance of peripheral NK cells were observed in AML patients who received short-term treatment with venetoclax (4).

2.2 BACKGROUND

2.2.1 Venetoclax + azacitidine

Azacitidine is chemical analog of the nucleoside cytidine. It functions as an anticancer agent by inhibiting DNA methylation, resulting in reversal of methylation-mediated silencing of tumor suppressor genes that prevent uncontrolled cell growth (9). Azacitidine is an approved therapy for the treatment of myelodysplastic syndromes and AML.

BCL-2 is one member of the large family of BCL-2 family proteins that function to regulate the process of cell death. BCL-2 promotes cell survival by inhibiting apoptosis and its expression is dysregulated in hematological and solid malignancies. Overexpression of BCL-2 is observed in AML cells and has been implicated in promoting their maintenance and survival. Further, high expression of BCL-2 in AML cells is associated with poor response to chemotherapy. Venetoclax is a small molecule inhibitor of BCL-2 and has shown promise in the treatment of patients with AML who are unfit for intensive chemotherapy. As a single agent, venetoclax showed modest results in the treatment of relapsed/refractory AML or untreated AML in a small cohort (n = 32) of patients who were unfit for intensive therapy (10). The utility of venetoclax increases substantially when used in a combination regimen.

When combined with a hypomethylating agent (eg. Azacitidine and Decitabine), venetoclax has proven to be a highly effective and well-tolerated drug, and established itself as a new standard for treating AML in patients who are unfit for standard intensive therapy.

As shown in the Phase 3 VIALE-A study, which showed survival benefit when azacitidine was combined with venetoclax, compared to azacitidine alone (1, 11). Four hundred and thirty-one patients with untreated AML who were unfit for intensive therapy were randomized to receive

azacitidine and venetoclax or azacitidine alone. The combination therapy resulted in a composite complete remission (CR+CRi) rate of 66%, compared to 28% in the azacitidine-only group (P<0.001) and occurred early, after a median of 1 cycle, and was durable (median of 17.5 months). Compared to azacitidine alone, there was no increase in 30-day mortality despite existing hematologic toxicity in the combination therapy group and VIALE-A established azacitidine and venetoclax combination therapy as the standard of care for this population (1, 12).

2.2.2 SAR443579

Please refer to master protocol.

2.3 BENEFIT/RISK ASSESSMENT

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of SAR443579 may be found in the Investigator's brochure (IB).

2.3.1 Risk assessment

2.3.1.1 SAR443579

Please refer to the master protocol for risk assessment for SAR443579.

Risk assessment of SAR443579 when combined with venetoclax and azacitidine results from anticipated risks for SAR443579 and from the label information (USPI and SmPC) for VENCLYXTO/VENCLEXTA® (venetoclax) and VIDAZA® (azacitidine), taking into account potential overlapping risks. The available safety data for venetoclax and azacitidine, along with proposed mitigation strategies are summarized below and also provided in appendix Section 10.11, Table 14 and Section 10.12, Table 15.

2.3.1.2 Venetoclax

Venetoclax is a potent, orally bioavailable small molecule inhibitor of the anti-apoptotic protein BCL-2. BCL-2 over-expression in AML has been implicated in the survival and maintenance of AML cells and a potential resistance mechanism to chemotherapeutics.

The important identified risks for venetoclax include the following: tumour lysis syndrome, neutropenia, infections, immunizations, embryo-fetal toxicity and concomitant use of CYP3A inducers.

The most common adverse reactions (incidence ≥20%) in patients with AML treated in clinical trials with the hypomethylating agent azacitidine are: thrombocytopenia, neutropenia, febrile neutropenia, nausea, diarrhoea, vomiting, anaemia, fatigue, pneumonia, hypokalaemia, and decreased appetite. The most common adverse reactions (incidence ≥20%) in patients with AML treated in clinical trials with the hypomethylating agent decitadine are: thrombocytopenia, febrile neutropenia, nausea, haemorrhage, pneumonia, diarrhoea, fatigue, dizziness/syncope, vomiting, neutropenia, hypotension, hypokalaemia, decreased appetite, headache, abdominal pain, and anaemia.

The most frequently reported serious adverse reactions (≥5%) in patients receiving venetoclax in combination with azacitidine were febrile neutropenia, pneumonia, sepsis and haemorrhage. The most frequently reported serious adverse reactions (≥5%) were febrile neutropenia, pneumonia, bacteraemia and sepsis.

Venetoclax is predominantly metabolised by CYP3A. There are multiple interactions to be noted with other medical products and other forms of interaction. Please see Section 10.13.

Please refer to the country-approved product labeling (eg, United States Package Insert [USPI], Summary of Product Characteristics [SmPC]) for venetoclax for more detailed prescribing information.

2.3.1.3 Azacitidine

Azacitidine, belongs to the group 'anti-metabolites'. Azacitidine is an analogue of cytidine, which means that it is incorporated into the genetic material of cells (RNA and DNA). It is thought to work by changing the way the cell turns genes on and off and also by interfering with the production of new RNA and DNA. These actions are expected to correct problems with the maturation and growth of blood cells in the bone marrow that cause myelodysplastic disorders, and to kill cancerous cells in leukemia.

The important identified risks of azacitidine include the following: haematological toxicity (anaemia, neutropenia, and thrombocytopenia, particularly during the first 2 cycles), hepatic impairment, renal impairment, cardiac and pulmonary disease, necrotizing fasciitis, differentiation syndrome (also known as retinoic acid syndrome) and embryo-fetal toxicity.

In adult population with MDS, CMML and AML (20% - 30% marrow blasts), adverse reactions considered to be possibly or probably related to the administration of azacitidine have occurred in 97% of patients. The most common serious adverse reactions noted from the pivotal study (AZA PH GL 2003 CL 001) included febrile neutropenia (8.0%) and anaemia (2.3%), which were also reported in the supporting studies (CALGB 9221 and CALGB 8921) (13). Other serious adverse reactions from these 3 studies included infections such as neutropenic sepsis (0.8%) and pneumonia (2.5%) (some with fatal outcome), thrombocytopenia (3.5%), hypersensitivity reactions (0.25%) and haemorrhagic events (eg, cerebral haemorrhage [0.5%], gastrointestinal haemorrhage [0.8%] and intracranial haemorrhage [0.5%]). The most commonly reported adverse reactions with azacitidine treatment were haematological reactions (71.4%) including thrombocytopenia, neutropenia and leukopenia (usually Grade 3-4), gastrointestinal events (60.6%) including nausea, vomiting (usually Grade 1-2) or injection site reactions (77.1%; usually Grade 1-2).

In adult population aged 65 years or older with AML with >30% marrow blasts, the most common serious adverse reactions (≥10%) noted from AZA-AML-001 within the azacitidine treatment arm included febrile neutropenia (25.0%), pneumonia (20.3%), and pyrexia (10.6%). Other less frequently reported serious adverse reactions in the azacitidine treatment arm included sepsis (5.1%), anaemia (4.2%), neutropenic sepsis (3.0%), urinary tract infection (3.0%), thrombocytopenia (2.5%), neutropenia (2.1%), cellulitis (2.1%), dizziness (2.1%) and dyspnoea (2.1%). The most commonly reported (≥30%) adverse reactions with azacitidine treatment were

gastrointestinal events, including constipation (41.9%), nausea (39.8%), and diarrhoea (36.9%; usually Grade 1-2), general disorders and administration site conditions including pyrexia (37.7%; usually Grade 1-2) and haematological events, including febrile neutropenia (32.2%) and neutropenia (30.1%; usually Grade 3-4).

Please refer to the country-approved product labeling (eg, United States Package Insert [USPI], Summary of Product Characteristics [SmPC]) for azacitidine for more detailed prescribing information.

2.3.1.4 SAR443579 combined with venetoclax and azacitidine

Combining SAR443579 with venetoclax and azacitidine may lead to an increased frequency and/or severity of adverse events (AEs) related to AEs which occur for each individual agent separately, or in combination (venetoclax + azacitidine). Specifically, the combination my lead to increased frequency and/or severity of overlapping AEs: tumor lysis syndrome, bone marrow suppression (anemia, neutropenia, thrombocytopenia) and infections. Finally, the combination of SAR443579 with venetoclax and azacitidine may lead to new AEs that do not occur for each individual agent separately, or in combination.

2.3.2 Benefit assessment

The benefit of SAR443579 in combination with venetoclax and azacitidine has not yet been demonstrated in the clinical setting. The mechanism of action (MOA) of SAR443579 with venetoclax and azacitidine may be synergistic with leading to deeper and/or more durable clinical responses.

2.3.3 Overall benefit/risk conclusion

More detailed information about the expected benefits of SAR443579 may be found in the master protocol.

Taking into account the measures taken to minimize risk to participants in this study, the potential risks identified in association with SAR443579 combined with venetoclax and azacitidine are justified by the anticipated benefits that may be afforded to participants with AML.

3 OBJECTIVES, ENDPOINTS, AND ESTIMANDS

Table 3 - Objectives and endpoints

Objectives	Endpoints
Primary	
• Escalation part: To determine the preliminary recommended dose(s) for optimization of SAR443579 when combined with venetoclax and azacitidine in participants with CD123 expressing ND-AML ineligible for intensive chemotherapy.	• Incidence of dose limiting toxicities (DLTs).Incidence of dose limiting toxicities (DLTs).
• Optimization part: To determine the RDE of SAR443579 with venetoclax and azacitidine in participants with CD123 expressing ND-AML ineligible for intensive chemotherapy (IC).	• Overall safety including AEs, SAEs, AESIs, laboratory abnormalities and preliminary anti-tumor activity.
• Expansion part: To assess the anti-tumor activity of SAR443579 at the identified RDE combined with venetoclax and azacitidine in participants with CD123 expressing ND-AML ineligible for intensive chemotherapy.	• Complete Remission (CR) rate: proportion of participants who have a CR (Complete Remission) determined by the Investigator according to 2022 European Leukemia Net (ELN) recommendations for diagnosis and management of AML.
Secondary	
• To assess overall safety and tolerability profile of SAR443579 when combined with venetoclax and azacitidine in participants with CD123 expressing ND-AML ineligible for IC (all parts).	• Incidence of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), clinically significant laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).Incidence of treatment emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events of special interest (AESIs), clinically significant laboratory abnormalities according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v 5.0 and American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading for cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).
• To assess minimal residual disease (MRD) in participants achieving a CR, CRh or CRi (expansion part).	• Percentage of participants with Minimal residual disease as defined by 2022 ELN recommendations for AML.
• To characterize the PK of SAR443579, venetoclax and azacitidine (all parts).	• PK parameters of SAR443579 (C_{trough}), venetoclax and azacitidine (C_{max} and AUC).

Objectives	Endpoints
• To evaluate the potential immunogenicity of SAR443579 (all parts). • To assess additional parameters of antitumor activity of SAR443579 at the RDE in combination with venetoclax and azacitidine (expansion part).	• Incidence anti-drug antibody (ADA) against SAR443579. • Composite Complete Remission (CRc) rate: proportion of participants who have a CR (Complete Remission) + CRh (complete remission with partial hematologic recovery) + CRi (Complete Remission with Incomplete Hematologic Recovery) determined by the Investigator according to 2022 European Leukemia Net (ELN) recommendations for diagnosis and management of AML. (CRc = CR + CRh + CRi)Composite Complete Remission (CRc) rate: proportion of participants who have a CR (Complete Remission) + CRh (complete remission with partial hematologic recovery) + CRi (Complete Remission with Incomplete Hematologic Recovery) determined by the Investigator according to 2022 European Leukemia Net (ELN) recommendations for diagnosis and management of AML. (CRc = CR + CRh + CRi). • Overall response rate: Proportion of participants who have a CR or CRi or CRh or PR or MLFS (morphological leukemia-free state) according to the 2022 ELN criteria. • Duration of CR defined as the time interval from the first documented evidence of CR until disease relapse as per 2022 ELN recommendations or death due to any cause, whichever comes first. • Duration of CR+CRh+CRi (Duration of CRc) defined as the time interval from first documented evidence of CRc (CR, CRh or CRi) until disease relapse as per 2022 ELN recommendations or death due to any cause, whichever comes first. • Duration of CR+CRi+CRh+PR+MLFS (Duration of overall response rate) defined as the time from the first documented evidence of CR or CRi or CRh or PR or MLFS until disease relapse as per 2022 ELN recommendations or death due to any cause, whichever comes first. • Alternative CR rate defined as proportion of participants with CR+CRh (complete remission with partial hematological recovery). • Duration of CR+CRh (Duration of alternative CR) defined as the time from the first documented evidence of CR or CRh until disease relapse as per 2022 ELN recommendations or death due to any cause, whichever comes first.

Objectives	Endpoints
	• Event-free survival (EFS) defined as the time interval from the first day of treatment assignment to the date of earliest evidence of relapse, treatment failure, or death. Event-free survival (EFS) defined as the time interval from the first day of treatment assignment to the date of earliest evidence of relapse, treatment failure, or death. • Overall survival (OS) defined as time interval from the day of treatment assignment to death from any cause. • Rate of hematopoietic stem cell transplantation (HSCT) procedures immediately following study treatment administration but prior to subsequent therapy for treatment of AML. • Time to treatment failure (TTF) defined as the time from first day of treatment assignment to discontinuation for any reason excluding remission, eg, relapsed disease, refractory disease, unacceptable AE, participant preference or death.
• To assess transfusion independence rate (TI) after treatment with SAR443579 in combination with venetoclax and azacitidine (all parts).	• Rate of conversion from transfusion dependence to transfusion independence and rate of participants who are transfusion independent at baseline and remain independent during 56-day post-baseline period.
Exploratory/Tertiary	
• To assess levels of cytokines following treatment administration, and their relationship with safety profile and clinical outcomes.	• Assessment of blood cytokine levels at specific time points following treatment administration to evaluate potential associations of cytokine levels with safety and clinical outcomes.
• To [redacted]	[redacted].
• [redacted]	• [redacted]
• To determine % reduction CD123 blasts.	• Assessment of the kinetics of treatment-induced reduction in the % of CD123+ blasts as a pharmacodynamic marker for response to the study treatment.

Objectives	Endpoints
• To assess the participant health-related quality of life (HRQL), disease and treatment related symptoms and impacts of symptoms (Expansion part).	• Assessment of the Quality of Life in Acute Myeloid Leukemia (AML-QOL) participant reported outcome instrument. • Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) scales will be utilized as anchors to estimate/confirm established clinically meaningful change scores for AML-QOL/domain scores.
• To assess qualitatively participant experience with treatment (Expansion part).	• Results from the Patient's Qualitative Assessment of Treatment version 2 (PQAT-v2) will be used to assess participant-perceived advantages and disadvantages of treatment.

For country specific requirements, please see Section 10.8 for details.

3.1 APPROPRIATENESS OF MEASUREMENTS

Please refer to master protocol.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a Phase 1/2, open-label, dose escalation study to determine the safety, PK, PDy, and preliminary efficacy of SAR443579 administered IV in combination with venetoclax and azacitidine treatment in adult participants with CD123-expressing ND-AML ineligible for IC.

The study will enroll adult participants with CD123-expressing ND-AML who are ineligible for IC. During the dose escalation part, only participants with disease with adverse risk cytogenetics according to ELN 2022 criteria will be enrolled. Study treatment consists of an Induction period followed by a Maintenance/continued therapy period. During the Induction period, SAR443579 will be administered by IV infusion once weekly (QW) on D1, D8, D15 and D22 of a 28 day cycle. Once a participant experiences a CR, CRi or CRh, and after a minimum of 3 cycles, they will transition to Maintenance/continued therapy . During the Maintenance/continued therapy period, SAR443579 will be administered by IV infusion every 4 weeks on D1 of a 28 day cycle. Alternative dosing schedules may be proposed based on emerging data.

The escalation part will test approximately 3 main dose levels starting by 0.6 mg/kg and will proceed to test 1 mg/kg and 1.5 mg/kg according to the incidence of DLTs occurring within the DLT observation period, which spans from the first administration of study treatment to the 28^{th} day, using a mTPI-2 approach. Lower DLs may be investigated if excessive toxicity is observed. The final decision to whether to escalate to the next DL, de-escalate or stay at the current DL, or to evaluate alternative lower dose level will be determined by the Study Board based on evaluation of available safety, PK, and PDy data. A backfilling of dose levels declared safe or lower ones may then be proposed based on the data obtained in escalation part. Timing to initiate and dose schedule of such backfilling will be decided by the Sponsor based on totality of tolerability (both DLT and treatment emergent adverse events (TEAE) which occurred during and after completion of DLT observation period, PDy, PK, and preliminary anti-tumor activity as available. This backfilling may increase the total number of participants enrolled in escalation. Following completion of the escalation part, protocol will be amended to include details of optimization and expansion parts based on the availability of data from escalation part. .

The duration of the study for a participant will include the following:

Screening period: up to 21 days.

Treatment period: a minimum of 3 Induction cycles (maximum of 6 induction cycles, 28 days each) followed by up to 21 Maintenance/continued therapy cycles (28 days each). Three additional induction cycles may be given if participant does not achieve CR, CRh or CRi within the first 3 induction cycles. Participants will remain on treatment until documented disease progression, unacceptable adverse events, participant’s decision to stop study treatment, or participant meets any criteria for discontinuation per protocol. Maximum treatment duration is 27 total cycles.

EOT: EOT visit will occur 30 days (+/-5 days) after the last study treatment administration or prior to the initiation of a new therapy. After the EOT visit, participants enter the follow-up period.

Follow-up: Ongoing treatment-related AEs, newly reported AEs, and all SAEs regardless of causal relationship will be followed up at least every 30 days until resolution or stabilization. Survival status of each participant will be collected every 3 months +/-14 days. Updated survival status may be requested at any time during the study. Survival follow-up will continue until death, or the participant's request to discontinue from follow-up, or until the last participant to enter survival follow-up has been followed for 2 years from the last study treatment administration, or upon cancellation of survival follow-up at the discretion of the Sponsor at any timepoint.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

The aim of this study is to test SAR443579 in combination with standard-of-care therapy in participants with CD123 expressing ND-AML who are not eligible for IC. Current standard-of-care treatment for this patient population is chemotherapy consisting of azacitidine or LoDAC in combination with venetoclax. Treatment with azacitidine and venetoclax is efficiacious and was able to elicit complete remission in 36.7% of patients with median overall survival of 14.7 months (1). The addition of SAR443579 to standard-of-care may result in increased complete response rate as well as prolonged duration of response.

The study will begin with an escalation part in order to establish the safety and tolerability of SAR443579 in combination with azacitidine and venetoclax in CD123- expressing ND-AML patients ineligible for IC. This approach leverages data available from the ongoing FIH study of SAR443579 in participants with relapsed/refractory acute myeloid leukemia (R/R AML), B-ALL or HR-MDS, in which SAR443579 administered by IV infusion either weekly (induction cycles) or every 4 weeks (maintenance/continued therapy cycles) was observed to be well tolerated across the tested dose levels. Further justification for the choice of dose is outlined in Section 4.3.

Following the identification of a preliminary RDE in the escalation part, the study will proceed to a dose optimization part. Details will be provided via a future protocol amendment about the dose and schedule.

4.3 JUSTIFICATION FOR DOSE

4.3.1 Rationale for dose escalation

The escalation part of the study will evaluate 3 main DLs by using the starting dose of 0.6 mg/kg dose of SAR443579 in combination with azacitidine and venetoclax in patients with CD123- expressing ND-AML. The dose was selected based on the totality of the available safety, tolerability, PK and preliminary efficacy data from the first-in-human (FIH) monotherapy Phase 1 study in participants with R/R AML, B-ALL or HR-MDS (14).

In the ongoing Phase 1 study, SAR443579 is administered by IV infusion either weekly (induction cycles) or every 4 weeks (maintenance/continued therapy cycles). As of 12 October 2023, 56 participants total have been treated with SAR443579 at 11 different dosing levels ranging from 10 µg/kg to 6 mg/kg. SAR443579 was well tolerated and no dose-limiting toxicities

were observed. The most common treatment-related adverse event was infusion-related reactions, which were observed in 32 participants (57.1%). The best overall response was CR in 4 of 54 AML participants (7.4%); CRi in 1 of 54 AML participants (1.9%); resistant disease in 38 of 54 participants (70.4%). Based on the available data, clinical activity was observed at 1 mg/kg and no safety concerns have been identified for the 1mg/kg dose level. Therefore, the escalation part of this study will start with lower dose by testing a dose of 0.6 mg/kg with planned dose escalations to the 1.0 mg/kg and 1.5 mg/kg and additional dose levels may be tested in order to fully characterize the risk-benefit profile for this patient population. The Study Board will decide whether an alternative dose should be tested prior to proceeding to the dose optimization part of the study based on their knowledge of the safety data, tolerability.

Escalation will proceed according to the incidence of dose limiting toxicities (DLTs) occurring within 28 days after the first dose of study treatment, using a modified toxicity probability interval 2 (mTPI-2) approach.

Decisions to move to another DL will take into account the results of clinical safety. Consecutive cohorts of participants will be treated at SAR443579 dose levels (DLs) per decisions of the Study Board. The DLT observation period is from the first administration to study treatment until the end of the 28th day. A participant in a cohort will be considered evaluable for DLT assessment if he/she receives at least 75% of his/her planned SAR443579 and 75% of the adjusted dose of venetoclax and azacitidine doses during the first 28 days of the treatment (ie, DLT observation period) and is evaluated for at least 28 days, or if a DLT occurs during the DLT observation period; participants who discontinued early before the end of DLT observation period due to an adverse reaction will also be considered evaluable for DLT assessment. Participants not evaluable for DLT assessment in the escalation part (eg, premature discontinuation for reasons other than safety) will be replaced if the minimum number of DLT-evaluable participants in the current cohort is not met.

Enrollment will be paused upon completion of Part 1: Dose Escalation. The available data including but not limited to safety, PK, PDy, and preliminary efficacy will be reviewed and the recommended doses and schedule for optimization will be selected by the study board. Enrollment in the Part 2: Dose optimization and Part 3: Dose expansion will not proceed until after a protocol amendment is submitted that defines the dose and schedule.

Table 4 - Dose: induction and maintenance/continued therapy (all doses in mg/kg)

Dose Level (DL)		
	Induction	Maintenance/continued therapy
	Days 1, 8, 15, 22[a]	Days 1
DL1	0.6	0.6
DL2	1	1
DL3	1.5	1.5

a Cycle duration is 28 days.

4.4 END-OF-STUDY DEFINITION

Please refer to master protocol.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be ≥18 years of age at the time of signing the informed consent.

Type of participant and disease characteristics

I 02. Confirmed diagnosis of AML by WHO 2022 criteria (15).

I 03. Ineligible for intensive chemotherapy. Ineligible for intensive chemotherapy is defined by the following criteria:

A) ≥75 years of age, OR

B) 18 to 74 years of age and meeting one or more of the following:

a) Eastern Cooperative Oncology Group (ECOG) performance status 2-3.

b) Cardiac history of congestive heart failure (CHF) requiring treatment or left ventricular ejection fraction (LVEF) ≤50% or symptomatic coronary heart disease confirmed by coronarography or cardiac imaging.

c) Diffusing capacity of the lungs for carbon monoxide (DLCO) ≤65% or forced expiratory volume (FEV1) ≤65%.

d) Creatinine clearance ≥30 to <45 mL/min calculated by modification of diet in renal disease (MDRD) formula.

e) Moderate hepatic impairment with total bilirubin >1.5 to ≤3.0x upper limit of normal (ULN).

I 04. Subject must have an ECOG performance status as follows:

A) 0 to 2 for participants ≥75 years of age or

B) 0 to 3 for participants 18 to 74 years of age.

I 05. For participants ≥75 years of age, adequate renal function demonstrated by a creatinine clearance ≥30 mL/min, calculated by MDRD.

I 06. Subject must have adequate liver function demonstrated by the following:

A) For participants 18 to 74 years of age, aspartate aminotransferase (AST) ≤3.0 × ULN, alanine aminotransferase (ALT) ≤3.0 × ULN and bilirubin ≤3.0 × ULN, unless considered due to leukemic organ involvement <5 × ULN.

B) For participants ≥75 years of age, aspartate aminotransferase (AST) ≤3.0 × ULN, alanine aminotransferase (ALT) ≤3.0 × ULN and bilirubin ≤1.5 × ULN, unless considered due to leukemic organ involvement <5 × ULN.

Weight

Not applicable.

Sex, contraceptive/barrier method and pregnancy testing requirements/breastfeeding

I 07. All

Contraceptive use by men and women should be highly effective consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

A) Male participants :

- Male participants are eligible to participate if they agree to the following during the study intervention period and for at least 3 months after study completion or the last dose of study treatment:
  - Refrain from donating or cryopreserving sperm

    PLUS, either**:**
  - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

    OR
  - Must agree to use contraception/barrier as detailed below:
    - A male condom and an additional highly effective contraceptive method as described in Section 10.4: Appendix 4 Contraceptive and barrier guidance when having sexual intercourse with a female of childbearing potential (FOCBP) who is not currently pregnant.

B) Female participants :

- A female participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
  - Is a female of non-childbearing potential (FONCBP) as defined in Section 10.4: Appendix 4 Contraception and barrier guidance,

    OR

- Is a FOCBP and agrees to use a contraceptive method that is highly effective (with a failure rate of <1% per year), preferably with low user dependency, or sexual abstinence if appropriate as described in Section 10.4: Appendix 4 Contraception and barrier guidance during the study intervention period (to be effective before starting the intervention) and for at least 6 months after the last administration of study intervention and agrees not to donate or cryopreserve eggs (ova, oocytes) for the purpose of reproduction during this period.

- A FOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 7 days before the first administration of study intervention, see Section 8.3.5 Pregnancy testing.
  - If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.

Informed Consent

Please refer to master protocol.

Criteria added in amended protocol 01:

I 08. For dose escalation part only: participants should have adverse risk cytogenetics as per ELN 2022.

I 09. For all participants: positive CD123 tumor expression as determined locally is required and needs to be documented in source data.

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Patient has Acute Promyelocytic Leukemia (APL).

E 02. Known active central nervous system involvement with AML at the time of enrollment as evidenced by cytology or pathology.

E 03. Cardiovascular disease of New York Heart Association (NYHA) Class ≥2.

E 04. Malabsorption syndrome or other condition that precludes enteral route of administration.

E 05. A baseline QTc interval of (using the Fridericia correction calculation) >470 msec.

Prior/concomitant therapy

E 06. Subject has received treatment with at least one of the following:

1. A hypomethylating agent, venetoclax and/or chemo therapeutic agent for AML other than hydroxyurea used for disease control prior to the initiation of study therapy.
2. Experimental therapies for AML.
3. Concomitant medications of strong and moderate CYP3A inducers within 7 days prior to the initiation of study treatment. (Appendix 13: Section 10.13).

E 07. Subject has consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Starfruit within 3 days prior to the initiation of study treatment.

Prior/concurrent clinical study experience

Please refer to master protocol.

Diagnostic assessments

E 08. White blood cell (WBC) count >25x10^9/L (hydroxyurea or leukapheresis to meet these criteria is allowed).

Other exclusion criteria

E 09. Any country-related specific regulation that would prevent the participant from entering the study - see Appendix 8: Section 10.8 of the protocol (country-specific requirements)

Please refer to master protocol.

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

- Refrain from consumption of red wine, Seville oranges, grapefruit or grapefruit juice, starfruit from 3 days before the start of study intervention until after the final dose due to possible CYP3A mediated metabolic interaction. (see exclusion criteria Section 5.2).

5.4 SCREEN FAILURES

Please refer to master protocol.

5.5 CRITERIA FOR TEMPORARILY DELAYING SCREENING, ENROLLMENT AND ADMINISTRATION OF STUDY INTERVENTION

Please refer to master protocol.

6 STUDY INTERVENTION(S) AND CONCOMITANT THERAPY

Study interventions are all pre-specified, study treatments and AxMPs, medical devices and other interventions (eg, surgical and behavioral) intended to be administered to the study participants during the study conduct.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Participants will receive study treatment until disease progression, unacceptable toxicity, other permanent discontinuation criteria as described in Section 7.1, or completion of the maximum cycles allowed in the study.

Dosing sequence: venetoclax, azacitidine, and SAR443579.

Premedication for SAR443579 should be done 30 to 60 minutes prior to start of SAR443579 infusion that should be administered over 1 hour (+/-10 minutes).

During the first cycle to optimize PK sampling for each IMP venetoclax should be administered first, followed by azacitidine 90 mins after the venetoclax dose and then SAR443579 120 minutes after the venetoclax dose. For cycle 2 and beyond venetoclax should be taken first, following by the azacitidine and then SAR443579. There is no required time interval between venetoclax, azacitidine and SAR443579 in cycle 2 and beyond.

6.1.1 Investigational medicinal product(s)

SAR443579

- **For formulation and route of administration details**, please refer to master protocol.
- **Dose regimen:**

During induction phase: SAR443579 will be administered once weekly, ie, on D1, D8, D15, D22 of a 28-day cycle. Participants will receive at minimum 3 induction cycles prior to switching to maintenance/continued therapy . If CR/CRi/CRh is not achieved within 3 induction cycles, induction therapy may continue for three additional cycles (Cycle 3.1, 3.2, 3.3) after discussion and agreement between the Investigator and the Sponsor.

During maintenance/continued therapy phase: Once a participant achieves CR or CRi or CRh, and after a minimum of 3 induction cycles are completed SAR443579 will be administered IV on D1 of a 28-day cycle for up to 21 cycles (Cycle 4 and beyond). As additional clinical data emerges, the dosing schedule within the maintenance/continued therapy cycle may be further adjusted to potentially include more or less frequent dosing within the cycle.

The IV dosing regimen will be weight-based; however, if a participant weight >133 kg, the participant's weight will be capped at 133 kg for dose calculations.

Venetoclax

- **Formulation:** Film-coated tablets containing 10, 50, 100 mg of venetoclax

- **Route(s) of administration :** Oral
- **Dose regimen:** The recommended dosage is 400 mg once daily after completion of the 4-day ramp-up dosing schedule (see Table 1 and Table 2).
- See venetoclax package insert for initial ramp-up phase in case of concomitant administration with CYP3A including P-gp Inhibitors (5).

Azacitidine

- **Formulation:** Lyophilized powder for suspension for injection
- **Route(s) of administration:** IV or SC
- **Dose regimen:** 75 mg/m^2 intravenously or subcutaneously once daily on Days 1-7 of each 28-day cycle. A full 7 days of azacitidine is required, but as per institutional practice, a schedule of 5 days of daily dosing, followed by no dose received on the weekend, and 2 daily doses given again at the start of the next week, is allowed. The same schedule and route of administration should be used for each participant throughout the duration of treatment, when possible.

Table 5 - Investigational medicinal product(s) administered

Intervention label	Venetoclax	Azacitidine
Intervention name	Venetoclax VENCLYXTO / VENCLEXTA	Azacitidine 100 mg/vial
Intervention description	ATC code: L01XX52	ATC code: L01BC07
Type	Drug	Drug
Dose formulation	Film-coated tablet	Lyophilized powder for suspension for injection
Unit dose strength(s)	10, 50 or 100 mg	100 mg
Dosage level(s)	10, 20, 50, 70, 100, 200, 400 mg PO	75 mg/m^2
Route of administration	Oral	IV or SC
Use	As per label	As per label
IMP and AxMP	IMP	IMP
Packaging and labeling	As per label	As per label
[Current/former name(s) or alias(es)]	As per label	As per label

6.1.2 Auxilliary medicinal product(s)

For generally used AxMPs, all participants should receive premedication (acetaminophen and diphenhydramine), to prevent or reduce the acute effect of infusion-related reactions (IRR) 30 to 60 minutes prior to SAR443579 infusion (no longer than 60 minutes) for the first cycle. Please refer to master protocol.

Premedication may be optional from Cycle 2 as described below:

- For participants who have no CRS or IRR during the first Cycle: premedication for the subsequent infusions is optional at the Investigator's discretion. However, if during subsequent infusions without premedication the participant experiences a CRS/IRR of any grade, premedication must be restarted for all subsequent infusions.
- If a participant develops a CRS/IRR Grade <3 during the first Cycle only, and then experiences no further CRS/IRR during their 2nd cycle, the Investigator may consider omitting premedication for the next cycle. If no CRS/IRR is observed during the next cycle without premedication, premedication is optional for the subsequent cycles at the Investigator's discretion. However, if during the next cycle without premedication the participant experience.

Hydration (oral and/or intravenous) and anti-hyperuricaemic agents should be done for all participants prior to initiation of first dose of IMP and during ramp up phase and is left to Investigator judgment for further administration. The choice of the agents should be based on regional guidelines or institutional standards.

Anti-infective prophylaxis for bacterial, viral and fungal infections are recommended. The choice of the agents should be based on regional guidelines or institutional standards. Potential for drug-drug interactions should be considered.

6.2 PREPARATION, HANDLING, STORAGE, AND ACCOUNTABILITY

Please refer to master protocol.

6.3 ASSIGNMENT TO STUDY INTERVENTION

Please refer to master protocol.

6.4 BLINDING

Not applicable.

6.5 STUDY INTERVENTION COMPLIANCE

Please refer to master protocol.

6.6 DOSE MODIFICATION

6.6.1 General rules

Study treatment includes the combination of venetoclax, azacitadine and SAR443579. **Cycle delay** (ie, delay of study treatment in 28-day induction or maintenance/continued therapy cycle), **dose reduction**, **dose interruption** and **dose omission** (ie, omission of a study treatment within a cycle) may be permitted in case of TEAEs as described below. Dose modifications different from those stated in the protocol should only be made in consultation with the Sponsor, unless required for immediate participant's safety. Dose modifications will be made according to the worst grade of toxicity observed within a cycle. If a participant experiences several toxicities and there are conflicting recommendations, the most conservative recommended dose adjustment should be followed. Once a dose has been decreased, intra-participant re-escalation back to the previous dose level is not permitted. Administration of the study treatment will be discontinued in the event of a TEAE that persists despite appropriate dose modifications or any other TEAE that, in the opinion of the Investigator, warrants discontinuation.

Participants who experience protocol defined DLTs will be required to delay study drug treatment. Such participants may be considered for continued treatment once the toxicity either resolves to Grade 1 or baseline, or the toxicity is stable and manageable through supportive therapy (eg, a participant with well-controlled hypertension that remains at Grade 3 due to the need for 2 anti-hypertension agents).

If one of the study treatments is prematurely permanently discontinued (ie, venetoclax and/or azacitidine), then SAR443579 may continue to be administered after consultation and agreement with sponsor until disease progression, unacceptable toxicity, participant's decision to stop study treatment, or the participant meets other criteria for discontinuation per study protocol (whichever occurs first). The end of study treatment in this case will be 30 days after the last dose of SAR443579 administration. In the situation when SAR443579 is permanently discontinued, venetoclax and azacitidine should be permanently discontinued as well.

6.6.2 Venetoclax/azacitidine dose reduction, delay and omission

The need for dose reduction of venetoclax and/or azacitidine and/or cycle delay (ie, delay of all study treatments) to manage toxicities is expected and is permitted as described in dose adjustment guidelines (see Appendix 11: Section 10.11 [azacitidine] and Appendix 12: Section 10.12 [venetoclax]) . Once a dose of venetoclax or azacitidine has been decreased, intra-participant reescalation back to the previous dose level is not permitted.

Participants who are not able to resume treatment with venetoclax/azacitidine within 6 weeks of the last treatment cycle will permanently discontinue all study treatment (see Section 7.1).

6.6.3 SAR443579 dose reduction, interruption, delay and omission

Dose reductions for SAR443579 are not permitted.

Dose interruption of SAR443579 is permitted to manage toxicity as defined in Section 6.6.5.

Dose delays for SAR443579 are allowed for up to 1 day during the induction phase (weekly dosing) and up to 3 days during the maintenance/continued therapy phase (monthly dosing) as described in the treatment widows (see SOA in Section 1.3). A cycle is deemed delayed if administered ≥4 days in the Induction and Maintenance/continued therapy period. Doses which cannot be administered within the cycle as per protocol-defined window will be omitted and cannot be replaced. Only one omission per cycle is permitted. Further omissions must be discussed on a case-by-case basis with the Sponsor. For delayed or omitted doses when administration of the IMP resumes, the originally scheduled DL and dose should be administered.

A cycle delay of up to 14 days for participant's convenience or scheduling reasons may be allowed after discussion with the Sponsor but should be avoided during the first 3 induction cycles.

All changes to study intervention administration must be recorded in the eCRF.

6.6.4 Guidelines for the management of treatment-related adverse events

Participants may delay study treatment up to 14 days for management of medical events. Delays greater than 14 days must be discussed with the study medical monitor.

No treatment discontinuation, delay or dose modification of any study treatment is required for Grade 1 or Grade 2 related TEAEs unless otherwise specified in the protocol, and management is left to the discretion of the Investigator.

Participants who experience Grade 3 related TEAEs, including clinically significant Grade 3 laboratory abnormalities, should omit (when occurs within a cycle) or delay all study treatment (SAR443579 + venetoclax + azacitidine), unless otherwise specified in the protocol. Participants may resume study treatment at the discretion of the Investigator and Sponsor, if it is determined to be in the best interest of the participant and the delay has not exceeded 14 days, except when specified otherwise in this protocol (ie, Grade 3 IRR). All study treatment should be permanently discontinued for Grade 3 related TEAE if it fails to improve to Grade 1 within 7 days or if the same Grade 3 related TEAE reoccurs.

Clinical status and lab tests must be reviewed prior to each cycle to confirm whether dose adjustments to venetoclax/azacitidine should be made and to confirm the adequate resolution of any toxicity to allow initiation of the next cycle.

Participants who experience Grade 4 related TEAEs, other than cytopenias, should permanently discontinue all study treatment (SAR443579 + venetoclax + azacitidine).

Recommended guidelines for the management of IRR, Anaphalyxis, CRS, ICANS, TLS, Hematological and non-hematological toxicities are presented in Section 6.6.5 below and in Section 10.6.

6.6.5 Guidelines for the management of specific adverse events.

6.6.5.1 Infusion-related reactions (IRR)

Participants should routinely receive premedication as detailed in Section 6.1.2 prior to SAR443579 administration, to prevent or reduce the incidence or severity of IRRs.

An infusion-related reaction in this study is defined as any signs or symptoms which develop during the infusion or up to 24 hours after the completion of the infusion. The term IRR indicates only a specific temporal relationship with the infusion and does not specify a particular mechanism underlying the signs or symptoms.

In TCD 17197/FIH/Monotherapy study, as of 12 October 2023, IRRs occurred in approximately 60% of participants across all dose levels. The majority of the events were non-serious, low grade (Grade 1-2), occurring during the infusion on Cycle 1/Day 1 (C1D1) of therapy and , managed with standard supportive care without SAR443579 dosing changes (reductions or withdrawals). While some participants may experience IRR multiple times, the majority of participants experience an IRR during C1D1 of therapy.

The most common symptoms of IRRs, (occurring in more than 2 participants) listed in order of frequency, are the following: chills, pyrexia, hypotension, hypoxia, tachycardia, hypertension, nausea, tachypnea, headache, cough, abdominal pain, pruritus and dizziness.

In participants who develop symptoms during infusion, the median time to onset from the start of the infusion to the onsent of IRR symptoms is 1 hour. The median duration of symptoms is <3 hours.

In participants who develop symptoms after infusion is completed, the median time to onset from the completion of the infusion to the onset of IRR symptoms is <2 hours. The median duration of symptoms is <3 hours.

Guidelines for the management of IRR events are provided in Table 6. Participants who develop Grade 2 IRR should have the next SAR443579 infusion given at half the infusion rate.
For instructions on premedication at subsequent dosing instructions, please see Section 6.1.2.

Table 6 - Guidelines for the treatment of infusion-related reactions (IRRs)

NCI CTCAE v.5.0 Grade	Treatment
Grade 1 Infusion interruption or intervention not indicated	If IRR occurs during infusion, continuation of SAR443579[a] infusion is per Investigator's judgment following close monitoring of the participant's clinical status. No change for venetoclax and azacitidine. SAR443579 infusion may be interrupted at any time if deemed necessary. If IRR occurs after completion of infusion, then increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the Investigator.

NCI CTCAE v.5.0 Grade	Treatment
Grade 2 Therapy or infusion interruption indicated but prompt response to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	SAR443579 infusion should be interrupted if not already completed. No change for venetoclax and azacitidine. If symptoms resolve within 4 hours of stopping drug infusion, then the infusion may be restarted at 50% of the original rate. Otherwise, dosing will not be resumed on the day of infusion, and the remainder of the dose will be omitted.The participant should be premedicated according to Section 6.1.2 for the next scheduled dose. The next scheduled infusion should be given at 50% of the original infusion rate. During or after completion of infusion, additional appropriate medical therapy may include but not limited to IV fluids, antihistamines, NSAIDs, acetaminophen, corticosteroids, narcotics. Increase monitoring of vital signs will be as medically indicated until the participant recovers.
Grade 3 Prolonged duration (eg, no rapid response to symptomatic treatment and/or brief interruption of infusion indicated); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	SAR443579 infusion should be interrupted if not already completed. SAR443579, venetoclax and azacitidine should be permanently discontinued. During or after completion of infusion, additional appropriate medical therapy may include but is not limited to epinephrine[b], IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids (eg, dexamethasone 10 mg IV or pediatric equivalent dose). Increase monitoring of vital signs as medically indicated until the participant recovers or improves to Grade 1.
Grade 4 Life-threatening; urgent intervention, pressors or ventilator support indicated	SAR443579 infusion should be interrupted if not already completed. SAR443579, venetoclax and azacitidine should be permanently discontinued. During or after completion of infusion, additional appropriate medical therapy may include but is not limited to epinephrine[b], IV fluids, antihistamines, NSAIDs, acetaminophen, narcotics, oxygen, vasopressors, corticosteroids (eg, dexamethasone 10 mg IV or pediatric equivalent dose). Increase monitoring of vital signs as medically indicated until the participant recovers or improves to Grade 1.

Abbreviations: CTCAE = Common Terminology criteria for adverse events; IRR = Infusion-Related Reaction; NCI = National Cancer Institute.

a Information for the preparation and storage of SAR443579 are provided in the Product Management Manual.

b In cases of anaphylaxis, epinephrine should be used immediately.

6.6.5.2 Anaphylaxis

Anaphylaxis should lead to immediate interruption of ongoing infusion, and to permanent discontinuation of SAR443579, venetoclax and azacitidine.

Management should be prompt and may include but is not limited to administration of epinephrine, IV fluids, antihistamines, oxygen, vasopressors, corticosteroids, as well as increased monitoring of vital signs as medically indicated, until the participant recovers (see guidelines in (16, 17, 18).

6.6.5.3 Fever, flu-like symptoms and cytokine release syndrome (CRS)

Fever can frequently happen with immune cell enhancers and may possibly evolve into flu-like symptoms or could be an early manifestation of CRS.

Fever or flu-like symptoms should be graded according to CTCAE v5.0 and managed according to institutional standards.

Cytokine-release syndrome should be graded and managed as per ASTCT guidelines below in Table 7. If a participant develops CRS ≥ Grade 2, sites are required to draw an additional blood sample for cytokines (by central laboratory), and CRP and ferritin (by local laboratory) prior to the administration of tocilizumab (19).

Following administration of tocilizumab, the following blood samples for the quantitation of tocilizumab PK levels will be collected:

- In case of single dose of tocilizumab, PK samples will be collected at 2h and 8h post start of infusion of tocilizumab then at the three next planned visits of SAR443579 after dosing.
- In case repeated dosing (2 administrations) of tocilizumab, PK samples will be collected at 2h and 8h post SOI of the first dose of tocilizumab then at 2h, 8h post SOI and at the three next planned visits of SAR443579 after the second dose of tocilizumab.
- In case repeated dosing (3 administrations) of tocilizumab, PK samples will be collected at 2h and 8h post SOI of the first dose of tocilizumab; at 2h and 8h post SOI of the second dose of tocilizumab; then at 2h, 8h post SOI and at the three next planned visits of SAR443579 after the third dose of tocilizumab.
- In case repeated dosing (4 administrations) of tocilizumab, PK samples will be collected at 2h and 8h post SOI of the first dose of tocilizumab; at 2h and 8h post SOI of the second dose of tocilizumab; at 2h and 8h post SOI of the third dose of tocilizumab then at 2h, 8h post SOI and at the three next planned visits of SAR443579 after the fourth dose of tocilizumab.

Sites should have tocilizumab available along with access to an intensive care unit (ICU), in case participants develop CRS. In the situation when the investigator may use another anti-cytokine agent due to the non-availability of Tocilizumab or in case of emergency, PK samples for this anti-cytokine agent will be collected following the same schema as for tocilizumab.

Guidelines for management of CRS events according to severity grading are provided in Table 7. ASTCT CRS consensus grading scale is provided in Section 10.6. The site may also use local standard of practices (SOP) for management.

Participants at risk for CRS should be advised not to drive a car, operate heavy machinery, or do other dangerous activities while on treatment.

Table 7 - Guidelines for management of cytokine release syndrome (CRS)

Event severity (ASTCT CRS Consensus Grading)	Recommended treatment dose modification and supportive care guidelines
Grade 1 • Fever (Temperature ≥38°C)[b]	No dose modification of SAR443579. No change for venetoclax and azacitidine[a].

Event severity (ASTCT CRS Consensus Grading)	Recommended treatment dose modification and supportive care guidelines
• No hypotension • No hypoxia	Appropriate symptomatic treatment may include but is not limited to IV fluids, antihistamines, NSAIDs and acetaminophen. Care should be taken to not excessively hydrate if evidence of vascular leak. Close direct monitoring of the participant's clinical status. Clinical and laboratory monitoring should initially be performed daily, then less frequently as the participant improves. If symptoms persist beyond 72 hours or refractory rever, then use of tocilizumab can be considered (see Grade 2 below for details).
Grade 2 • Fever[b] (Temperature ≥38°C) • Hypotension not requiring vasopressors • and/or[c] hypoxia requiring low-flow nasal cannula[d] or blow-by.	SAR443579, should be interrupted if not already completed. Venetoclax and azacitidine may continue at the Investigator's discretion. SAR443579 may be resumed when clinical symptoms have resolved or improved to Grade 1 within 14 days. If symptoms resolve within 4 hours of stopping drug infusion, then the infusion may be restarted at 50% of the original rate. Otherwise, dosing will not be resumed on that day of administration, and the remainder of the dose will be omitted. No dose modification of SAR443579 is allowed but decreasing to half the infusion rate can be considered. If CRS occurs after infusion is completed, then the next dose of SAR443579 may be administered only after participant recovery or improvement to Grade 1 within 14 days. The missed doses of SAR443579 will not be replaced. Participant who do not improve to Grade 1 within 14 days should permanently discontinue study treatment. Monitoring of vital signs, cardiac and other organ functions closely as medically indicated should be increased until the participant recovers. Transfer to ICU may be required. Additional appropriate medical therapy may include but is not limited to IV fluids (care should be taken to not excessively hydrate if evidence of vascular leak), antihistamines, NS AIDs and acetaminophen. For participants with comorbidities, older age, or with oxygen requirement, hypotension, or participants in whom symptoms (eg, high grade fever) that do not respond to antipyretics within 72 hours, treatment with corticosteroids and/or tocilizumab,should be considered : Administer tocilizumab at a dose of 8 mg/kg IV over 1 hour (max dose of 800 mg). If no clinical improvement in the signs and symptoms of CRS occurs after the first dose, up to 3 additional doses of tocilizumab may be administered. The interval between consecutive doses of tocilizumab should be at least 8 hours. If hypotension persists after 2 fluid boluses and after one or 2 doses of tocilizumab, then consider dexamethasone 10 mg IV every 12 hours for 1 or 2 doses and then reassess. Manage per Grade 3 if no improvement within 24 hours of starting tocilizumab. Tocilizumab may be considered earlier based on clinical judgment.
Grade 3 • Fever[b] (Temperature ≥38°C) • Hypotension requiring a vasopressor with or without vasopressin • And/or[c] hypoxia requiring high-flow nasal cannula[d], face mask, nonrebreather mask, or Venturi mask	SAR443579, should be interrupted if not already completed. Venetoclax and azacitidine may continue at the Investigator's discretion. SAR443579 may be resumed when clinical symptoms have resolved or improved to Grade 1 within 14 days. If symptoms resolve within 4 hours of stopping drug infusion, then the infusion may be restarted at 50% of the original rate. Otherwise, dosing will not be resumed on that day of administration and the remainder of the dose will be omitted. No dose modification of SAR443579 is allowed but decreasing to half the infusion rate can be considered. If CRS occurs after infusion is completed, then the next dose of SAR443579 may be administered only after participant recovery or improvement to Grade 1 within 14 days. The missed doses of SAR443579 will not be replaced. Participant who do not improve to Grade

Event severity (ASTCT CRS Consensus Grading)	Recommended treatment dose modification and supportive care guidelines
	1 within 14 days should permanently discontinue study treatment. Monitoring of vital signs, cardiac and other organ functions closely as medically indicated should be increased until the participant recovers. Transfer to ICU advised. Additional appropriate medical therapy may include but is not limited to IV fluids (care should be taken to not excessively hydrate if evidence of vascular leak), antihistamines, NS AIDs, acetaminophen., vasopressors, dexamethasone and supplemental oxygen. For participants with comorbidities, older age, or with oxygen requirement, hypotension, or participants in whom symptoms (eg, high grade fever) that do not respond to antipyretics within 72 hours, treatment with corticosteroids and/or tocilizumab should be considered. Dexamethasone 10 mg IV every 6 hours with maximum of 8 doses or until resolution of CRS to ≤ Grade 1; if necessary, then increase to 20 mg IV every 6 hours. Administer tocilizumab at a dose of 8 mg/kg IV over 1 hour (max dose of 800 mg). If no clinical improvement in the signs and symtpoms of CRS occurs after the first dose, up to 3 additional doses of tocilizumab may be administered. The interval between consecutive doses of tocilizumab should be at least 8 hours. Tocilizumab may be considered earlier based on clinical judgment. If no clinical improvement in oxygenation, hypotension, fever, and other CRS manifestations is observed within 24 to 72 hours, management for persistent or worsening CRS should be initiated. Re-evaluation for other contributing conditions should be done, such as infection, cardiac, thromboembolic and other complications.
Grade 4 Life-threatening consequences; urgent intervention indicated • Fever[b] (Temperature ≥38°C) • Hypotension requiring multiple vasopressors (excluding vasopressin) • And/or[c] hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	SAR443579, venetoclax and azacitidine should be permanently discontinued. Same as Grade 3, in addition for participants with severe CRS who fail to improve after repetitive treatment with both tocilizumab, and steroids, alternative options should be discussed with clinical site specialists such as multiple vasopressors and/or mechanical ventilation (positive pressure).

Abbreviations: AE = Adverse event; ASTCT = American Society for Transplantation and Cellular Therapy; BiPAP = Bilevel Positive Airway Pressure; CPAP = Continuous Positive Airway Pressure; CRS = cytokine release syndrome; ICU=intensive care unit; IL = Interleukin; IMP = investigational medicinal product; IV = Intravenous; NSAIDs = Non-steroidal anti-inflammatory drugs.

a Information for preparation and storage of SAR443579, venetoclax and azacitidine are provided in the product management manual.

b Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab, or alternative therapies per site practice in CRS management, or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

c CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

d Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

6.6.5.4 Immune cell-associated neurotoxicity syndrome (ICANS)

Immune cell-associated neurotoxicity syndrome is a neuropsychiatric syndrome which is frequently associated with CRS; however, it is specifically excluded from the definition of CRS and can occur during the course of CRS, after its resolution, or independently from CRS. Clinical findings can be progressive and may include aphasia, altered level of consciousness, impairment of cognitive skills, motor weakness, seizure, and cerebral edema. Severity is evaluated using the ASTCT Consensus grading scale, with ICE score for encephalopathy assessment (Section 10.6). Recommendations for ICANS management mainly include the use steroids, whereas tocilizumab should only be used in the context of CRS, as outlined in Table 8. The proposed management should be considered only as recommendations and in light of recommendations from site specialist. The site may also use local SOP for management.

Table 8 - Guidelines for the management of ICANS

Event severity (ASTCT Consensus Grading criteria)	**Recommended treatment dose modification and supportive care guidelines**
Grade 1 ICE score 7-9. Awakens spontaneously	No intervention required other than close clinical monitoring.
Grade 2 ICE score 3-6. Awakens to voice.	SAR443579, should be interrupted if not already completed. venetoclax and azacitidine may continue at the Investigator's discretion. Treatment with IV corticosteroids should be initiated as needed. The next scheduled infusion of SAR443579 may be administered only after participant recovery or improvement to Grade 1, within 14 days. The missed doses of SAR443579 will not be replaced. Participant who does not improve to Grade 1 within 14 days should permanently discontinue study treatment.
Grade 3: ICE score 0-2. Awakens only to tactile stimulus. Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention. Focal/local edema on neuroimaging	SAR443579, should be interrupted if not already completed. venetoclax and azacitidine may continue at the Investigator's discretion. Treatment with IV corticosteroids should be initiated as needed. The next scheduled infusion of SAR443579 may be administered only after participant recovery or improvement to Grade 1, within 14 days. The missed doses of SAR443579 will not be replaced. Participant who does not improve to Grade 1 within 14 days should permanently discontinue study treatment. Permanently discontinue of SAR443579, venetoclax and azacitidine if more than one seizure occurs.
Grade 4: ICE score: 0 (patient is unarousable and unable to perform ICE). Participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma. Life-threatening prolonged seizure (>5 min): or Repetitive clinical or electrical seizures without return to baseline in between. Deep focal motor weakness such as hemiparesis or paraparesis. Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad.	SAR443579, venetoclax and azacitidine should be permanently discontinued. Treatment with IV corticosteroids should be initiated. Concomitant CRS may require tocilizumab and should be handled as described in Table 7. Corticosteroids can then be administered IV or orally every 8 hours for up to 3 days, then tapered over 4 days. For both Grade 3 and Grade 4 ICANS: If there is no clinical improvement within 24 to 72 hours, re-evaluation for other contributing conditions should be done. Administration of IV tocilizumab at 8 mg/kg, as per Table 7. (total dose should not exceed 800 mg), should be considered, and steroids should be administered concurrently and repeated as previously mentioned for CRS. Neurologist and other relevant specialties should be involved whenever indicated.

Abbreviations: AE = adverse event; ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; EEG = electroencephalography; ICE = immune effector cell-associated encephalopathy; IV = intravenous.

6.6.5.5 Tumor lysis syndrome

During Cycle 1 prophylaxis for tumor lysis syndrome, including adequate hydration and anti-hypouricemic agents, should be initiated prior to C1D1 and continue through C1D4 and is left to Investigator judgment for further administration based on regional guidelines or institutional standards. Blood chemistry (potassium, uric acid, phosphorus, corrected calcium and creatine) should be assessed and corrected prior to C1D1. Blood chemistries should be reassessed 6 to 8 hours after C1D1, C1D2, C1D3 and C1D4, and 24 hours after C1D4 for SAR443579, venetoclax and azacitidine. For participants with risk factors for tumor lysis syndrome, consider increased monitoring and/or reducing venetoclax starting dose. If TLS occurs, then appropriate treatment will be initiated that will include correction of serum corrected calcium, potassium, or phosphorus abnormalities, and treatment of hyperuricemia with allopurinol and/or rasburicase, at the Investigator's discretion. Decision regarding dose interruptions or modifications will be made by the investigator in consultation with the sponsor based on the clinical evaluation of the participant.

6.6.5.6 Management of hematological toxicities

Myelosuppression and the related adverse events (thrombocytopenia, anemia, neutropenia, and febrile neutropenia) are common in participants with AML. Subjects with baseline neutropenia or those with secondary AML might be particularly at high risk. In addition to decreasing/delaying the doses of venetoclax and azacitidine as per Section 6.6.2.

Table 9 - Dose adjustment instructions for hematological toxicity

Hematological toxicity	Occurrence	Dose adjustment
Grade 4 neutropenia (ANC <500/microliter) with or without fever or infection **OR** Grade 4 thrombocytopenia (platelet count <25 × 10^3/µL)	Occurrence prior to achieving remission	Interruption of venetoclax in combination with azacitidine due to cytopenias prior to achieving remission is not recommended in most instances.
	First occurrence after achieving remission and lasting at least 7 days	-Omit venetoclax and azacitidine within cycle and delay subsequent cycle of SAR443579, venetoclax and azacitidine on CnD1 and monitor blood counts. -Administer granulocyte-colony stimulating factor (G-CSF) if clinically indicated for neutropenia. Upon resolution to Grade 1 or 2: -For SAR443579: resume treatment with the same dose at the next cycle. -**For venetoclax**: resume venetoclax at the same dose at the next cycle. -**For azacitidine:** resume Azacitidine at the next cycle: • Participants without reduced baseline blood counts at baseline: If recovery is achieved within 14 days, no dose adjustment is necessary for the resumed dose. If recovery has not been achieved within 14 days, the resumed dose should be reduced by 50%. • Participants with reduced baseline blood counts at baseline: If recovery is achieved within 14 days, no dose adjustment is necessary for the resumed dose. If recovery has not been achieved within 14 days, bone marrow cellularity should be evaluated. If the bone marrow cellularity is 15-50%, the resumed dose should be reduced according by 50%. If the bone marrow cellularity is <15%, the resumed dose should be reduced by 33%.

Hematological toxicity	Occurrence	Dose adjustment
	Subsequent occurrences after achieving remission and lasting at least 7 days	-Omit venetoclax and azacitidine within cycle and delay subsequent cycle of SAR442579, venetoclax and azacitidine and monitor blood counts. -Administer granulocyte-colony stimulating factor (G-CSF) if clinically indicated for neutropenia. -For SAR443579: resume treatment with the same dose at the next cycle. **-For venetoclax**: Upon resolution to Grade 1 or 2, resume treatment with venetoclax at the same dose at the next cycle and reduce venetoclax treatment duration by 7 days during each subsequent cycle, such as 21 days instead of 28 days. -**For azacitidine:** • Same recommendation as above for first occurrence

Note: Please also refer to latest labelling information available.

6.6.5.7 Management of non-hematological toxicities:

Table 10 - Dose adjustments instructions for non-hematological toxicity

Non-Haematological toxicity	Dose adjustment
Renal impairment (CrCl ≥15 ml/min and <90 ml/min)	-No dose adjustment for Venetoclax, Azacitidine and SAR443579 is required. -Monitor patient closely for signs of TLS, particularly during ramp-up phase.
Hepatic impairment ((defined by Child-Pugh Classification).	-No dose adjustment for Azacitidine or SAR443579 is required. Child-Pugh A or B. No Venetoclax dose adjustment is recommended Child-Pugh C: A dose reduction of Venetoclax of at least 50% throughout treatment is recommended.
Other Grade 3-4 toxicities related to Venetoclax (Please refer to NCI CTCAE V5.0)	No dose adjustment of Azacitidine or SAR443579 is required. Omit venetoclax if not resolved with supportive care. Upon resolution to grade 1 or baseline level, resume Venetoclax at the same dose at the next cycle.
Seizure ≥2 (in the absence of ICANS)	Permanently Discontinue SAR443579, Venetoclax and Azacitidine.

Note: Please also refer to latest labelling information available.
Abbreviations: CrCl = clearance of creatinine; TLS = tumor lysis syndrome; ALT = alanine aminotransferase, AST = aspartate aminotransferase
Child-Pugh Scoring system in Appendix 6.

6.6.6 Retreatment criteria

Not applicable.

6.7 CONTINUED ACCESS TO INTERVENTION AFTER THE END OF THE STUDY

Not applicable.

6.8 TREATMENT OF OVERDOSE

For definition of IMPs overdose, please refer to master protocol.

Agent specific instructions are as follows:

- SAR443579 overdose
  - SAR443579 overdose is defined as a participant receiving>30% of a single dose specified SAR443579 dose within a 24-hour time period. The Sponsor does not recommend specific treatment for an overdose.
- Azacitidine overdose
  - In the event of overdose, the participant should be monitored with appropriate blood counts and should receive supportive treatment, as necessary. There is no known specific antidote for azacitidine overdose.
  - Decision regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor based on the clinical evaluation of the participant.
- Venetoclax overdose
  - There is no specific antidote for venetoclax.
  - Participants who experience overdose should be closely monitored and appropriate supportive treatment provided.
  - During ramp-up phase, treatment should be interrupted, and participants should be monitored carefully for signs and symptoms of TLS (fever, chills, nausea, vomiting, confusion, shortness of breath, seizures, irregular heartbeat, dark or cloudy urine, unusual tiredness, muscle or joint pain, abdominal pain, and distension) along with other toxicities. Based on venetoclax large volume of distribution and extensive protein binding, dialysis is unlikely to result in significant removal of venetoclax.
  - Decision regarding dose interruptions or modifications will be made by the Investigator in consultation with the Sponsor based on the clinical evaluation of the participant.

For Auxiliary medicinal product overdose (accidental or intentional) please refer to master protocol.

6.9 PRIOR AND CONCOMITANT THERAPY

Please refer to master protocol.

6.9.1 Acceptable concomitant medications

Please refer to master protocol.

Concomitant medications should be kept to a minimum during the study. However, all treatments that are not prohibited per study protocol and that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the electronic case report form (e-CRF) including all prescription, OTC, herbal supplements, and IV medications. If changes occur during the trial period, documentation of route, and date will also be included on the e-CRF.

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery or radiotherapy for tumor control is not permitted during the study; however, radiotherapy or procedures for symptom management is allowed after discussion with and approval by the Sponsor.

All concomitant medications received within 28 days before the first dose of trial treatment through the End of Treatment Visit and post EOT if associated with ongoing SAEs should be recorded.

Once participants have received at least 2 weeks of both SAR443579 and azacitidine and venetoclax in Cycle 1, hydroxyurea can be started if felt to be required for disease control after discussion between the Investigator and Sponsor Medical Monitor. Use of hydroxyurea within the first 2 weeks of treatment in Cycle 1 may also be considered on a case-by-case basis.

Concurrent therapy for CNS prophylaxis/treatment as per institutional standards is permitted (eg, intrathecal methotrexate).

Concurrent hydration and anti-hyperuricaemic agents for TLS prophylaxis as per institutional standards is permitted. Concurrent anti-infective prophylaxis and growth factor support are allowed per institutional guidelines.

There are currently no specific restrictions on the use of vaccines authorized today by local regulatory health authorities to prevent COVID-19.

6.9.2 Concomitant therapy requiring careful monitoring

The cytokines release after SAR443579 administration is anticipated to be limited and transient. However, since cytokines release may lead to CYP450 mediated drug interactions, caution should be taken with sensitive CYP substrates with narrow therapeutic range (NTR) (see Appendix 12: List of sensitive cyp substrated with narrow therapeutic range of Master protocol) for which circulating exposure may increase.

6.9.3 Prohibited concomitant medications

The following concomitant treatments are not permitted during this study:

- Concurrent treatment with other investigational drugs.
- Concurrent treatment with any other anticancer therapy not specified in the protocol, including immunotherapy, hormonal therapy (adjuvant hormonal therapy is allowed), targeted therapy or biological therapies.
- Radiotherapy, even if palliative in intent, may not be given during the study.
- Systemic glucocorticoids >10 mg/day of prednisone or equivalent and other immunosuppressive therapies such as anti-TNF, anti-IL6, etc, **except for**:
  - Treatment of immune-mediated AEs when indicated (IRR, CRS, and ICANS,…).
  - Treatment of any life-threatening emergency.

  - Physiologic replacement as long as they are not being administered for immunosuppressive intent, and
  - Use of systemic corticosteroid for prophylaxis for the treatment of non-autoimmune conditions should be discussed and approved by the medical monitor.
- Consumption of red wine, Seville oranges, grapefruit or grapefruit juice, starfruit from 3 days before the start of study intervention until after the final dose of venetoclax.
- Live attenuated vaccines within 28 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, seasonal flu (seasonal flu vaccines that do not contain live virus are permitted), nasal H1N1 flu, rabies, Bacillus Calmette-Guérin (BCG), and typhoid.

Drug interactions with venetoclax (see Section 10.13):

- Drugs that are strong or moderate CYP3A inducers are not permitted throughout the active treatment phase as they may decrease venetoclax exposure.
- Drugs that are strong or moderate CYP3A inhibitor including P-gp inhibitors increases venetoclax exposure: dosage of venetoclax must be adjusted.
- Concomitant use of venetoclax should be avoided with P-gp substrates as it increases P-gp substrates exposure. If a concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before venetoclax.
- Concomitant use of venetoclax increases warfarin exposure which may increase the risk of bleeding. Closely monitor international normalized ratio (INR) in participants using warfarin concomitantly with venetoclax.

Participants who, as per assessment by the Investigator, require the use of any of the afore mentioned treatments for clinical management should be removed from the trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy may be required. The Investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy or vaccination rests with the Investigator and/or the participant's primary physician. However, the decision to continue the participant on trial therapy schedule requires the mutual agreement of the Investigator, the Sponsor and the participant.

The exclusion criteria describe other medications which are prohibited in this trial.

There are no prohibited therapies during the follow-up period.

6.9.4 Rescue medicine

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Appendix 1 (Section 10.1).

7.1 DISCONTINUATION OF STUDY INTERVENTION

Please refer to master protocol for general statement. Sub-study specificity is described below:

7.1.1 Permanent discontinuation

- If the participant didn't reach CR/CRi/CRh after 6 induction cycles.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Please refer to master protocol.

7.3 LOST TO FOLLOW UP

Please refer to master protocol.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.

For common details please refer to master protocol.

8.1 ADMINISTRATIVE PROCEDURES

Not applicable.

8.2 EFFICACY ASSESSMENTS

Planned timepoints for all efficacy assessments are provided in the SoA in Section 1.3.
Efficacy assessments will be performed to meet the primary objective (dose optimization/expansion parts) for assessing anti-tumor activity of SAR443579 + azacitidine + venetoclax using CR rate determined by the Investigator according to 2022 ELN recommendations for AML. Additional efficacy objectives include overall response rate (CR+CRi+CRh+PR+MLFS), CRc rate (CR+CRh+CRi), alternative CR rate (CR+CRh), duration of CR, CRc and alternative CR, overall response rate, event-free survival rate, survival rate. Preliminary evidence of hematologic response will also be evaluated in the escalation part.

8.3 SAFETY ASSESSMENTS

This section presents safety assessments other than adverse events which are presented in Section 8.4.

Planned timepoints for all safety assessments are provided in the SoA.

8.3.1 Physical examinations

Please refer to master protocol for details on physical examinations.

8.3.2 Vital signs

For common details please refer to master protocol

- Vital signs will be measured at screening, during SAR443579 administrations, and at the EOT visit. For collections during SAR443579 treatments, vital signs will be collected 5 minutes (+/-5 minutes) before starting SAR443579 infusion, every 30 minutes (+/-15 minutes) during infusion, end of infusion time, and 1 and 2 hours (+/-30 minutes) following completion of SAR443579 administration. Monitoring of vital signs shall be made continuously if CRS Grade ≥2 develops.
- The monitoring can be reduced to 1 hour monitoring during expansion part.

8.3.3 Electrocardiograms and LVEF

Please see master protocol for details on electrocardiograms.

8.3.4 Clinical safety laboratory tests

Please refer to master protocol.

8.3.5 Pregnancy testing

Please refer to master protocol and Section 5.1 for pregnancy testing criteria.

8.3.6 Dose limiting toxicities

Dose limiting toxicities:

DLT is defined as the occurrence, within the first 28-days after the first dose of study treatment, of any of the following using National Cancer Institute Common Terminology Criteria for adverse Events (NCI CTCAE) Version 5.0 or ASTCT criteria, whether related or not to the study treatment in the absence of clear evidence to the contrary, and if not related to disease progression:

Hematologic abnormalities:

- Grade 4 hematologic toxicities, ie, new onset or worsening of hematologic abnormalities after administration of SAR443579, in absence of underlying leukemia:
  - Grade 4 bone marrow hypocellularity, if not caused by disease progression and not improved to baseline value or Grade ≤1 within 14 days.
  - Grade 4 decreased absolute neutrophil count (ANC) lasting past cycle Day 42.
  - Grade 4 febrile neutropenia.
  - Grade 4 decreased platelet count lasting past Cycle 1 Day 42.
  - Grade 4 anemia, if not improved to baseline value or Grade ≤1 within 14 days.
- Grade 3 thrombocytopenia with bleeding requiring transfusion.

Non-hematologic abnormalities:

- Any Grade 4 non hematologic organ toxicities, in absence of underlying leukemia.
- Any Grade 4 infusion reaction.
- Any Grade 3 infusion reaction lasting >24 hours.
- Hy's law cases.
- Any Grade 3-4 infection lasting more than 7 days in the absence of active AML.

- Grade 3 electrolyte abnormalities (NA, K, Cl, CO2, Ca, Mg, phosphate) that do not return to Grade 1 or lower within 72 hours.
- Grade 3 transaminitis (AST/ALT) elevation that that does not return to Grade 1 or lower within 72 hours.
- Any Grade ≥3 toxicities excluding:
  - Alopecia.
  - Grade 3 fatigue, asthenia, fever, anorexia, or constipation.
  - Grade 3 nausea, vomiting or diarrhea not requiring tube feeding, total parenteral nutrition, or requiring or prolonging hospitalization.
  - Infection, bleeding, or other expected direct complication of cytopenias due to active underlying leukemia.
  - Grade 3 cytokine release syndrome (CRS), if successfully managed and which resolves within 72 hours.
  - Grade 3 or 4 tumor lysis syndrome (TLS) if it is successfully managed clinically and resolves within 7 days without end-organ damage.
  - Grade 3 laboratory abnormalities that resolve to ≤ Grade 2 within 72 hours.
- Any toxicity related to SAR443579 resulting in a treatment delay of >2 weeks due to delayed recovery to baseline or Grade ≤1.
- Any adverse reaction regardless of grade that leads to dose reduction or withdrawal.

8.4 ADVERSE EVENTS (AES), SERIOUS ADVERSE EVENTS (SAES) AND OTHER SAFETY REPORTING

The definitions of adverse events (AEs) and serious adverse events (SAEs) can be found in Appendix 3 (Section 10.3). The definition of AESI is provided in Section 8.4.8.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative) that meet the definition of an AE or SAE and remain responsible for following up (see Section 7). This includes events reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

8.4.1 Time period and frequency for collecting AE and SAE information

All AEs (serious or nonserious), including adverse events of new onset, ASE and AESIs and worsening of baseline signs and symptoms, will be collected throughout the study period from the signing of the informed consent form (ICF) until 30 days following the last administration of study treatment.

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE or AESI data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.4.2 Method of detecting AEs and SAEs

Please refer to master protocol.

8.4.3 Follow-up of AEs and SAEs

Please refer to master protocol.

8.4.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Serious adverse events that are considered expected will be specified in the reference safety information (IB for SAR443579, venetoclax and azacitidine).
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an SAE, SUSAR or any other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB/IDFU/package insert and will notify the IRB/IEC, if appropriate according to local requirements. It is the responsibility of the Sponsor to assess whether an event meets the criteria for a SUSAR, and therefore, is expedited to regulatory authorities.

8.4.5 Pregnancy

Please refer to master protocol.

8.4.6 Cardiovascular and death events

Not applicable.

8.4.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable.

8.4.8 Adverse events of special interest

Please refer to the master protocol.

8.4.9 Medication errors or misuses of medicinal product

Please refer to master protocol.

8.4.10 Guidelines for reporting product complaints

Please refer to master protocol.

8.5 PHARMACOKINETICS

- Blood samples will be collected for measurement of plasma concentrations of SAR443579, venetoclax and azacitidine and tocilizumab as specified in the PK flowchart (Section 1.3)
- The sampling may be reduced or removed during the course of the study based on the updated knowledge of drugs behavior to ensure appropriate monitoring.
- Samples will be used to evaluate the PK of SAR443579, venetoclax, azacytidine and tocilizumab. Samples collected for analyses may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

The pharmacokinetic parameters may be calculated using non-compartmental methods or by population PK analysis from plasma venetoclax and azacitidine concentrations. A population PK analysis will be performed on SAR443579 data. Population PK analyses will be reported in a standalone report.

For tocilizumab, a modeling approach may be used.

For the NCA, the parameters will include, but may not be limited to, the following Table 11:

Table 11 - List of pharmacokinetic parameters and definitions

Parameters	Drug	Matrix	Definition/calculation
C_{max}	venetoclax, azicitidine	Plasma	Maximum concentration observed
AUC	venetoclax, azicitidine	Plasma	AUC from time zero extrapolated to infinity according to the following equation: $AUC = AUC_{last}+(C_{last}/\lambda_z)$ Extrapolation should not exceed more than 30% of total AUC.
C_{trough}	SAR443579/venetoclax	Plasma	Concentrations observed at the end the dosing period during repeated administration

In case of tocilizumab administration, concentrations at different time-point.

8.6 PHARMACODYNAMICS

- To identify biomarkers that help to predict and/or evaluate biological activities induced by SAR443579, this study will evaluate tertiary/exploratory biomarkers in bone marrow (solid biopsy and aspiration) and blood (plasma and serum).
- Collection of biological samples for this biomarker research is an important part of this study. The following samples for biomarker research are required and will be collected from all participants in this study as specified in Section 1.3 and the attached Schedule of Activities (SoA) Tables, Pharmacodynamics (PDy) Flowcharts and in the Laboratory Manual provided separately to sites. Note that some of the scheduled sample collection and analysis will be limited to the expansion part of the study.
- Please, refer to separate laboratory manual for details concerning sample collection, handling and shipping logistics.
- **Prospective real time analysis** of critical biomarkers in freshly isolated samples will be used to evaluate safety, biological activity, association with the observed clinical responses (including duration of response, progression or early relapse), and to identify RDE for the expansion part of the study. Samples will be tested for the following PDy and response biomarkers:
  - **Morphology and % blasts** of bone marrow biopsy and/or aspiration: for evaluation of disease status and clinical responses.
  - **Flow Cytometry (Blast- and Immuno-phenotyping**): flow cytometry analysis of fresh whole blood and bone marrow aspiration samples will be performed for time course evaluation of leukemic blasts characteristics and depletion, including immunophenotyping to evaluate the impact of SAR443579 on the activation status and effector functions of relevant immune subsets including NK cells. Effector/target ratios as well as CD123 prevalence and receptor density at baseline and on treatment will also be analyzed. The potential correlation between CD123 expression on leukemic cells and clinical response will be explored.
  - **MRD** Multiparameter flow cytometry (MFC) will be used to assess the MRD status in participants who achieved CR (any form).

- **Cytokine responses in blood:** to monitor pro-inflammatory cytokines including chemokines such as MIP-1b to assess CRS and PDy responses. Potential correlations with other parameters such as safety and participants' clinical parameters will be explored.
- **CBC with differential of whole blood**: to monitor changes in leukemic blasts and blood leukocyte subpopulations.

8.7 GENETICS

Please refer to master protocol.

8.8 BIOMARKERS

[redacted]

For country specific requirements please refer to Section 10.8.

8.9 IMMUNOGENICITY ASSESSMENTS

Antibodies against SAR443579 will be evaluated in plasma samples collected from all participants according to the PK/ADA flowchart and SoA. Additionally, plasma samples should also be collected at the final visit from participants who discontinued study intervention or were withdrawn from the study.

8.10 CLINICAL OUTCOMES ASSESSMETS

Participant-reported outcome measures to be included are the assessment of the Quality of Life in Acute Myeloid Leukemia (AML-QOL), the Patient Global Impression of Severity (PGIS), the Patient Global Impression of Change (PGIC) and the Patient's Qualitative Assessment of Treatment version 2 (PQAT-v2). Each questionnaire is described in this section and presented in appendices.

The AML-QOL is a recently developed instrument specifically designed for AML and HR-MDS population to capture specific concepts of interest for these participants and fill the gaps from other non-disease-specific COAs. The AML-QOL is an AML and HR-MDS-specific instrument that contains 27 items and provides a multi-dimensional assessment of HRQL. The AML-QOL provides a comprehensive assessment of the principal HRQL dimensions identified in AML participants (physical, social, cognitive, anxiety, mood, pain, disease/treatment effects). Regarding responses options, the AML-QOL has a 5-point Likert type scale ranging from 1: "Never" to 5: "Almost always" for the 26 items included in domains and ranging from 1: "Excellent" to 5: "Poor" for the QOL item. Scores can be calculated reported for each of 7 domains as well as for the single item assessing QOL. Additionally, a total summative score can be reported. AML-QOL validity and reliability has been already established (20). In order to select concepts for AML-QOL based on prevalence and impact, 82 participants with AML and High-risk MDS were interviewed (semi-structured/open-ended interview) to elicit symptoms or situations (ie, concepts) impacting their QOL during a cross-sectional study (21).

The PGIS and PGIC scales are based on the original Physician Global Impression of Change scale created by Hurst and Bolton (22) and adapted as global participant reported outcome measures of severity and change. The PGIS scale is a 1 item questionnaire designed to assess the participant's impressions of their disease severity during a specified recall period, while the PGIC scale is a 1 item questionnaire designed to assess the participant's impression of change in disease severity overall/since started study medication. The PGIS and PGIC will be used utilized as anchors to estimate/confirm established clinically meaningful change scores for AML-QOL domains/items.

In order for regulatory agencies to approve a drug or regimen, the drug or regimen must be safe and effective, and the overall benefits must outweigh the risks in the target participant population. Besides an assessment of risk and benefit based on objective laboratory/imaging measurements and Investigator assessments, Sanofi has developed an internal measure to assess participant-reported assessment of benefit and disadvantages (B/R) (PQAT-v2) to help contribute to the overall B/R assessment (23) The PQAT-v2 provides participant insights on the advantage and disadvantage of treatment combining score-based quantitative questions and open-ended

qualitative questions, providing also an overall Benefit/Disadvantages ratio. The 6-item PQAT-v2 is an internally created, non-disease specific, self-administered assessment of the advantage and disadvantage associated with treatment. The PQAT-v2 takes approximately 4 minutes to complete.

8.11 MEDICAL RESOURCE UTILIZATION AND HEALTH ECONOMICS

Please refer to the master protocol for details.

8.12 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Please refer to the master protocol for details.

9 STATISTICAL CONSIDERATIONS

The statistical analysis plan will be finalized prior to the start of the dose expansion part and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.1 POPULATIONS FOR ANALYSES

The following populations for analyses are defined.

Table 12 - Populations for analyses

Population	Description
Enrolled (escalation only)	All participants from screened population who have been allocated to an intervention regardless of whether the intervention was received or not.
DLT-evaluable (escalation only)	All participants who complete the DLT observation period and receive at least 75% of the planned dose of SAR443579, and the adjusted dose of venetoclax and azacitidine during that period. Participants who discontinued early before the end of DLT observation period due to an adverse reaction will also be considered evaluable for DLT assessment .Any participant who experiences any DLT in the DLT observation period will also be DLT evaluable.
Efficacy	All participants from the exposed population.
Pharmacodynamics	All participants from the exposed population with at least one post-baseline PDy parameter assessed after the first dose of study intervention.
ADA immunogenicity	All enrolled/randomized participants treated with IMP with at least one post-baseline ADA result (positive, negative or inconclusive).

Abbreviations: ADA = anti-drug antibodies DLT = dose limiting toxicity, PK = pharmacokinetic, PDy = Pharmacodynamics.

For additional details please refer to master protocol.

9.2 STATISTICAL ANALYSES

The statistical analysis plan will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.2.1 General considerations

Please refer to master protocol for details.

9.2.2 Primary endpoint(s) analyses

9.2.2.1 Dose escalation

The primary endpoint is the incidence of DLTs. All DLT modeling will be performed on the DLT-evaluable population or those who experienced a DLT. Statistical descriptive analysis will be used to summarize the incidence of DLT by dose level and overall.

9.2.2.2 Dose optimization

CR rate per 2022 European Leukemia Net (ELN) criteria will be summarized with descriptive statistics. A 90% two-sided confidence interval will be computed using Clopper-Pearson method. Concentration of SAR443579 and/or its respective combination partners will be summarized with descriptive statistics. The overall safety & tolerability will be analyzed according to Section 9.2.5.

9.2.2.3 Dose expansion

The primary efficacy endpoint is the complete remission (CR) rate determined by the Investigator according to ELN recommendations for diagnosis and management of AML. The CR rate is defined as the proportion of participants who have a response of CR as best overall response (BOR) as assessed by the Investigator. The BOR assessment window is from the first administration of study treatment until 6 cycles. The statistical analysis plan (SAP) will provide details on the BOR derivation for participants with AML.

9.2.2.4 Main analytical approach

During the course of the study several endpoints will be evaluated based on the part (escalation, optimization and expansion). They will be analyzed and reported as described below.
The DLT incidence rate, CR rate and CR rate difference between two arms in expansion part will be summarized with descriptive statistics. The 90% two-sided CI computed using Clopper-Pearson method will be provided.

9.2.2.5 Sensitivity analysis

The sensitivity analyses will be described in the SAP finalized before database lock.

9.2.2.6 Supplementary analyses

Not applicable.

9.2.3 Secondary endpoint(s) analyses

Please refer to the master protocol for common main secondary endpoints.

Main secondary efficacy endpoints are described below. All will be evaluated on the efficacy population and the per-protocol efficacy population. The SAP will provide more details on other secondary endpoints and analysis plan.

Minimal residual disease (MRD) rate

The minimal residual disease rate is defined as the proportion of participants with minimal residual disease as defined by 2022 ELN in participants achieving a CR, CRh or CRi.

Overall response rate (ORR)

The overall response rate is defined as the proportion of participants who have a response of CR, CRh, CRi, PR, or morphological leukemia-free state (MLFS) as BOR as assessed by the Investigator.

Composite Complete Remission (CRc) rate

The CRc rate is defined as the proportion of participants who have a response of CR, CRh or CRi as BOR as assessed by the Investigator.

Alternative CR (CR+CRh) rate

The alternative CR rate is defined as the proportion of participants who have a response of CR or CRh as BOR as assessed by the Investigator.

Duration of CR

Duration of CR is defined as the time from the first documented evidence of CR until disease relapse (DR) as determined by the Investigator according to the 2022 ELN recommendations for diagnosis and management of AML or death due to any cause, whichever comes first. In the absence of the specified events (DR or death due to any cause), participant will be censored at the date of the last valid disease assessment not showing disease relapse performed prior to initiation of a further anti-leukemic treatment (if any) or the analysis cut-off date, whichever comes first. Duration of CR will not be calculated for participants who do not achieve a CR.

Duration of CR+CRh+CRi (Duration of CRc)

Duration of CR+CRh+CRi is defined as the time from the first documented evidence of CRc (CR, CRh, or CRi) until disease relapse (DR) as determined by the Investigator according to the 2022 ELN recommendations for diagnosis and management of AML or death due to any cause, whichever comes first. In the absence of the specified events (DR or death due to any cause), participant will be censored at the date of the last valid disease assessment not showing disease relapse performed prior to initiation of a further anti-leukemic treatment (if any) or the analysis cut-off date, whichever comes first. Duration of CRc will not be calculated for participants who do not achieve a CRi or better.

Duration of CR+CRh (Duration of alternative CR)

Duration of CR+CRh is defined as the time from the first documented evidence of alternative CR (CR or CRh) until disease relapse (DR) as determined by the Investigator according to the 2022 ELN recommendations for diagnosis and management of AML or death due to any cause, whichever comes first. In the absence of the specified events (DR or death due to any cause), participant will be censored at the date of the last valid disease assessment not showing disease relapse performed prior to initiation of a further anti-leukemic treatment (if any) or the analysis cut-off date, whichever comes first. Duration of CR+CRh will not be calculated for participants who do not achieve a CR or CRh.

Event-Free survival (EFS)

Event-free survival is defined as the time from the first day of treatment assignment until treatment failure, relapse from remission, or death from any cause, whichever occurred first. Treatment failure was defined as failure to achieve CR, CRh, or CRi after the first 6 treatment cycles. Subjects who do not achieve CR, CRh, or CRi after 6 treatment cycles will be considered to have had an event at Day 1 of treatment. For the remaining CR, CRh, or CRi responders, the event time will be the time of either disease relapse or death, whichever occurs first. Event-free survival will be censored upon initiation of a new anticancer therapy should a new therapy be initiated prior to any EFS event.

Overall Survival (OS)

Overall survival is defined as the time from the first day of treatment assignment to death due to any cause. If death is not observed before the analysis cut-off date, OS will be censored at the last date participant is known to be alive or at the analysis cut-off date, whichever occurs first. Survival rate is the probability of participant surviving. Survival rate at 6 months, 1 year and 2 years will be provided, as well as median survival.

Hematopoietic stem cell transplantation (HSCT) rate

The HSCT rate is defined as the proportion of such participants who undergo HSCT through study treatment treatment but before subsequent therapy, among the safety/exposed population.

Time to treatment failure (TTF)

Time to treatment failure (TTF) is defined as the time from the first day of treatment assignment to the first discontinuation for any reason excluding remission, ie, disease relapse, refractory disease, unacceptable AE, patient preference, or death, whichever occurs first. In the absence of specified events (discontinuation for any reason excluding remission), participant will be censored at the date of the last valid disease assessment performed prior to initiation of a further anti leukemic treatment (if any) or the analysis cut-off date, whichever comes first. In the situation of no postbaseline disease assessment, participants will be censored at the date of the first study treatment administration.

Transfusion independence (TI) rate

The transfusion dependency (TD) at baseline is based on the receipt of any red blood cell or platelets transfusions within at least 28 days prior to the start of study treatment. For post baseline treatment, transfusion independency (TI) will be defined as the absence of transfusion during any 56 consecutive day period during treatment. The TI rate is defined differently for participants who were TD at baseline and participants who were TI at baseline. For subgroup of participants with TD at baseline, the TI rate is defined as the proportion of participants who convert from baseline TD to TI during on-treatment period; For subgroup of participants with TI at baseline, the TI rate is defined as the proportion of participants who remain TI during 56-day post-baseline period during treatment.

The ORR, CRc rate, alternative CR rate, HSCT, MRD and TI rate will be summarized with descriptive statistics. If applicable, the 90% two-sided CI computed using Clopper-Pearson method may be provided.

For Duration of CR, Duration of CRc, Duration of alternative CR, EFS, OS, and TTF, the following descriptive analyses will be performed:

- Number of participants who have events or have been censored will be summarized for each time-to-event endpoint.
- The Kaplan-Meier estimates of the 25th, 50th, and 75th percentiles and their associate 90% confidence intervals will be provided for each time-to-event endpoint.
- Number (%) of participants at risk as well as the probabilities of being event-free at different time points with 90% CIs using the Kaplan-Meier method.
- A listing of participants who achieve a response ≥ CRi will be provided.

For OS rates at 6 months, 1 year and 2 years, the Kaplan-Meier estimates and their associate 90% confidence intervals will be provided.

9.2.4 Tertiary/exploratory endpoints

[redacted]

9.2.5 Safety analyses

Please refer to the master protocol.

9.2.6 Pharmacokinetics

The pharmacokinetic parameters may be calculated using non-compartmental methods or by population PK analysis from plasma venetoclax and azacitidine concentrations.

A population PK analysis will be performed on SAR443579 data and reported in a standalone report. For the NCA, the parameters will include, but may not be limited to Table 11 (Please see Section 8.5).

A population PK approach may be used for tocilizumab.

The PK analyses will be described in the SAP finalized before database lock.

9.2.7 Pharmacodynamics

Individual, baseline and PDy parameters will be tabulated and summarized by descriptive statistics (such as mean, geometric mean, median, SD, standard error of the mean, coefficient of variation, minimum, and maximum). Potential correlation with other parameters such as safety and pharmacokinetic endpoints will be also investigated. Results will be also correlated with participants' clinical parameters as described in the Study Analysis Plan.

9.2.8 Other analysis

Please refer to the master protocol.

9.2.9 Timing of planned analysis

The first cut-off date will be at the end of the first cycle of the last participant treated and evaluable for DLT in the dose escalation part, in order to evaluate data from at least the first cycle for all participants when identifying the MTD, MAD, and preliminary RDE.

The second cut-off date will be when the last participant in the "optimization" part has completed 3 cycles of induction (or the required allowed additional induction cycles), has early discontinuation, or has reached CR, CRh or CRi, whichever occurs first, in order to assess malignancy response.

The third cut-off date will be when the last participant in the "expansion" part has completed 3 cycles of induction (or the required allowed additional induction cycles), has early discontinuation, or has reached CR, CRh or CRi, whichever occurs first, in order to assess malignancy response.

Different data extraction dates may apply depending on the timing of enrollments and data maturity.

The study completion date will be when the last participant in the "optimization/expansion" part has been followed for 24 months or until death (whichever occurs first), to document prolonged remission and survival rate at 2 years.

All primary analysis and key secondary analysis will be conducted at the third cut-off date. Safety results and efficacy results including but not limited to OS, TTF and EFS will be updated at the study completion date. After the third cut-off date, participants can continue to receive IMP, if clinical benefit is observed, until permanent discontinuation criteria described in Section 7 are met, and will continue to undergo all assessments as per the study schedule of activities unless otherwise specified in the protocol.

9.3 INTERIM ANALYSES

9.3.1 Dose expansion stopping rule based on safety

Stopping rules are defined in the master protocol.

9.4 SAMPLE SIZE DETERMINATION

Approximately 9-18 participants will be enrolled in dose escalation part.

9.5 DOSE ESCALATION DECISION RULES

A minimum of three DLT evaluable participants will be included in the dose escalation cohort. The target toxicity rate for the candidate dose is 0.20, with the acceptable toxicity probability interval of (0.15,0.25). The decision by the study board for dose escalation/de-escalation/stay will be performed after the completion of the DLT evaluation period of the last DLT evaluable participant at each dose level. The mTPI-2 decision rules are based on calculating the unit probability mass (UPM) of intervals as following: (0, 0.05), (0, 0.15), (0.15, 0.25), (0.25, 0.35), (0.35, 0.45), (0.45, 0.55) …… (0.85, 0.95), (0.95, 1). The interval with the largest UPM will be the winning interval and implies the corresponding -escalation decision. The winning interval with an upper limit lower than 0.15 indicates dose escalation; the winning interval being the equivalence interval (0.15,0.25) indicates staying at the current dose level; and the winning interval with a lower limit higher than 0.25 indicates dose de-escalation. The detailed mTPI-2 rules calculated with prior Beta (1/3, 1/3) are displayed in Table 13. When using Table 13, note the following:

- If the next dose level is considered to have unacceptable high toxicity, ie, the probability that the DLT rate is larger than 0.20 at the next dose is more than 0.80, then the next enrolled cohort should be kept into the last current dose and the higher dose will never be used (Decision “DU” in Table 13).
- If the current dose is the lowest dose and the rule indicates dose de-escalation, the Study Board and Sponsor will discuss if another 3 participants may be tested at this dose level.
- If the current dose is the highest dose and the rule indicates dose escalation, treat the new participants at the highest dose, until at least 6 participants had been treated at the highest dose, when the determination of candidate dose(s) will be made.
- The dose-escalation will proceed in a sequential manner, starting from a minimal of 3 DLT-evaluable participants at the lower dose level, and continuing by the mTPI-2 model recommendation.

Table 13 - Dose escalation rule of the modified toxicity probability interval-2 method

Number of participants treated at current dose					
# of participants with DLT	3	4	5	6	7
0	E	E	E	E	E
1	S	E	E	E	E
2	DU	DU	DU	D	S
3	DU	DU	DU	DU	DU
4		DU	DU	DU	DU
5			DU	DU	DU
6				DU	DU
7					DU

P = Escalate to the next higher dose level.
S = Add additional participants at this dose level.
D = De-escalate the dose level.
DU = Unacceptable toxicity at this dose level and no further evaluation will proceed.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

Please refer to master protocol.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

Please refer to master protocol

10.3 APPENDIX 3: AES AND SAES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTINGS

Please refer to master protocol.

10.4 APPENDIX 4: CONTRACEPTIVE AND BARRIER GUIDANCE

10.4.1 Definitions

See master protocol for details.

10.4.2 Contraception guidance

See master protocol for details.

10.5 APPENDIX 5: GENETICS

See master protocol for details.

10.6 APPENDIX 6: OTHER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS

10.6.1 Cytokine release syndrome (CRS)

ASTCT CONSENSUS GRADING FOR CRS (19)

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[a]	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		with		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		and/or[b]		
Hypoxia	None	Requiring low-flow nasal cannula[c] or blow-by	Requiring high-flow nasal cannula[c], facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.

a Fever is defined as temperature ≥38°C not attributable to any other cause. In participants who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

b CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a participant with temperature of 39.5°C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as Grade 3 CRS.

c Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

10.6.2 Immune effector cell-associated neurotoxicity syndrome (ICANS)

ASTCT CONSENSUS GRADING FOR ICANS (ADULTS)

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (participant is unarousable and unable to perform ICE)
Depressed level of consciousness[a]	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Participant is unarousable or requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 min); or Repetitive clinical or electrical seizures without return to baseline in between
Motor findings[b]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuroimaging[0]	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

Abbreviations: ICAN = Immune effector cell-associated neurotoxicity syndrome; N/A = not applicable.

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised ICP/cerebral edema) not attributable to any other cause; for example, a participant with an ICE score of 3 who has a generalized seizure is classified as Grade 3 ICANS.

* A participant with an ICE score of 0 may be classified as Grade 3 ICANS if awake with global aphasia, but a participant with an ICE score of 0 may be classified as Grade 4 ICANS if unarousable.

a Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

b Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading.

Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

10.6.3 Child-Pugh Scoring System

Child-Pugh Scoring System (24):

- Encephalopathy: None = 1 point, Grade 1 and 2 = 2 points, Grade 3 and 4 = 3 points
- Ascites: None = 1 point, slight = 2 points, moderate = 3 points
- Bilirubin: under 2 mg/ml = 1 point, 2 to 3 mg/ml = 2 points, over 3 mg/ml = 3 points
- Albumin: greater than 3.5mg/ml = 1 point, 2.8 to 3.5mg/ml = 2 points, less than 2.8mg/ml = 3 points
- Prothrombin Time* (sec prolonged): less than 4 sec = 1 point, 4 to 6 sec = 2 points, over 6 sec = 3 points

Frequently INR will be used as a substitute for PT, with INR under 1.7 = 1 point, INR 1.7 to 2.2 = 2 points, INR above 2.2 = 3 points

The severity of cirrhosis:

- Child-Pugh A: 5 to 6 points
- Child-Pugh B: 7 to 9 points
- Child-Pugh C: 10 to 15 points

10.7 APPENDIX 7: MEDICAL DEVICES AES, ADES, SAES, SADES, USADES AND DEVICE DEFICIENCIES: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING IN MEDICAL DEVICE STUDIES

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC/REGION REQUIREMENTS

10.8.1 China specific requirements

In the participants treated with SAR443579 in China during the expansion part:

- In Cycle 1, blood samples will be collected according to the PK/PDy flowcharts corresponding to the same dose level and administration route during the escalation phase from the main protocol as described in Section 1.3.1 and Section 1.3.3.
- From Cycle 2, blood samples will be collected according to the PK/PDy flowcharts corresponding to the adult expansion phase as described in Section 1.3.2 and Section 1.3.4.

These samples will be used for the measurement of plasma concentrations of SAR443579 to calculate the PK parameters and to assess the immunogenicity as a potential impact on PK, safety, and efficacy of SAR443579 in these Chinese participants.

Samples will be collected as described in Section 8.5 and Section 8.9, respectively.

Tertiary/exploratory biomarker samples related to safety (cytokines and soluble factors), target engagement (immune cell phenotyping) and predictive & prognostic (IgG) as described in Section 1.3 and Section 8.8 will only be collected and tested strictly following the guidance from local regulations in China.

Tertiary/exploratory genetics, genomics, transcriptomics and tumor biomarker samples will not be collected for participants in China. Therefore, tertiary/exploratory genetics, genomics, transcriptomics and other tumor biomarker sample collections as described in Section 1.3 and Section 8.8 are not applicable to participants in China.

In accordance with local requirements, the use of biological samples as described in Section 8.12 are not applicable for participants in China.

10.8.2 Germany

Informed consent process: All references to "legally authorized representative" are not applicable in Germany; only participants who can give written consent themselves are included in the study.

10.8.3 France

Exclusion criterion specific to France:

E 10. The participant is not affiliated to a social security scheme.

E 11. The participant is under tutorship or curatorship; the participant is under safeguard of justice or deprived of his/her liberty by an administrative or court decision.

10.8.4 European Union

10.8.4.1 Safety reporting to the agency

In the European Union, the Sponsor will comply with safety reporting requirements and procedures as described in the European Clinical Trials Regulation (EU) No 536/2014. All SUSARs to study treatment will be reported to the EudraVigilance database within the required regulatory timelines.

A single Annual Safety Report, aligned with ICH E2F, will include safety information for all study treatments (including the reference compound[s]).

Safety reporting with regard to authorized AxMPs shall be made in accordance with Chapter 3 of Title IX of Directive 2001/83/EC, irrespective if they are used in accordance with the terms of the marketing authorizations of these products. The Investigator is requested to report any suspected adverse reactions assessed as solely related to an authorized AxMP to the National Competent Authority via the national reporting system.

10.9 APPENDIX 9: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY THAT IS DECLARED BY A GOVERNMENTAL AGENCY

For European countries contingency measures are currently only applicable for the COVID-19 pandemic.

10.10 APPENDIX 10: COLLECTION, STORAGE AND FUTURE USE OF DATA AND HUMAN BIOLOGICAL SAMPLES

10.10.1 Compliance with Member State applicable rules for the collection, storage and future use of human biological samples (Article 7.1h)

This appendix is provided separately.

10.10.2 Compliance with Member State applicable rules for the collection, storage and future use of (personal) data (Article 7 (1 d) of EU Regulation 536/2014)

This appendix is provided separately.

10.11 APPENDIX 11: AZACITIDINE RISK ASSESSMENT

Please refer to the most recent country-approved product labeling (eg, United States Package Insert [USPI], Summary of Product Characteristics [SmPC]) for azacitidine for the most updated, detailed prescribing information

Table 14 - Risk assessment of azacitidine

Identified risk of clinical significance	Summary of data	Mitigation strategy
Haematological toxicity (anemia, neutropenia, thrombocytopenia)	Most commonly occurs in the first 2 cycles.	Routine: Monitor complete blood count (as detailed in the SoA Section 1.3). Monitoring of signs or symptoms of bleeding and infection. After administration of the recommended dose for the first cycle, the dose for subsequent cycles should be reduced or its administration delayed based on nadir counts and haematological response. Patients should be advised to promptly report febrile episodes.
Tumor Lysis Syndrome	The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment.	See Table 15 Venetoclax risk table TLS mitigation.
Hepatotoxicity/Hepatic Impairment	No formal studies have been conducted in patients with hepatic impairment. Patients with extensive tumour burden due to metastatic disease have been reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients with baseline serum albumin <30 g/L.	Routine: Exclusion criteria - Participants must have adequate liver function to be included (see inclusion/exclusion criteria) During treatment, regular monitoring of liver function tests (as detailed in the SoA Section 1.3). Monitor clinical signs and symptoms of hepatic impairment as part of TEAE.
Renal toxicity/Renal Impairment	Renal abnormalities ranging from elevated serum creatinine to renal failure and death were reported in patients treated with intravenous azacitidine in combination with other chemotherapeutic agents.	Routine: Exclusion criteria - Participants must have adequate renal function to be included (see inclusion/exclusion criteria). During treatment, regular monitoring of blood chemistry (as detailed in the SoA Section 1.3). Patients should be advised to report oliguria and anuria to the health care provider immediately.
Cardiac and pulmonary disease	Patients with a history of severe congestive heart failure, clinically unstable cardiac disease or pulmonary disease were excluded from the pivotal registration studies (AZA PH GL 2003 CL 001 and AZA-AML-001) and therefore the safety and efficacy of azacitidine in these patients has not been established. Recent data from a clinical study in patients with a known history of cardiovascular or pulmonary disease showed a significantly increased incidence of cardiac events with azacitidine.	Routine: Exclusion criteria: Participants must have adequate cardiac and pulmonary function to be included (see inclusion/exclusion criteria). Baseline Pulmonary function tests and assessment of LVEF (MUGA or echo) done at screening.

Identified risk of clinical significance	Summary of data	Mitigation strategy
Necrotizing fasciitis	Necrotizing fasciitis, including fatal cases, have been reported in patients treated with azacitidine.	Azacitidine therapy should be discontinued in participants who develop necrotizing fasciitis and appropriate treatment promptly initiated.
Differentiation syndrome (also known as retinoic acid syndrome)	Noted in patients treated receiving injectable azacitidine. May be fatal.	Routine: Monitor for symptoms and clinical findings which include the following: respiratory distress, pulmonary infiltrates, fever, rash, pulmonary oedema, peripheral oedema, rapid weight gain, pleural effusions, pericardial effusions, hypotension and renal dysfunction. Treatment: high dose IV steroids and hemodynamic monitoring. Temporary discontinuation of azacitidine should be considered until resolution of symptoms and if resumed, caution is advised.
Embryo-fetal toxicity		Routine: Exclusion of participants who are pregnant or breastfeeding. FOCBP must use highly effective contraceptive method for at least **6 months** after the last study treatment administration as per the Master Protocol.

10.12 APPENDIX 12: VENETOCLAX RISK ASSESSMENT

Please refer to the most recent country-approved product labeling (eg, United States Package Insert [USPI], Summary of Product Characteristics [SmPC]) for venetoclax for the most updated, detailed prescribing information.

Table 15 - Risk assessment of venetoclax

Identified risk of clinical significance	Summary of data	Mitigation strategy
Tumor Lysis Syndrome (TLS)	TLS including fatal events and renal failure requiring dialysis may result. Venetoclax can cause rapid reduction in tumour, and thus poses a risk for TLS at initiation and during the ramp-up phase. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase. During post-marketing surveillance, TLS, including fatal events, has been reported	Routine: Exclusion Criteria: All patients should have white blood cell count <25 × 10^9/ L prior to initiation of venetoclax and cytoreduction prior to treatment may be required. Prior to initiation of first dose of venetoclax and during ramp-up phase, all patients should be adequately hydrated per institution guidelines and receive anti-hyperuricaemic agents per standard guidelines. Assess blood chemistry (potassium, uric acid, phosphorus, corrected calcium, and creatinine) and promptly correct all abnormalities: • Prior to initiation of treatment with venetoclax. • Every 6 to 8 hours after each new dose during ramp-up and 24 hours after reaching final dose. • For patients with risk factors for TLS (eg, circulating blasts, high burden of leukaemia involvement in bone marrow, elevated pre-treatment lactate

Identified risk of clinical significance	Summary of data	Mitigation strategy
	after a single 20 mg dose of venetoclax.	dehydrogenase [LDH] levels, splenomegaly or reduced renal function) additional measures should be considered, including increased laboratory monitoring and reducing venetoclax starting dose. Employ more intensive measures (intravenous hydration, frequent monitoring, hospitalization) as overall risk increases. See Section 6.6.5.5 Tumor Lysis Syndrome (additional guidance).
Neutropenia	In patients with AML, grade 3 or 4 neutropenia are common before starting treatment. The neutrophil counts can worsen with venetoclax in combination with a hypomethylating agent. Neutropenia can recur with subsequent cycles of therapy.	Routine: Monitor CBC throughout the treatment period. • Monitor CBC with differential at pre-dose, and prior to each new dose during ramp-up (Day 1-3). • Monitor CBC with differential daily through resolution of Grade 3-4 neutropenia. Dose modifications and interruptions for cytopenias is dependent on remission status.
Infections	Fatal and serious infections, such as pneumonia and sepsis, have occurred in patients treated with venetoclax.	Routine: Monitoring of any signs and symptoms of infection is required. Suspected infections are to receive prompt treatment, including antimicrobials, dose interruption or reduction, and use of growth factors (eg, G-CSF) as appropriate. Withhold venetoclax for Grade 3 and 4 infection until resolution.
Immunizations	The safety and efficacy of immunization with live attenuated vaccines during or following venetoclax therapy have not been studied.	**Exclusion criteria:** **Participants should not receive live vaccines up to 28 days prior to enrollment, during or after treatment** until B-cell recovery.
Embryo-fetal toxicity	Based on findings in animals and its mechanism of action, venetoclax may cause embryofetal harm when administered to a pregnant woman. In an embryo-fetal study conducted in mice, administration of venetoclax to pregnant animals at exposures equivalent to that observed in patients at a dose of 400 mg daily resulted in post-implantation loss and decreased fetal weight. Advise pregnant women of the potential risk to a fetus.	Exclusion criteria: Exclusion of participants who are pregnant or breastfeeding. FOCBP must use highly effective contraceptive method for at least 6 months after the last study treatment administration as per the Master Protocol.
CYP3A Inducers	Co-administration may lead to decreased exposure and risk a lack of efficacy.	Concomitant use of venetoclax with strong or moderate CYP3A4 inducers should be avoided.

10.13 APPENDIX 13: DRUG-DRUG INTERACTIONS VENETOCLAX

Concomitant administration of medications that are strong or moderate CYP3A inducers are not permitted throughout the active treatment phase.

The following tables were extracted in October 2023 from the Drug Interaction Database from the University of Washington (www.druginteractionsolution.org).

STRONG AND MODERATE CYP3A INDUCERS				
CYP 3A Inducers	**Therapeutic Class**	**Clinical substrate used in DDI**	**Max AUCR**	**Perpetrator Dose**
Strong Inducers (AUCR ≤0.2 or CL Ratio ≥5)				
apalutamide	Antiandrogens	midazolam	0.08	240 mg - QD duration: 29 days
avasimibe	Other Antilipemics	midazolam	0.06	750 mg/day - NP duration: 7 days
carbamazepine	Anticonvulsants	quetiapine	0.13	200 mg - TID duration: 26 days
enzalutamide	Antiandrogens	midazolam	0.14	160 mg - QD duration: 85 ±3 days
ivosidenib	Cancer Treatments	midazolam	0.17 (PBPK)	500 mg - QD duration: 19 days
lumacaftor	Cystic Fibrosis Treatments	ivacaftor	0.20	NP - NP duration: NP
mitotane	Other Antineoplastics	midazolam	0.06	≤3500 mg - TID duration: chronic administration
phenytoin	Anticonvulsants	nisoldipine	0.11	200-450 mg/day - NP duration: chronic administration
rifampin	Antibiotics	budesonide	0.003	600 mg - QD duration: 7 days
rifapentine	Antibiotics	midazolam	0.07	20 mg/kg - QD duration: 14 days
st. John's wort (Hypericum perforatum)	Herbal Medications	midazolam	0.20	300 mg - TID duration: 14 days
Moderate Inducers (AUCR ≤0.2 or CL Ratio ≥5)				
asunaprevir and beclabuvir and daclatasvir	Antivirals	midazolam	0.42	200 mg / 150 mg / 30 mg -BID duration:15 days
bersacapavir	Antivirals	midazolam	0.46	170 mg -QD duration: 20 days
bosentan	Endothelin Receptor Antagonists	sildenafil	0.31	62.5-125 mg -BID duration:8 weeks
cenobamate	Anticonvulsants	midazolam	0.28	200 mg -QD duration: 98 days
dabrafenib	Kinase Inhibitors	midazolam	0.26	150 mg -BID duration: repeated dosing
efavirenz	NonNucleoside Reverse Transcriptase Inhibitors (NNRTIs)	alfentanil	0.24	600 mg -QD duration:20 days
elagolix	Other	midazolam	0.45	300 mg -BID duration:11 days
etravirine	NonNucleoside Reverse Transcriptase Inhibitors (NNRTIs)	sildenafil	0.43	800 mg -BID duration:13.5 days
JTE-761	Anti-inflammatory Drugs	midazolam	0.46	400 mg -QD duration:15 days
lersivirine	NonNucleoside Reverse Transcriptase Inhibitors (NNRTIs)	midazolam	0.49	1000 mg -BID duration:14 days
lesinurad	Antigout and Uricosuric Agents	sildenafil	0.29	600 mg -QD duration:10 days

STRONG AND MODERATE CYP3A INDUCERS				
CYP 3A Inducers	**Therapeutic Class**	**Clinical substrate used in DDI**	**Max AUCR**	**Perpetrator Dose**
lopinavir	Protease Inhibitors	amprenavir	0.40	400 mg -BID duration:4 weeks
lorlatinib	Kinase Inhibitors	midazolam	0.36	150 mg -QD duration:15 days
metamizole (dipyrone)	Other Analgesics	midazolam	0.32	1000 mg -QID duration:7 days
mitapivat	Miscellaneous Agents	midazolam	0.43 (PBPK)	50 mg -BID duration:14 days
modafinil	Psychostimulants	triazolam	0.42	200-400 mg -QD duration:28 days
nafcillin	Antibiotics	nifedipine	0.37	500 mg -QID duration:5 days
pexidartinib	Kinase Inhibitors	midazolam	0.43	400 mg -BID duration:11 days
PF-06282999	Myeloperoxidase Inactivators	midazolam	0.43	500 mg -BID duration:14 days
phenobarbital	Anticonvulsants	nifedipine	0.39	100 mg -QD duration:8 days
rifabutin	Antibiotics	midazolam	0.32	300 mg -QD duration:26 days
semagacestat	Alzheimer's Disease & Dementia Treatments	midazolam	0.24	140 mg -QD duration:10 days
sotorasib	Kinase Inhibitors	midazolam	0.47	960 mg -QD duration:21 days
talviraline	NonNucleoside Reverse Transcriptase Inhibitors (NNRTIs)	indinavir	0.38	500 mg -TID duration:14 days
telotristat ethyl	Antidiarrheals	midazolam	0.49	500 mg -QD duration:5 days
thioridazine	Antipsychotics	quetiapine	0.31	100-300 mg -QD duration:15 days
tipranavir and ritonavir	Protease inhibitors	saquinavir	0.24	500 mg / 200 mg -BID duration:14 days

Concomitant administration of medications that are strong or moderate CYP3A inhibitor or P-gp inhibitor increases venetoclax exposure.

The following tables were extracted in October 2023 from the Drug Interaction Database from the University of Washington (www.druginteractionsolution.org).

STRONG AND MODERATE CYP3A INHIBITORS				
P-gp inhibitors Inducers	**Therapeutic Class**	**Clinical substrate used in DDI**	**Max AUCR**	**Perpetrator Dose**
Strong CYP3A Inhibitors (AUCR ≥5 or CL Ratio ≤0.20)				
adagrasib	Cancer Treatments	midazolam	20.50	400 mg - BID duration: 9 days
boceprevir	Antivirals	midazolam	5.05	800 mgTID6 days
ceritinib	Kinase Inhibitors	midazolam	5.42	750 mgQD28 days
clarithromycin	Antibiotics	midazolam	8.39	500 mgBID7 days
cobicistat	Pharmacokinetic Enhancer	midazolam	19.03	200 mgQD14 days
danoprevir and ritonavir	Antivirals	midazolam	13.42	200 mg / 100 mgQD14 days

STRONG AND MODERATE CYP3A INHIBITORS				
P-gp inhibitors Inducers	**Therapeutic Class**	**Clinical substrate used in DDI**	**Max AUCR**	**Perpetrator Dose**
elvitegravir and ritonavir	Treatments of AIDS	midazolam	12.80	150 mg / 100 mgQD10 days
ensitrelvir	Antivirals	midazolam	8.80	250 mgQD 6 days
grapefruit juice - double strength	Food Products	midazolam	5.95	240 mLTID2 days
idelalisib	Kinase Inhibitors	midazolam	5.37	150 mgBID8 days
indinavir	Protease Inhibitors	midazolam	9.67	800 mgQD4 doses over 2 days
indinavir and ritonavir	Protease Inhibitors	alfentanil	36.50	800 mg / 100 mgBID1 day
itraconazole	Antifungals	midazolam	10.80	200 mgQD4 days
josamycin	Antibiotics	ivabradine	7.70	NPNPNP
ketoconazole	Antifungals	midazolam	17.08	400 mgQD5 days
LCL161	Cancer Treatments	midazolam	8.80	600 mgSDNA
lonafarnib	Other	midazolam	7.39	100 mgBID5 days
lopinavir and ritonavir	Protease Inhibitors	alfentanil	11.47	400 mg / 100 mgBID2 days
mibefradil	Calcium Channel Blockers	midazolam	8.86	100 mgSDNA
mifepristone	Antiprogestins	simvastatin	10.40	1200 mgQD10 days
nefazodone	Antidepressants	midazolam	5.44	100-200 mgBID12 days
nelfinavir	Protease Inhibitors	midazolam	5.29	1250 mgBID14 days
nirmatrelvir and ritonavir	Antivirals	midazolam	14.30	300 mg / 100 mgBID9 doses
ombitasvir and paritaprevir and ritonavir	Antivirals	tacrolimus	85.92	25 mg / 150 mg / 100 mgQD28 days
ombitasvir and paritaprevir and ritonavir and dasabuvir	Antivirals	tacrolimus	55.76	25 mg / 150 mg / 100 mg / 800 mgNP28 days
posaconazole	Antifungals	midazolam	6.23	400 mgBID7 days
relacorilant	Anti-Inflammatory Drugs	midazolam	8.93	350 mgQD13 days
ribociclib	Kinase Inhibitors	midazolam	5.17	600 mgQD8 days
ritonavir	Protease Inhibitors	midazolam	26.41	100 mgTID3 doses
saquinavir	Protease Inhibitors	midazolam	5.18	1200 mgTID5 days
saquinavir and ritonavir	Protease Inhibitors	midazolam	12.48	1000 mg / 100 mgBID14 days
telaprevir	Antivirals	midazolam	13.50	750 mgTID16 days
telithromycin	Antibiotics	midazolam	6.20	800 mgQD6 days
tipranavir and ritonavir	Protease Inhibitors	midazolam	26.91	500 mg / 200 mgBID2 days
troleandomycin	Antibiotics	midazolam	14.80	500 mgSDNA
tucatinib	Kinase Inhibitors	midazolam	5.74	300 mgBID10 days
voriconazole	Antifungals	midazolam	9.63	200 mgBID9 days

STRONG AND MODERATE CYP3A INHIBITORS				
P-gp inhibitors Inducers	**Therapeutic Class**	**Clinical substrate used in DDI**	**Max AUCR**	**Perpetrator Dose**
Moderate CYP3A Inhibitors (2.0 ≤ AUCR <5.0 or 0.20 < CL Ratio ≤0.50)				
ACT-178882	Renin Inhibitors	midazolam	2.19	PO - 300 mg duration: QD
ACT-539313	Hypnotics - Sedatives	midazolam	4.53	PO - 200 mg duration: BID
amprenavir	Protease Inhibitors	rifabutin	2.93	PO - 1200 mg duration: BID
aprepitant	Neurokinin-1 Receptor Antagonists	midazolam	3.29	PO - 80-125 mg duration: QD
atazanavir	Protease Inhibitors	maraviroc	3.57	PO - 400 mg duration: QD
atazanavir and ritonavir	Protease Inhibitors	maraviroc	4.90	PO - 300 mg / 100 mg duration: BID
berotralstat	Immune System Agents	midazolam	2.24	PO - 150 mg duration: QD
casopitant	Neurokinin-1 Receptor Antagonists	midazolam	3.13	PO - 120 mg duration: QD
ciprofloxacin	Antibiotics	sildenafil	2.12	PO - 500 mg duration: SD
clofazimine	Antiinfective Agents	ivacaftor	2.98 (PBPK)	PO - 100 mg duration: QD
conivaptan	Vasopressin Antagonists	midazolam	3.39	IV - 20 mg then 40 mg duration: QD
crizotinib	Kinase Inhibitors	midazolam	3.65	PO - 250 mg duration: BID
darunavir	Protease Inhibitors	saquinavir	4.90	PO - 1200 mg duration: BID
darunavir and ritonavir	Protease Inhibitors	sildenafil	4.00	PO - 400 mg / 100 mg duration: BID
diltiazem	Calcium Channel Blockers	midazolam	4.06	PO - 60 mg duration: TID
dronedarone	Antiarrhythmics	simvastatin	3.66	PO - 400 mg duration: BID
duvelisib	Kinase Inhibitors	midazolam	4.30	PO - 25 mg duration: QD
erythromycin	Antibiotics	midazolam	4.99	PO - 1000 mg duration: SD
faldaprevir	Antivirals	midazolam	2.92	PO - 240 mg duration: BID
fedratinib	Kinase Inhibitors	midazolam	3.52	PO - 500 mg duration: QD
FK1706	Central Nervous System Agents	midazolam	2.01	PO - 60 mg duration: QD
fluconazole	Antifungals	midazolam	4.93	PO - 400 mg duration: SD
fosravuconazole (ravuconazole)	Antifungals	midazolam	3.01	PO - 400 mg then 200 mg duration: BID / QD
grapefruit juice	Food Products	midazolam	2.39	PO - 240 mL duration: QD
GSK2647544	Alzheimer's Disease & Dementia Treatments	simvastatin	3.30	PO - 80 mg duration: BID
imatinib	Kinase Inhibitors	simvastatin	2.92	PO - 400 mg duration: QD
ipatasertib	Kinase Inhibitors	midazolam	2.22	PO - 600 mg duration: QD
isavuconazonium sulfate (isavuconazole)	Antifungals	midazolam	2.03	PO - 200 mg duration: TID
lefamulin	Antibiotics	midazolam	3.18	PO - 600 mg duration: BID
lenacapavir	Antivirals	midazolam	4.08	PO - 600 mg duration: BID

STRONG AND MODERATE CYP3A INHIBITORS				
P-gp inhibitors Inducers	**Therapeutic Class**	**Clinical substrate used in DDI**	**Max AUCR**	**Perpetrator Dose**
letermovir	Antivirals	midazolam	3.44 (PBPK)	PO - 480 mg duration: QD
netupitant	Antiemetics	midazolam	2.44	PO - 300 mg duration: SD
nilotinib	Kinase Inhibitors	midazolam	2.40	PO - 400 mg duration: BID
ritlecitinib	Immunosuppressants	midazolam	2.69	PO - 200 mg duration: QD
Schisandra sphenanthera	Herbal Medications	midazolam	2.05	PO - 3 capsules duration: BID
tofisopam	Benzodiazepines	midazolam	2.36	PO - 100 mg duration: TID
treosulfan	Alkylating Agents	midazolam	2.23 (PBPK)	IV - 14 g/m2 duration: QD
verapamil	Calcium Channel Blockers	midazolam	2.92	PO - 80 mg duration: TID
voxelotor	Hemoglobin S Polymerization Inhibitors	midazolam	2.05 (PBPK)	PO - 1500 mg duration: QD

P-gp INHIBITORS				
P-gp inhibitors Inducers	**Therapeutic Class**	**Clinical substrate used in DDI**	**Max AUCR**	**Perpetrator Dose**
abrocitinib	Kinase Inhibitors	dabigatran	1.53	200 mg - SD duration: NA
adagrasib	Cancer Treatments	digoxin	1.48 (PBPK)	600 mg - BID duration: steady-state
alogliptin	Dipeptidyl Peptidase-4 Inhibitors	fexofenadine	1.26	100 mg - QD duration: 7 days
amiodarone	Antiarrhythmics	dabigatran	1.58	600 mg - SD duration: NA
amiodarone	Antiarrhythmics	digoxin	1.68	800 mg/day - NP duration: 7 days
asian ginseng (Panax ginseng)	Herbal Medications	fexofenadine	1.31	70 mL - NP duration: 14 days
asunaprevir	Antivirals	digoxin	1.30	200 mg - BID duration: 13 days
AZD5672	CCR5 Receptor Antagonists	digoxin	1.33	150 mg - QD duration: 13 days
azithromycin	Antibiotics	fexofenadine	1.72	250 mg - QD duration: 5 days
berotralstat	Immune System Agents	digoxin	1.48	300 mg - QD duration: 11 days
boceprevir	Antivirals	digoxin	1.19	800 mg - TID duration: 10 days
canagliflozin	Sodium-dependent Glucose 2 (SGLT2) Inhibitors	digoxin	1.20	300 mg - QD duration: 7 days
capmatinib	Kinase Inhibitors	digoxin	1.63	400 mg - BID duration: 22 days
captopril	Angiotensin Converting Enzyme (ACE) Inhibitors	digoxin	1.39	12.5 mg - TID duration: 7 days
carvedilol	Alpha/Beta Adrenergic Antagonists	digoxin	1.57	6.25 mg - BID duration: 7 days
CC-90001	Other	digoxin	1.16	400 mg - QD duration: 6 days

P-gp INHIBITORS				
P-gp inhibitors Inducers	**Therapeutic Class**	**Clinical substrate used in DDI**	**Max AUCR**	**Perpetrator Dose**
cimetidine	H-2 Receptor Antagonists	digoxin	1.26	400 mg - 6 doses at 1 h before, then 4, 8, 12, 24, and 36 h post cocktail object dosing duration: 1.5 days
clarithromycin	Antibiotics	dabigatran	4.02	500 mg - BID duration: 5 days
clarithromycin	Antibiotics	fexofenadine	2.54	500 mg - BID duration: 7 days
clarithromycin	Antibiotics	digoxin	1.68	500 mg - BID duration: 7 days
clopidogrel	Anticoagulants and Antiplatelets	dabigatran	1.35	300 mg - SD duration: NA
cobicistat	Pharmacokinetic Enhancer	dabigatran	2.37	150 mg - QD duration: 22 days
conivaptan	Vasopressin Antagonists	digoxin	1.43	40 mg - BID duration: 10 days
cremophor EL	Excipients	fexofenadine	1.28	1440 mg - SD duration: NA
cremophor RH40	Excipients	digoxin	1.21	600 mg - TID duration: 9 days
curcumin	Food Products	talinolol	1.54	1000 mg - QD duration: 14 days
cyclosporine	Immunosuppressants	edoxaban	1.73	500 mg - SD duration: NA
daclatasvir	Antivirals	digoxin	1.27	60 mg - QD duration: 10 days
diltiazem	Calcium Channel Blockers	digoxin	1.44	60 mg - TID duration: 10 days
diosmin	Herbal Medications	fexofenadine	1.66	150 mg - QD duration: 10 days
dronedarone	Antiarrhythmics	dabigatran	2.14	400 mg - SD duration: NA
dronedarone	Antiarrhythmics	digoxin	2.57	400 mg - BID duration: 10 days
elacestrant	Antineoplastic Hormonal	digoxin	1.13	345 mg - SD duration: NA
elagolix	Other	digoxin	1.32	200 mg - SD duration: NA
eliglustat	Glucosylceramide Synthase Inhibitors	digoxin	1.49	100 mg or 150 mg - BID duration: 7 days
enasidenib	Cancer Treatments	digoxin	1.20	100 mg - QD duration: 28 days
ensitrelvir	Antivirals	digoxin	1.31	500 mg - SD duration: NA
entrectinib	Kinase Inhibitors	digoxin	1.18	600 mg - SD duration: NA
enzalutamide	Antiandrogens	digoxin	1.35	160 mg - QD duration: 64 days
erythromycin	Antibiotics	talinolol	1.52	2000 mg - SD duration: NA
erythromycin	Antibiotics	fexofenadine	2.09	500 mg - TID duration: 7 days
felodipine	Calcium Channel Blockers	digoxin	1.49	2.5 mg - SD duration: NA
flibanserin	Central Nervous System Agents	digoxin	1.93	100 mg - QD duration: 8 days
fluvoxamine	Selective Serotonin Reuptake Inhibitors (SSRIs)	fexofenadine	1.78	50 mg - QD duration: 7 days
fostamatinib	kinase inhibitor	digoxin	1.37	100 mg - BID duration: 7 days
ginkgo (Ginkgo biloba)	Herbal Medications	talinolol	1.25	120 mg - TID duration: 14 days

P-gp INHIBITORS				
P-gp inhibitors Inducers	**Therapeutic Class**	**Clinical substrate used in DDI**	**Max AUCR**	**Perpetrator Dose**
glecaprevir and pibrentasvir	Antivirals	dabigatran	2.38	300 mg / 120 mg - QD duration: 10 days
glecaprevir and pibrentasvir	Antivirals	digoxin	1.48	400 mg / 120 mg - QD duration: 12 days
ibrexafungerp	Antifungals	dabigatran	1.40	750 mg - BID / QD duration: 4 days
indinavir	Protease Inhibitors	fexofenadine	3.31	80 mg - TID duration: 21 days
indinavir and ritonavir	Protease Inhibitors	fexofenadine	4.84	800 mg / 100 mg - BID duration: 1 day
isavuconazonium sulfate (isavuconazole)	Antifungals	digoxin	1.25	NP - NP duration: NP
istradefylline	Other Antiparkinsonians	digoxin	1.21	40 mg - QD duration: 21 days
itraconazole	Antifungals	fexofenadine	3.01	200 mg - SD duration: NA
itraconazole	Antifungals	dabigatran	6.92	200 mg - QD duration: 5 days
itraconazole	Antifungals	digoxin	2.09	200 mg - QD duration: NP
ivacaftor	Other	digoxin	1.32	150 mg - NP duration: 9 days
ketoconazole	Antifungals	fexofenadine	2.74	400 mg - QD duration: 7 days
ketoconazole	Antifungals	dabigatran	2.53	400 mg - QD duration: 8 days
lapatinib	Kinase Inhibitors	digoxin	2.80	NP - NP duration: NP
lenacapavir	Antivirals	tenofovir alafenamide fumarate	1.32	600 mg - BID duration: 5 doses
lonafarnib	Other	fexofenadine	1.24	100 mg - BID duration: 5 days
lopinavir and ritonavir	Protease Inhibitors	fexofenadine	4.00	400 mg / 100 mg - SD duration: NA
lopinavir and ritonavir	Protease Inhibitors	digoxin	1.81	400 mg / 100 mg - BID duration: 14 days
maribavir	Antivirals	digoxin	1.22	400 mg - BID duration: 8 days
mibefradil	Calcium Channel Blockers	digoxin	1.31	150 mg - QD duration: 7 days
mifepristone	Antiprogestins	digoxin	1.40	1200 mg - QD duration: 10 days
milk thistle (Silybum marianum)	Herbal Medications	talinolol	1.30	140 mg - TID duration: 14 days
mirabegron	Beta3-Adrenoreceptor Agonist	digoxin	1.26	100 mg - QD duration: 14 days
nelfinavir	Protease Inhibitors	digoxin	1.35	1250 mg - BID duration: 14 days
neratinib	Kinase Inhibitors	digoxin	1.32	240 mg - QD duration: multiple doses
nifedipine	Calcium Channel Blockers	digoxin	1.23	10 mg - TID duration: 7 days
nirmatrelvir and ritonavir	Antivirals	dabigatran	1.95	300 mg / 100 mg - BID duration: 5 doses
ombitasvir and paritaprevir and ritonavir	Antivirals	digoxin	1.35	25 mg / 150 mg / 100 mg - QD duration: 19 days

P-gp INHIBITORS				
P-gp inhibitors Inducers	**Therapeutic Class**	**Clinical substrate used in DDI**	**Max AUCR**	**Perpetrator Dose**
osimertinib	Kinase Inhibitors	fexofenadine	1.54	80 mg - SD duration: NA
paroxetine	Selective Serotonin Reuptake Inhibitors (SSRIs)	fexofenadine	1.38	20 mg - QD duration: 7 days
piperine	Food Products	fexofenadine	1.70	20 mg - QD duration: 10 days
pirtobrutinib	Kinase Inhibitors	digoxin	1.35	200 mg - QD duration: NP
propafenone	Antiarrhythmics	digoxin	1.29	300 mg - TID duration: 12 days
quercetin	Herbal Medications	fexofenadine	1.56	500 mg - TID duration: 7 days
quinidine	Antiarrhythmics	dabigatran	1.53	1000 mg - Q2H duration: 5 doses
quinidine	Antiarrhythmics	fexofenadine	2.14	25 mg - SD duration: NA
quinidine	Antiarrhythmics	digoxin	2.66	600 mg - BID duration: 8 days
ranolazine	Cardiovascular Drugs	digoxin	1.88	750 mg - BID duration: 6 days
rifampin	Antibiotics	fexofenadine	3.21-3.57	600 mg - SD duration: NA
rifampin	Antibiotics	dabigatran	2.32	600 mg - SD duration: NA
rifampin	Antibiotics	digoxin	1.46	600 mg - QD duration: 28 days
ritonavir	Protease Inhibitors	fexofenadine	2.75	200 mg / 300 mg / 400 mg - TID / BID / BID duration: 1 day / 7 days / 13 days
ritonavir	Protease Inhibitors	digoxin	1.86	300 mg - BID duration: 11 days
ritonavir	Protease Inhibitors	digoxin	1.47	400 mg - BID duration: 14 days
ritonavir	Protease Inhibitors	dabigatran	1.69	100 mg - Q12H duration: 2 days
rolapitant	Antiemetics	digoxin	1.27	180 mg - SD duration: NA
rucaparib	Cancer Treatments	digoxin	1.21	600 mg - BID duration: 12 days
saquinavir and ritonavir	Protease Inhibitors	digoxin	1.68	1000 mg / 100 mg - BID duration: 16 days
Schisandra chinensis	Herbal Medications	talinolol	1.52	300 mg - BID duration: 14 days
simeprevir	Antivirals	digoxin	1.39	150 mg - QD duration: 7 days
sofosbuvir and velpatasvir and voxilaprevir	Antivirals	dabigatran	2.59	400 mg / 100 mg / 200 mg - QD duration: 11 days
sotorasib	Kinase Inhibitors	digoxin	1.21	960 mg - SD duration: NA
st. John's wort (Hypericum perforatum)	Herbal Medications	fexofenadine	1.31	900 mg - SD duration: NA
suvorexant	Hypnotics - Sedatives	digoxin	1.27	40 mg - QD duration: 11 days
talinolol	Alpha/Beta Adrenergic Antagonists	digoxin	1.23	100 mg - SD duration: NA
telaprevir	Antivirals	digoxin	1.85	750 mg - TID duration: 16 days
telithromycin	Antibiotics	digoxin	1.36	800 mg - QD duration: 5 days
telmisartan	Angiotensin II Inhibitors (Angiotensin Receptor Blockers or ARBs)	digoxin	1.22	120 mg - QD duration: 7 days
tepotinib	Kinase Inhibitors	dabigatran	1.51	500 mg - QD duration: 8 days

P-gp INHIBITORS				
P-gp inhibitors Inducers	**Therapeutic Class**	**Clinical substrate used in DDI**	**Max AUCR**	**Perpetrator Dose**
tezacaftor and ivacaftor	Other	digoxin	1.30	100 mg / 150 mg - QD / Q12H duration: 14 days
ticagrelor	Anticoagulants and Antiplatelets	digoxin	1.28	400 mg - QD duration: 16 days
tipranavir and ritonavir	Protease Inhibitors	digoxin	1.65	500 mg / 200 mg - BID duration: 2 days
tipranavir and ritonavir	Protease Inhibitors	digoxin	1.46	500 mg / 200 mg - BID duration: 2 days
tocophersolan (TPGS, Vitamin E-TPGS)	Excipients	talinolol	1.20	0.0004 - SD duration: NA
tolvaptan	Vasopressin Antagonists	digoxin	1.18	60 mg - QD duration: 5 days
tucatinib	Kinase Inhibitors	digoxin	1.50	300 mg - BID duration: 14 days
tucatinib	Kinase Inhibitors	digoxin	1.46	300 mg - Q12H duration: 14 days
valbenazine	Central Nervous System Agents	digoxin	1.36	80 mg - SD duration: NA
valspodar	Transporter Modulators	digoxin	3.05	200 mg - BID duration: 5 days
vandetanib	Kinase Inhibitors	digoxin	1.23	300 mg - SD duration: NA
velpatasvir	Antivirals	digoxin	1.34	100 mg - QD duration: 4 days
vemurafenib	Kinase Inhibitors	digoxin	1.91	960 mg - BID duration: 28 days
verapamil	Calcium Channel Blockers	dabigatran	2.42	120 mg - SD duration: NA
verapamil	Calcium Channel Blockers	fexofenadine	2.51	80 mg - TID duration: 6 days
verapamil	Calcium Channel Blockers	digoxin	1.50	80 mg - BID / TID duration: 4 days / 10 days
verapamil	Calcium Channel Blockers	digoxin	1.24	80 mg - BID / TID duration: 4 days / 10 days
vilazodone	Serotonin Modulators	digoxin	1.20	NP - NP duration: NP
voclosporin	Immunosuppressants	digoxin	1.25	0.4 mg/kg - Q12H duration: 11 days

10.14 APPENDIX 14: MODIFIED ELN 2022 CRITERIA

Category	Definition
Response	
Complete Remission (CR)†*	Bone marrow blasts <5%; absence of circulating blasts[c]; absence of extramedullary disease; ANC >1.0 × 10^9/L (1000/µL); platelet count >100 × 10^9/L (100 000/µL)
CR with partial hematologic recovery (CRh)†*	ANC >0.5 × 10^9/L (500/µL) and platelet count >50 × 10^9/L (50 000/µL), otherwise all other CR criteria met

Category	Definition
Response	
CR with incomplete hematologic recovery (CRi)†*[a]	All CR criteria except for residual neutropenia ≤1.0 × 10^9/L (1000/µL) or thrombocytopenia ≤100 × 10^9/L (100 000/µL)
Morphologic leukemia-free state (MLFS)[b]	Bone marrow blasts <5%; absence of circulating blasts; absence of extramedullary disease; no hematologic recovery required
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pre-treatment bone marrow blast percentage by at least 50%
No response	Patients evaluable for response but not meeting the criteria for CR, CRh, CRi, MLFS or PR are categorized as having no response prior to the response landmark. Patients failing to achieve CR, CRh, CRi response by the designated landmark are designated as having refractory disease
Non evaluable for response	Non-evaluable for response will include patients lacking an adequate bone marrow response evaluation. This category will include patients with early death, withdrawal prior to response assessment, or a technically suboptimal bone marrow sample precluding assessment
Response (if including assessment of MRD) CR, CRh, or Cri without MRD‡ (CR_{MRD-}, CRh_{MRD} or Cri_{MRD-})	CR, CRh or CRi with MRD below a defined threshold for a genetic marker by qPCR, or by MFC. Response without MRD should be confirmed with a subsequent assessment at least 4 wk apart. The date of response without MRD is the first date in which the MRD was below the defined threshold Response with MRD detection at low-level (CR_{MRD-LL}) is included in this category of CR, CRh or CRi without MRD. CR_{MRD-LL} is currently only defined for NPM1- mutant and CBF-AML
Refractory disease	No CR, CRh, CRi at the response landmark
Relapsed disease (after CR, CRh or CRi)	Bone marrow blasts ≥5%; or reappearance of blasts in the blood in at least 2 peripheral blood samples at least one week apart; or development of extramedullary disease
MRD relapse (after CR, CRh or CRi without MRD	1. Conversion from MRD negativity to MRD positivity, independent of method, or 2. Increase of MRD copy numbers ≥1 $\log_{10}$ between any two positive samples in patients with CR_{MRD-LL}, CRh_{MRD-LL} or Cri_{MRD-LL} by qPCR The result of 1. or 2. should be rapidly confirmed in a second consecutive sample from the same tissue source

Sources:(25, 26)

† For patients with CR, CRh, or CRi, the presence of a low percentage of circulating blasts in the blood may represent a regenerating marrow and should not be interpreted as persistent disease.

‡ A response landmark for CR, CRh, or CRi should be stated, eg, after 2 cycles of intensive therapy; this landmark may be longer for nonintensive based treatment options, eg, 180 days.

* Patients should not have received G-CSF, nor platelet transfusions within 7 days prior to hematologic response determination.

a CRi should only include patients not meeting the definition of CRh

b Marrow should not merely be "aplastic"; bone marrow spicules should be present; at least 200 cells should be enumerated in the aspirate or cellularity should be at least 10% in the biopsy.

c Absences of leukemic blast in periphery should be assessed by morphology.

10.15 APPENDIX 15: CYTOGENETIC RISK

Table 16 - 2022 ELN risk classification by genetics at initial diagnosis

Risk category	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11* • Mutated *NPM1* without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*
Intermediate	• Mutated *NPM1* with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A* • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11;p13)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2*, *MECOM(EVI1)* • t(3q26.2;v)/*MECOM(EVI1)*-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype, monosomal karyotype • Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2 • Mutated *TP53*

10.16 APPENDIX 16: CLINICAL OUTCOME ASSESSMENT (COA)

10.16.1 Quality of life in acute myeloid leukemia (AML-QoL)

AML-QOL

Please mark the answer for how you felt over the last **7 days**...

	Never	Rarely	Sometimes	Often	Almost always
Physical					
1. I felt fatigued	1	2	3	4	5
2. I had enough energy to go about my day.	1	2	3	4	5
3. I had enough energy to enjoy the things I do for fun	1	2	3	4	5
4. I felt weak all over	1	2	3	4	5
5. I felt short of breath	1	2	3	4	5
6. I have been able to get a good night's sleep	1	2	3	4	5
Social					
7. I felt satisfied with my current level of social activity	1	2	3	4	5
8. I felt isolated from others	1	2	3	4	5
Cognitive					
9. I had trouble concentrating	1	2	3	4	5
10. This disease / treatment has taken a toll on my ability to remember things	1	2	3	4	5
Anxiety					
11. I felt anxious	1	2	3	4	5
12. My worries overwhelmed me	1	2	3	4	5
13. I worried about the impact my disease is having on my family	1	2	3	4	5
14. It troubled me that I don't feel in control of my own life	1	2	3	4	5
15. I was self-conscious about how my appearance has changed	1	2	3	4	5
16. I worried about the cost of my treatment	1	2	3	4	5

Sanofi

Please mark the answer for how you felt over the last **7 days**...

Mood	Never	Rarely	Sometimes	Often	Almost always
17. I felt sad	1	2	3	4	5
18. I felt that I have nothing to look forward to	1	2	3	4	5
19. I felt hopeless	1	2	3	4	5
20. I felt emotionally exhausted	1	2	3	4	5

Disease / Treatment Effects					
21. I was bothered by changes in the way food tastes	1	2	3	4	5
22. I have been bleeding easily	1	2	3	4	5
23. I had nausea	1	2	3	4	5
24. I had fevers	1	2	3	4	5
25. I had trouble with my bowels (constipation, diarrhea, cramping, etc.)	1	2	3	4	5
26. I had pain	1	2	3	4	5

Quality of Life	Excellent	Very Good	Good	Fair	Poor
27. In general, would you say your quality of life is...	1	2	3	4	5

Sanofi

Please mark the answer for how you felt over the last **7 days**...

Mood	Never	Rarely	Sometimes	Often	Almost always
17. I felt sad	1	2	3	4	5
18. I felt that I have nothing to look forward to	1	2	3	4	5
19. I felt hopeless	1	2	3	4	5
20. I felt emotionally exhausted	1	2	3	4	5

Disease / Treatment Effects					
21. I was bothered by changes in the way food tastes	1	2	3	4	5
22. I have been bleeding easily	1	2	3	4	5
23. I had nausea	1	2	3	4	5
24. I had fevers	1	2	3	4	5
25. I had trouble with my bowels (constipation, diarrhea, cramping, etc.)	1	2	3	4	5
26. I had pain	1	2	3	4	5

Quality of Life	Excellent	Very Good	Good	Fair	Poor
27. In general, would you say your quality of life is...	1	2	3	4	5

Sanofi

10.16.2 Patient global impression of severity (PGIS)

Patient Global Impression of Severity (PGIS) - Blood cancer

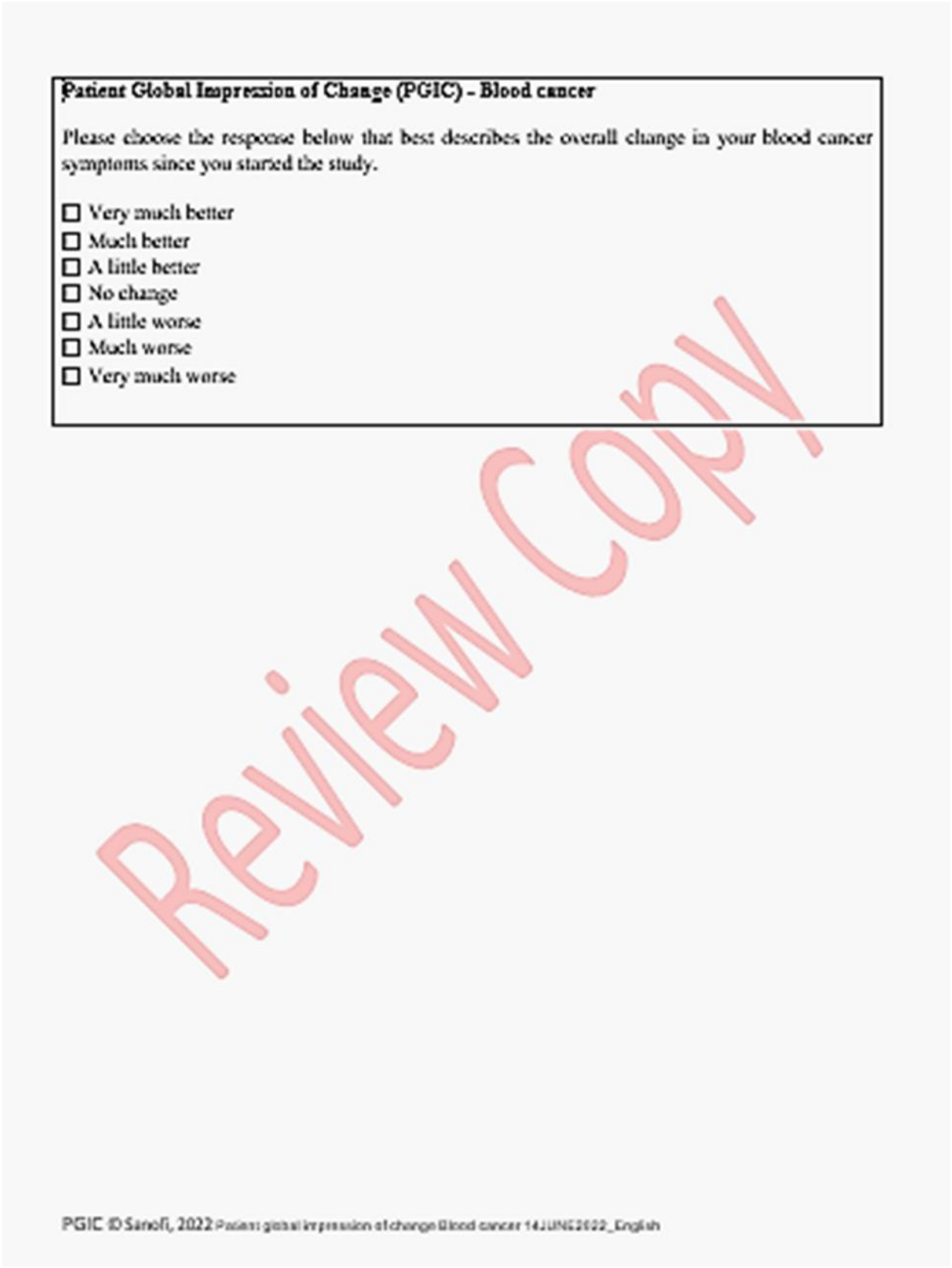
Please choose the response below that best describes the severity of your blood cancer symptoms over the past week.

☐ None
☐ Mild
☐ Moderate
☐ Severe

Review Copy

PGIC © Sanofi, 2022 Patient global impression of Severity Blood cancer 14JUNE2022_English

10.16.3 Patient global impression of change (PGIC)



Patient Global Impression of Change (PGIC) – Blood cancer

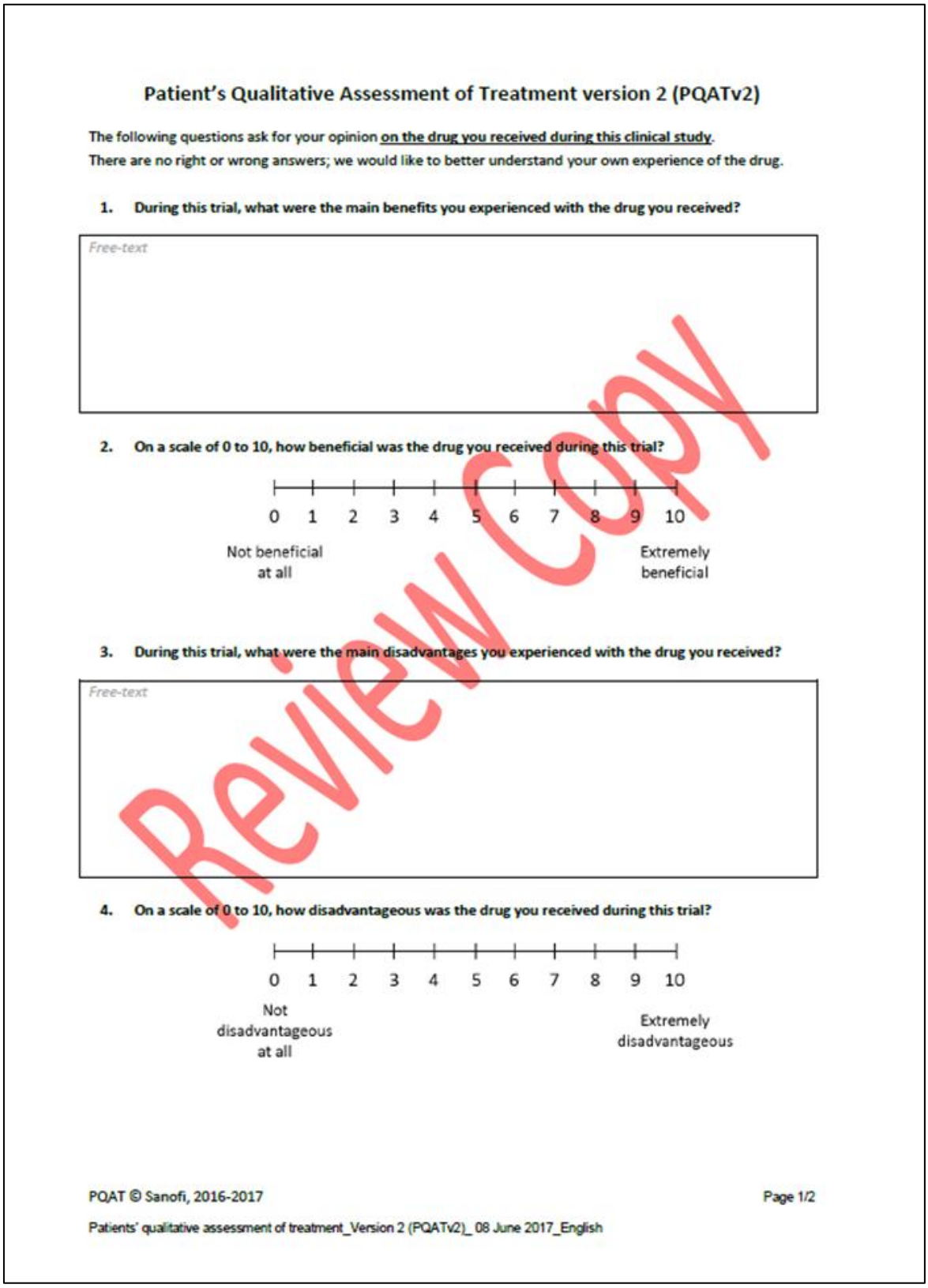
Please choose the response below that best describes the overall change in your blood cancer symptoms since you started the study.

- ☐ Very much better
- ☐ Much better
- ☐ A little better
- ☐ No change
- ☐ A little worse
- ☐ Much worse
- ☐ Very much worse

PGIC © Sanofi, 2022 Patient global impression of change Blood cancer 14JUNE2022_English

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10.16.4 Patients' qualitative assessment of treatment version 2



Patient's Qualitative Assessment of Treatment version 2 (PQATv2)

The following questions ask for your opinion on the drug you received during this clinical study.
There are no right or wrong answers; we would like to better understand your own experience of the drug.

1. During this trial, what were the main benefits you experienced with the drug you received?

Free-text

2. On a scale of 0 to 10, how beneficial was the drug you received during this trial?

0 1 2 3 4 5 6 7 8 9 10

Not beneficial at all — Extremely beneficial

3. During this trial, what were the main disadvantages you experienced with the drug you received?

Free-text

4. On a scale of 0 to 10, how disadvantageous was the drug you received during this trial?

0 1 2 3 4 5 6 7 8 9 10

Not disadvantageous at all — Extremely disadvantageous

PQAT © Sanofi, 2016-2017 Page 1/2

Patients' qualitative assessment of treatment_Version 2 (PQATv2)_ 08 June 2017_English

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5. **After this trial, would you be willing to continue using the drug you received during this trial?**

Yes ☐ No ☐

Please explain why?

Free-text

6. **Based on your own experience in this trial, please select a response on the scale below**

☐ -3	☐ -2	☐ -1	☐ 0	☐ 1	☐ 2	☐ 3
The disadvantages of the drug I received significantly outweigh the benefits			There were equal benefits and disadvantages of the drug I received			The benefits of the drug I received significantly outweigh the disadvantages

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10.17 APPENDIX 17: PROTOCOL AMENDMENT HISTORY

Amended protocol 01 (06 May 2024)

This amended protocol 01 (Amendment 01) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment is to align health authorities' recommendations combining SAR443579 with other drugs in participants with CD123 expressing hematological malignancies.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Cover page, Protocol amendment summary of changes and headers throughout the document	The description of the protocol was updated to Amended Clinical Trial Protocol (Substudy 01).	Administrative change.
Throughout the document	"safety run-in" has been replaced by "dose escalation" or "escalation" in alignment of new 3 dose levels scheme.	In alignment with HA's recommendation of new dosing scheme.
Throughout the document	Any bridging week notion has been removed from the document (Tables and footnotes included).	In alignment with HA's recommendation to remove bridging weeks.
Throughout the document	CD123 expressing" is added whenever ND-AML is mentioned.	In alignment with HA's recommendation to provide more details on study population characteristic.
Throughout the document	"/continued therapy" was added whenever "maintenance" is mentioned.	As per HA's recommendation to clarify that patients who reach CRi/CRh are also allowed to continue treatment, so that the treatment plan will be considered continued therapy rather than maintenance.
Throughout the document	The additional cycles for induction has been renamed Cycle 3.1, 3.2, 3.3.	For better clarity within phases and corresponding cycles.
Section 1.1 Synopsis And Section 3 Objectives, endpoints, and estimands	In the Objectives and endpoints table, the primary endpoint for complete remission (CR) has been revised to exclude CRh and CRi as per the following: ~~Composite~~ Complete Remission (CR) rate: proportion of participants who have a CR (Complete Remission) ~~+ CRh (complete remission with partial hematologic recovery) + CRi (Complete Remission with Incomplete Hematologic Recovery)~~ determined by the Investigator according to 2022 European Leukemia Net (ELN) recommendations for diagnosis and management of AML. ~~(CRc = CR + CRh + CRi).~~	In alignment with HA's recommendation that composite of CR + CRh + Cri is not an acceptable efficacy endpoint for treatment trial of newly diagnosed AML using an azacitidine-based regimen, and should be used as CR as the primary efficacy endpoint.

Section # and Name	Description of Change	Brief Rationale
	Previous Composite Complete remission description has been moved as a secondary endpoint.	
Section 1.1 Synopsis And Section 3 Objectives, endpoints, and estimands	• In Objectives and endpoint table: In the Secondary endpoints Event free survival, Overall survival and Time to treatment failure, "first day of treatment administration" has been replaced by "first day of treatment assignment". • A new endpoint has been added: "Duration of CR defined as the time interval from the first documented evidence of CR until disease relapse as per 2022 ELN recommendations or death due to any cause, whichever comes first. "	Updated to be in alignment with the statistical section.
Section 1.1 Synopsis And Section 3 Objectives, endpoints, and estimands	• In "exploratory objective part" text for transfusion independence rate (TI) has been updated and "at RDE" has been removed from : "treatment with SAR443579 ~~at the RDE~~ in combination with venetoclax and azacitidine (all parts)."	Correction
Section 1.1 Synopsis and Section 4.1 Overall design	In "Brief summary: the Dose escalation part" (previously safety run-in) and the "Overall design" section have been updated to reflect the new recommended strategy to have 2 dose levels: • In "dose escalation par"t and "overall design" section 4.1: "1 main dose level" was replaced by "2 dose levels and "treated at one DL" by "per each DL" and "Participants with disease with adverse risk cytogenetics per ELN 2022 criteria will be enrolled in dose escalation. Escalation" was added.	In alignment with HA's recommendation to provide a new dosing scheme.
Section 1.1 Synopsis and Section 4.1 Overall design	In "Brief summary and Overall design" section: • In optimization /expansion part number of participants were revised from "6-12 participants per dosage level" to "at least 12 participants per dosage level". In the same alignment "approximately 46-52 participants will be treated" has been revised to "approximately 52 participants will be treated".	In alignment with HA's recommendation to conduct dose optimization in a sufficient number of patients.
Section 1.1 Synopsis and Section 4.1 Overall design	In "Brief summary (Number of participants) escalation part": "approximately 6 DLT-evaluable participants will be enrolled" has been revised to "approximately 6 DLT-evaluable participants per each DL may be enrolled" In same alignment "1 main DL" has been replaced by "3 main DLs". Under Optimization part "Up to 12 participants" has been replaced by "At least 12 participants". The number of participants enrolled to investigational intervention has also been updated from 90 participants to 96 participants.	In alignment with HA's recommendation to update study design and number of participants.
Section 1.1 Synopsis and Section 4.1 Overall design	In "Brief summary: dose escalation part" a modification has been made on DLT observation period text " each study treatment" was replaced by "SAR443579 and 75% of the adjusted dose of venetoclax and azacitidine".	Added for better clarification of the DLT period description.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis and Section 4.1 Overall design	In "Brief summary: dose escalation part", it was specified that " A backfilling of dose levels declared safe".	Clarification as per HA's recommendation to revise the protocol to include the specific criteria used to determine the dose levels eligible to be backfilled.
Section 1.1 Synopsis and Section 4.1 Overall design	In "Brief summary: dose escalation part" , the following sentence was added "Participants who discontinued early before the end of DLT observation period due to an adverse reaction will also be considered evaluable for DLT assessment."	Under HA's recommendation for revision of definition of DLT evaluable population.
Section 1.1 Synopsis and Section 4.3.1 Rationale for dose escalation and Section 4.3.2 Dose optimization and recommended dose for expansion (RDE)	Additional descriptive text has been added for enrollment , dose escalation and dose expansion process rules.	Under HA's recommendation, for clarification on process followed between different study parts.
Section 1.1 Synopsis	In "Brief summary: dose escalation part" , the following sentence was added "Participants who discontinued early due to an adverse reaction will also be considered evaluable for DLT assessment."	Under HA's recommendation for revision of definition of DLT evaluable population.
Section 1.1 Synopsis	In "Statistical considerations" primary endpoints for dose escalation has been updated and the following text has been added: "Primary endpoint for dose escalation part: The primary endpoint is incidence of dose limiting toxicity (DLTs). All DLT modeling will be performed on the DLT evaluable population or those who experienced a DLT (dose escalation part). Statistical descriptive analysis will be used to summarize the incidence of DLT by dose level and overall. " And the main secondary endpoints has also been updated to add "CRc rate" and "duration of CR".	Clarification as per HA's recommendation to revise statistical text for primary endpoint.
Section 1.2 Schema	Figure 1 Graphical study design has been updated to include 3 dose levels in Part 1 and Part 1 has been renamed "dose escalation".	In alignment with HA's recommendation of new dosing scheme.
Section 1.3 Schedule of activities (SOA)	Visit window for D1 induction cycle has been updated to ±3 day. New assessment at D8, D15, D22 of induction cycle has been added to Blood hematology/CBC and Blood chemistry. "CD123 Status" assessment has been added and the footnotes have been updated accordingly.	Update/correction on table to be aligned with expected assessment visit.
Section 1.3.1 All parts: PK and ADA flowchart (Cycle 1)	Footnote *b* has been updated and "D28 samples may be drawn on D1 of the subsequent cycle before the start of the infusion." has been added.	For clarification of samples schedule.
Section 1.3.1 All parts: PK and ADA flowchart (Cycle 1)	Table has been updated and a new row has been added for Tocilizumab PK to specify that in case of administration	In alignment with HA's recommendation to provide information on dose, schedule to

Section # and Name	Description of Change	Brief Rationale
	of tocilizumab, PK samples of tocilizumab will be collected as described in Section 6.6.5.3	be used, and the plan for the assessment of PK and PD in case tocilizumab is used.
Section 1.3.2 All parts: PK and ADA flowchart (Cycle 2 and beyond)	Footnote *b* has been updated per the following: "strictly" and "Predose of next cycle administration" have been removed and "D28 samples may be drawn on D1 of the subsequent cycle before the start of the infusion." has been added. Footnote *c* has been updated and "in Maintenances/contued therapy" has been added. Footnote d has been updated to explain when the ADA samples will be collected.	For clarification of scheduled samples
Section 1.3.2 All parts: PK and ADA flowchart (Cycle 2 and beyond)	Table has been updated and new columns created to split induction period from maintenance period. Assessments and footnotes have been updated accordingly. A new assessment row has been added (PK tocizumab).	For better readability and to be aligned on assessment description following update of treatment plan description.
Section 1.3.3 All parts PDy flowchart (Cycle 1) and Section 1.3.4 All parts PDy flowchart (Cycle 2 and beyond)	The following footnote has been added to both PDY flowchart tables : "MRD flow sample will be collected at screening for all patients and further on only in patients with confirmed CR, CRh or CRi, during the subsequent bone marrow aspirations."	For clarification of scheduled samples.
Section 1.3.3 All parts PDy flowchart (Cycle 1) and Section 1.3.4 All parts PDy flowchart (Cycle 2 and beyond)	Tables have been updated: assessment for AML MRD modified and footnote b has been removed from Genomics including MRD.	For correction, to be aligned with study requirement and assessment.
Section 1.3.4 All parts PDy flowchart (Cycle 2 and beyond)	Footnote *c* "Cytokines" has been updated and following text has been added : During maintenance, cytokines must be collected pre-dose every cycle and not every third cycle.	For clarification on cytokines assessments.
Section 4.1 Overall design	The following additional text has been added to treatment period definition: "maximum of 6 induction cycles" and "Three additional induction cycles may be given if participant does not achieve CR, CRh or CRi within the first 3 induction cycles." The following sentence has been added: "During the dose escalation part, only participants with disease with adverse risk cytogenetics according to ELN 2022 criteria will be enrolled." Additional changes have been made to the praragraph to align with study design changes as descrived in the SoA and the schema.	For clarification of definition of induction treatment plan.
Section 4.3.1 Rational for dose escalation	Dose level has been revised and text has been updated accordingly. It has been added that 3 main DLs will be used starting with a lower dose of 0.6mg/kg and a planned dose escalation to the 1.0 mg/kg and 1.5 mg/kg A clarification on DLT assessment has been made by adding "and 75% of the adjusted dose of venetoclax and azacitidine".	To align with HA's request and the new study design elements.

Section # and Name	Description of Change	Brief Rationale
Section 4.3.1 Rational for dose escalation	Table 4 Dose: Induction and maintenance has been updated to reflect you study strategy with 3 DLs of 0.6, 1 and 1,5 mg/kg.	To align with HA's request and the new study design elements.
Section 4.3.1 Rational for dose escalation	The sentence: "participants who discontinued early due to an adverse reaction will also be considered evaluable for DLT assessment." was added.	Under HA's recommendation for revision of DLT evaluable population definition.
Section 4.3.1 Rational for dose escalation	A footnote to specify cycle duration was added to Table 4 - Dose: induction and maintenance (all doses in mg/kg).	Under HA's recommendation for better clarity.
Section 4.3.2 Dose optimization and recommended dose for expansion (RDE)	The following text was added: "which will not exceed the preliminary RDE identified during the escalation part."	To better detail the 2 potential doses.
Section 4.3.2 Dose optimization and recommended dose for expansion (RDE)	Text on elements to take into consideration for the dose determination has been added.	To better detail dose determination environment.
Section 4.3.2 Dose optimization and recommended dose for expansion (RDE)	The preliminary efficacy data bullet point text was updated and "defined by CR/Cri" was removed from "including but not limited to CR rate, observed at the identified doses ~~defined by CR/Cri~~".	In alignment with HA's recommendation for CR definition.
Section 5.1 Inclusion criteria	A new type of participant and disease characteristics inclusion criteria has been added, "For dose escalation part only: participants should have adverse risk cytogenetics as per ELN 2022." Therefore, as per standard of procedure a new section "Criteria added in amended protocol" has been created and the above new I08 inclusion criteria has been added. An additional inclusion criterion has also been added I09: "I I 09. For all participants: positive CD123 expression on tumor tissue as determined locally is required and needs to be documented in source data."	In alignment with HA's recommendation to indicate that patients with CD123-expressing hematological neoplasms are eligible and to confirms that our local assessment of CD123 for determination of eligibility will be used.
Section 6.1 Study intervention(s) administered	Premedication for SAR443579 text has been updated and time window for SAR443579 infusion has been clarified by adding the following statement "that should be administered over 1 hour (+/- 10 minutes)."	Added for clarification of time window for SAR443579 infusion.
Section 6.1 Study intervention(s) administered	A paragraph for PK sampling has been added "During the first cycle to optimize PK sampling for each IMP venetoclax should be administered first, followed by azacytidine 90 mins after the venetoclax dose and then SAR443579 120 minutes after the venetoclax dose. For cycle 2 and beyond venetoclax should be taken first, following by the azacytidine and then SAR443579. There is no required time interval between venetoclax, azacytidine and SAR443579 in cycle 2 and beyond".	Added for clarification on PK sampling and corresponding timing.
Section 6.1.1 Investigational medicinal product(s)	Descriptive texts on formulation, route of administration, and dose regimen for IMP (SAR443579, venetoclax, azacitidine) have been added.	For a better description or depiction of the treatment plan, as per HA's recommendation.
Section 6.1.1 Investigational medicinal product(s)	Table 5 - Investigational medicinal product(s) administered has been corrected for venetoclax dosage levels and 300 mg has been removed.	For correction of dosage levels available for venetoclax.

Section # and Name	Description of Change	Brief Rationale
Section 6.1.2 Auxilliary medicinal product(s)	Cytokine release syndrome (CRS) has been removed from the sentence: " [...] to prevent or reduce the acute effect of infusion-related reactions (IRR) ~~or cytokine release syndrome (CRS~~	Correction under HA's notification as the proposed premedications do not affect the risk of CRS.
Section 6.2 Auxilliary medicinal product(s)	Text has been updated to specify the premedication usage and timing: "all participants should receive premedication such as (acetaminophen and or diphenhydramine), to prevent or reduce the acute effect of infusion-related reactions (IRR) or cytokine release syndrome (CRS), 30 to 60 minutes prior to SAR443579 infusion (no longer than 60 minutes) for the first cycle."	Added for clarification on premedication usage.
Section 6.6.1 General rules	Text has been added to clarify the dose modification: "Dose modifications different from those stated in the protocol should only be made in consultation with the Sponsor, unless required for immediate participant's safety". A paragraph has been added for participants with DLTs: "Participants who experience protocol defined DLTs will be required to temporarily delay study drug treatment. Such participants may be considered for continued treatment once the toxicity either resolves to Grade 1 or baseline, or the toxicity is stable and manageable through supportive therapy (eg, a participant with well-controlled hypertension that remains at Grade 3 due to the need for 2 anti-hypertension agents)." A clarification has been added for IMP permanent discontinuation with the followings the sentence : "In the situation when SAR443579 is permanently discontinued, venetoclax and azacitidine should be permanently discontinued as well."	To align with HA's recommendation for clarification of dose modification, DLT, and permanent discontinuation rule.
Section 6.6.2 Venetoclax/azacitidine dose reduction, delay and omission	"or per institutional dosing guidelines" has been removed.	Updated as per HA's recommendation to avoid referring to institutional guidelines and better introduce standardized instructions.
Section 6.6.3 SAR443579 dose reduction, interruption, delay and omission	Dose delay text has been updated per the following: "A cycle is deemed delayed if administered ≥4 days in the Induction and Maintenance period. […] and only one omission per cycle is permitted. Further omissions must be discussed on a case-by-case basis with the Sponsor. For delayed or omitted doses when administration of the IMP resumes, the originally scheduled DL and dose should be administered."	Added for clarification of dose delay process.
Section 6.6.4 Guidelines for the management of treatment-related adverse events	The following paragraph for clinical status and lab tests has been added: "Clinical status and lab tests must be reviewed prior to each cycle to confirm whether dose adjustments to venetoclax/azacitidine should be made and to confirm the adequate resolution of any toxicity to allow initiation of the next cycle."	Under HA's recommendation to revise the protocol to specify the minimum criteria for organ function and resolution of toxicity required prior to the start of subsequent cycles.
Section 6.6.5.1 Infusion-related reactions (IRR)	In Table 6 Guidelines for the treatment of IRRs "If interrupted, IRR will be classified as Grade 2 as per NCI-CTCAE v5.0 definition" has been removed.	Correction

Section # and Name	Description of Change	Brief Rationale
Section 6.6.5.1 Infusion-related reactions (IRR)	Additional descriptive text was added to the section	Under HA's recommendation to assist the Investigator with recognizing infusion reactions and have a better description or listing of the anticipated infusion-related reactions for SAR443579.
Section 6.6.5.3 Fever, flu-like symptoms and cytokine release syndrome (CRS)	A descriptive text for collection of PK samples of tocilizumab has been added.	In alignment with HA's recommendation to provide information such as dose, schedule to be used and plan to assess PK and PD in case tocilizumab is used.
Section 6.6.5.3 Fever, flu-like symptoms and cytokine release syndrome (CRS)	The following text "or other institutional recommended interventions available " has been removed from the sentence "Sites should have tocilizumab ~~or other institutional recommended interventions available~~ along with access to an intensive care unit (ICU), in case participants develop CRS." And the following text was added :" In the situation when the investigator may use another anti-cytokine agent due to the non-availability of Tocilizumab or in case of emergency, PK samples for this anti-cytokine agent will be collected following the same schema as for tocilizumab."	Updated as per HA's recommendation to avoid referring to institutional guidelines or methods and better introduce standardized instructions.
Section 6.6.5.3 Fever, flu-like symptoms and cytokine release syndrome (CRS)	Table 7 - Guidelines for management of cytokine release syndrome (CRS) has been updated and additional details on usage of tocilizumab in case of CRS have been added.	For clarification of use of tocilizumab as per HA's recommendation.
Section 6.6.5.4 Immune cell-associated neurotoxicity syndrome (ICANS)	Table 8 - Guidelines for the management of ICANS has been updated and sentence "Permanently discontinue SAR443579 if more than one seizure occurs." has been added to Grade 3 ICANS.	Under HA's recommendation to complete instructions for discontinuation of SAR443579.
Section 6.6.5.5 Tumor lysis syndrome	"C1D1" has been added to "Blood chemistries should be reassessed 6 to 8 hours after C1D1, C1D2, C1D3 and C1D4".	Correction.
Section 6.6.5.6 Management of hematological toxicities	The following text has been deleted: "sites should further manage cytopenias and infections according to their institutional guidelines. No adjustment or delay of SAR443579 is required for cytopenias. The guidelines described in Table 9 are just provided as suggestion. Please refer to the latest version of label and institutional guidelines for further consideration." Table 9 has been renamed to: Dose adjustment instructions for hematological toxicity. The following text within the table was updated: "SAR443579 treatment may continue weekly on the bridging schedule during induction phase as outlined in SoA (Section 1.3) and Section 6.6." was removed and "For SAR443579: resume treatment with the same dose at the next cycle." was added for first and subsequent occurrence after achieving remission and lasting at least 7 days.	Updated in alignment with HA's recommendation.

Section # and Name	Description of Change	Brief Rationale
Section 6.6.5.7 Management of non-hematological toxicities and Section 10.6.3 Child-Pugh Scoring System	The following text "The guidelines described in Table 10 are just provided as suggestion. Please refer to the latest version of label and institutional guidelines for further consideration." was removed. Table was updated and renamed "Dose adjustments instructions for non-hematological toxicity." Hepatic impairment row was updated to be defined by Child-Pugh Classification and other Grade 3-4 toxicities to NCI CTCAE V5.0. And in Grade 3-4 toxicities row, the sentence: "No dose adjustment of Azacitidine or SAR443579 is required." has been added. A row has been added for Seizure ≥2 (in the absence of ICANS) with the instruction of "Permanently discontinue SAR443579, Venetoclax and Azacitidine". Accordingly, a section in annex has been added to detail Child-Pugh Scoring System.	Updated in alignment with HA's recommendation for referring to Child-Pugh classification in severe hepatic Impairment and clarifying/updating dose management strategy for non-hematological toxicities.
Section 6.9.1 Acceptable concomitant medications	Section has been updated and following text has been added: "All concomitant medication will be recorded on the electronic case report form (e-CRF) including all prescription, OTC, herbal supplements, and IV medications. If changes occur during the trial period, documentation of route, and date will also be included on the e-CRF. Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery or radiotherapy for tumor control is not permitted during the study; however, radiotherapy or procedures for symptom management is allowed after discussion with and approval by the Sponsor. All concomitant medications received within 28 days before the first dose of trial treatment through the End of Treatment Visit and post EOT if associated with ongoing SAEs should be recorded."	For clarification as per HA's recommendation to detail concomitant therapy in substudy as concomitant medications will depend in large part on the other drugs used in the combination.
Section 8.2 Efficacy assessments	The following text was updated: CRc was replace by CR and CRc rate (CR+CRh+CRi), and alternative CR rate (CR+CRh) was added to additional efficacy objectives.	To align with new objectives and endpoint organization.
Section 8.3.6 Dose limiting toxicities	Text for hematologic abnormalities Grade 4 decreased absolute neutrophil and Grade 4 decreased platelet count has been revised.	In alignment of HA recommendation on DLT definition.
Section 8.3.6 Dose limiting toxicities	Text for non-hematologic abnormalities: Grade 3 electrolyte abnormalities and Grade 3 transaminitis (AST/ALT) elevation has been revised.	In alignment of HA recommendation on DLT definition.
Section 8.3.6 Dose limiting toxicities	Following sentence was added in non-hematologic abnormalities "Any adverse reaction regardless of grade that leads to dose reduction or withdrawal."	In alignment of HA recommendation on DLT definition. Definition has been aligned to encompass any adverse reaction regardless to grade that

Section # and Name	Description of Change	Brief Rationale
		leads to dose reduction or withdrawal.
Section 8.5 Pharmacokinetics	The text has been updated to include tocilizumab in PK description.	In alignment with HA's recommendation to provide information such as dose, schedule to be used, and plan to assess PK and PD in case tocilizumab is used.
Section 8.6 Pharmacodynamics	Flow Cytometry (Blast- and Immuno-phenotyping) text was updated: ", T cells, and myeloid cells" was removed and the "The potential correlation between CD123 expression on leukemic cells and clinical response will be explored." was added. MRD Multiparameter flow cytometry (MFC) text was revised. Original text was removed and replace by "will be used to assess the MRD status in participants who achieved CR (any form)." Cytokine responses in blood text was revised and "pharmacokinetic endpoints will be investigated as well. Results will be also correlated" was removed and "clinical parameters will be explored." was added.	For clarification of definition.
Section 8.8 Biomarkers	MRD definition was revised to: "NGS based retrospective MRD analysis will be selected in participants achieving CR, CRh or Cri".	For clarification of definition.
Section 9.1 Population for Analyses	DLT-evaluable population for analyses subsection in Table 12 has the following text added : "and the adjusted dose of" And the definition for evaluable DLT assessment has been updated and the following text has been added : "Participants who discontinued early before the end of DLT observation period due to an adverse reaction will also be considered evaluable for DLT assessment" Efficacy Population definition has been updated.	Under HA's recommendation to better define the "DLT-evaluable", "Efficacy" population.
Section 9.2.2.1 Dose escalation	Title and contents of the section have been updated.	Tittle and contents of section have been updated to reflect changes made in the primary endpoint.
Section 9.2.2.4 Main Analytical Approach	The LRV and TV for the CR rate difference between study treatment and control arm was changed to 17%.	Updated per HA's request.
Section 9.2.3 Secondary endpoint analyses	Changes and additions to the following definitions have been made: CRc, Duration of CR.	To align with the modified endpoints.
Section 9.2.4 Tertiary/exploratory endpoints	The endpoint has been modified.	To align with the modified endpoints.
Section 9.2.6 Pharmacokinetics	Text of the section has been updated.	To avoir redundancy and for better clarity
Section 9.4 Sample size determination	The number of patients to be enrolled has been updated to 102. Additional numbers that calculate power have been updated.	To align with the modified endpoints.

Section # and Name	Description of Change	Brief Rationale
Section 9.5 Dose escalation decision rules	The entire section has been updated to reflect the dose escalation change in the protocol.	To align with the modified endpoints.
Section 9.5 Dose escalation decision rules.	DLT rate was corrected for larger than 0.20.	Corrected to align with modified target toxicity range.
Section 10.6.3 Child-Pugh Scoring System	A section in annex has been added to detail Child-Pugh Scoring System.	Updated in alignment with HA's recommendation for referring to Child-Pugh classification in severe hepatic Impairment.
Section 10.16 Appendix 16: statistical details about bac+3odm	Statistical values and percentage has been revised to be align with the one for CR.	To align with CR rate as primary endpoint.

In addition, minor typographical error/editorial corrections were implemented throughout the protocol.

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