An open-label, first-in-human, dose-escalation/expansion study of SAR443579 administered as single agent by intravenous infusion in adult and pediatric participants with relapsed or refractory acute myeloid leukemia (R/R AML), B-cell acute lymphoblastic leukemia (B-ALL), high risk-myelodysplasia (HR-MDS) or blastic plasmacytoid dendritic cell neoplasm (BPDCN)

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This study has been transitioned to CTIS with ID 2023-508357-58-00 check the CTIS register for the current data. The aim of the escalation portion of this study, in which SAR443579 is administered for the first time in humans, is to establish the...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON55908

Source
ToetsingOnline

Brief title
TCD17197

Condition

- Leukaemias

Synonym
Acute leukemia; bloodcancer

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi BV
Source(s) of monetary or material Support: Sanofi

Intervention

Keyword: B-cell acute lymphoblastic leukemia (B-ALL), blastic plasmacytoid dendritic cell neoplasm (BPDCN), high risk-myelodysplasia (HR-MDS), relapsed or refractory acute myeloid leukemia (R/R AML)

Outcome measures

Primary outcome

Dose Escalation Part:

To determine the maximum tolerated dose (MTD) or maximum administered dose

(MAD) of SAR443579 administered as a single agent in participants with relapsed

or refractory acute myeloid leukemia (R/R AML), high risk myelodysplastic

syndrome (HR-MDS), B-cell acute lymphoblastic leukemia (B-ALL) or blastic

plasmacytoid dendritic cell neoplasm (BPDCN).

Expansion Part:

To assess the anti-leukemic activity of SAR443579 administered as of single

agent at the confirmed recommended Phase 2 dose (RP2D) in participants with R/R

AML.

Secondary outcome

To select the preliminary RP2D (pRP2D) (Escalation Part) and confirm RP2D

(Expansion Part).

To assess preliminary evidence of hematologic response (Escalation Part)

In Escalation and Expansion Parts:

- To characterize the overall safety and tolerability profile of SAR443579

- To characterize the PK profile of SAR443579 when administered as a single

agent

- To evaluate the potential immunogenicity of SAR443579

In Expansion Parts:

- To assess alternative CR rate

- To assess overall complete remission rate

- To assess duration of response (DoR)

- To assess duration of event-free survival (EFS)

- To assess survival rate

Study description

Background summary

The intensive first-line treatment for AML usually includes cytosine arabinoside and anthracycline induction therapy, followed by consolidation chemotherapy with cytarabine or other agents. Recent innovations for first-line therapy include the use of liposomal daunorubicin/cytarabine or the addition of an FLT3 inhibitor. For patients who cannot tolerate initial intensive chemotherapy combinations, the BCL2 inhibitor venetoclax in combination with a hypomethylating agent or low dose cytarabine (LDAC) provides better results than previous monotherapy regimens. Allogeneic stem cell transplantation is offered to patients with high-risk disease in first or subsequent remission, provided they have adequate organ function and a suitable source of stem cells. Despite this aggressive therapeutic approach, the most recent 5-year US survival rate based on 2011-2017 data was 29.5%. Despite advances in

understanding the pathophysiology of AML and recognizing its molecular heterogeneity, it is challenging to develop viable therapies for patients with AML. New agents are needed to achieve a better response that prolongs overall survival, especially for patients with relapsed or refractory disease, and to improve quality of life.
Recent studies support the need for more tolerable and highly effective therapies for hematologic malignancies. As for AML, the most effective therapies for B-ALL and HR-MDS include intensive multi-agent chemotherapy and/or allogeneic stem cell transplantation. However, many patients with these diseases are of advanced age or have co-morbidities that preclude these aggressive, highly toxic therapies. In addition, not all patients recover with intensive therapy and/or allogeneic transplantation and the risk of treatment-related toxicity is high. Although approximately 15% of patients >60 years and 40% of patients <60 years who receive intensive induction chemotherapy and/or allogeneic stem cell transplantation for AML are cured, AML patients with relapsed or refractory disease have a poor prognosis after initial therapy . The most recent 5-year US survival rate based on 2011-2017 data is 29.5%. There has been progress in understanding the pathophysiology of AML and recognizing its molecular heterogeneity, but developing viable therapies for patients with AML remains challenging.
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But despite the development of several new agents for relapsed or refractory AML, it is mostly incurable. Short remission duration (ie < 6 months), adverse genetic factors, prior allogeneic transplantation, advanced age, and poor general health are factors associated in part with poorer survival outcomes in the setting of R/R AML, in part because these factors affect the limit the

possibility of further intensive treatment.
As with AML, healing of B-ALL requires aggressive therapy that can be associated with significant toxicity. For B-ALL, a two-year course of intensive multi-agent chemotherapy and/or allogeneic stem cell transplantation can cure a significant proportion of younger patients (aged <40 years), but the outcomes for older adults are much worse. Although treatment with a CD19-targeted chimeric antigen receptor T (CAR-T) has resulted in durable remissions, it is not approved for administration to patients older than 25 years of age. In addition, CD123 is frequently expressed on B-ALL cells both at diagnosis and relapse, indicating that CD123-targeted therapy could be effective in this indication, even in disease resistant to CD19-targeted therapy. For HR-MDS, hypomethylating agents were the main treatment, while other treatment options are limited. Allogeneic stem cell transplantation provides the only known cure for HR-MDS, but is not always a treatment option, given the patient's age and possible co-morbidities.
The haematological indications selected for the dose escalation (B-ALL, HR-MDS, AML) and dose expansion (AML) have a high prevalence of CD123 positivity. This supports not to pre-screen for CD123 expression.
There are several reasons to justify the inclusion of adolescents with relapsed or refractory AML, B-ALL and HR-MDS. In accordance with recent FDA draft guidelines, adolescent participants (12-17 years of age) are included in this study when the first adult to be treated with DL3 has completed Cycle 1 without the occurrence of a DLT and upon availability of sufficient PK data. demonstrate exposure. In this study, adolescents will be included with relapsed or refractory disease for which standard therapies with curative intent are available. However, there are no CD123-targeted therapies approved for children or adolescents. For patients with relapsed or refractory disease who are currently ineligible for allogeneic stem cell transplantation (all indications) or for CAR-T therapy (B-ALL), there are no standard therapies available with curative intent, so participation in clinical trials is encouraged.
Initiation of maintenance treatment is supported by recent evidence suggesting that long-term therapy in which CR or CRi is not achieved may provide a benefit in overall survival or disease-free survival, especially for patients with R/R AML. Once CR or CRi is achieved, the effector:target ratio will be significantly improved, which will improve both efficacy and exposure after a dose of SAR443579. Thus, dosing of SAR443579 every 8 weeks is expected to be sufficient for maintenance dosing, but the dose and schedule for maintenance therapy can be refined based on clinical data.

With PA#5, patients with BPDCN were added to the research group. Treatment options for BPDCN typically include a combination of chemotherapy (usually ALL-targeted), targeted therapy, stem cell transplantation, and supportive care. Tagraxofusp (Elzonris) is an FDA-approved targeted therapy that specifically targets CD123, a surface marker expressed in BPDCN cells. Notably, participants with BPDCN treated with tagraxofusp were shown to maintain CD123 expression across disease progression, supporting the inclusion of participants with prior tagraxofusp treatment. Tagraxofusp validates the use of a

CD123-targeted agent in BPDCN and warrants further investigation of this SAR443579 in this indication.

Study objective

This study has been transitioned to CTIS with ID 2023-508357-58-00 check the CTIS register for the current data.

The aim of the escalation portion of this study, in which SAR443579 is administered for the first time in humans, is to establish the safety profile, determine the maximum tolerated dose (MTD/MAD) and recommended phase II dose (RP2D), and determine the PK profile. to characterize. The expansion portion of the study assesses preliminary clinical activity at the RP2D in participants with AML. Assessment of preliminary activity in HR-MDS or other indications may be considered later in this study.

Study design

An open-label, first-in-human, dose-escalation study

Intervention

SAR443579 will be administered as a single agent by intravenous (IV) infusion in participants aged >=12 years with R/R AML, B-ALL, HR-MDS or (BPDCN). Treatment consists of 3 cycles of 28 days in the Induction Phase, followed by up to 13 cycles of 56 days in the Maintenance Phase.

The study includes a dose Escalation Part and a dose Expansion Part. During the Escalation Part, dose escalation is planned through up to 6 main doselevels (DLs). Depending on the DL, SAR443579 will be administered twice weekly or once weekly in the first 1 or 2 weeks of Cycle 1 on Days 1, 4, 8 and 11 and once-weekly during the last 2 weeks of Cycle 1 (Day 15 and Day 22) and all subsequent induction cycles (Days 1, 8, 15, and 22). When supported by PK data, alternative schedules may be tested.

In the Expansion Part, the recommended phase II dose will be confirmed.

Study burden and risks

The risks are related to the blood samples and the biopies taken, and also the possible side effects of the study drug and infusion reactions.

The burden for the patient are the frequent visits to the hospital including the hospitalization on day 1 to 12 of the first cycle.

Contacts

Public
Sanofi BV

Paasheuvelweg 25
Amsterdam 1105 BP
NL
Scientific
Sanofi BV

Paasheuvelweg 25
Amsterdam 1105 BP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)
Babies and toddlers (28 days-23 months)

Inclusion criteria

- Participant must be >=1 year old at the time the trial participant or legal guardian signs the informed consent form and will be assigned as follows:
• Adult arm: aged >=12 years old.
• Pediatric arm: aged 1 to 17 years old.
For participants of the Escalation Part only:
- Adult and Pediatric Arms: Confirmed diagnosis of primary or secondary AML [any subtype except acute promyelocytic leukemia (APL) and juvenile myelomonocytic leukemia (JMML)] according to World Health Organization (WHO)

classification. Patients with AML must meet one of the following criteria, a), b) c) or d) and are limited to those with no available (or are ineligible) therapy with known clinical benefit.
a) Primary Induction Failure (PIF) AML
b) Early relapse (ER) AML
c) Leukemia in first or higher relapse
d) For participants aged 1 to 17 years old, primary induction failure is defined as disease refractory after two cycles of induction therapy according to Children*s Oncology Group (COG) protocol guidelines (40).
- Adult arm only: Confirmed diagnosis of cluster of differentiation 123 (CD123) + HR-MDS
-- Not eligible for induction therapy and having completed >=2 cycles of any of the following: hypomethylating agent (eg, 5 azacitidine or decitabine) and/or venetoclax, chemotherapy, or targeted agents.
-- Not eligible for autologous stem cell transplant (ASCT) and having completed >=1 course of induction therapy.
- Adult and Pediatric arms and escalation part only: Confirmed diagnosis of CD123+ B-ALL without extramedullary lesions that have no available (or are ineligible) therapy with known clinical benefit. Participants with non-CNS chloromatous disease are not allowed in the study.
For Participants in the Expansion Part Only (adults only):
- For participants in Cohort A: Participants meeting inclusion criteria for AML patients that have been primary refractory (PIF) to prior induction treatment or who have had ER occurring 6 months or less after an initial remission on prior induction treatment.
- For participants in Cohort B: Participants meeting inclusion criteria for AML patients that have had late relapse (LR), occurring more than 6 months after an initial remission on prior induction treatment.
- Pediatric arm and escalation part only: Confirmed diagnosis of BPDCN according to World Health Organization (WHO) 2022 classification (39), who have relapsed or refractory disease with no available (or are ineligible) therapy with known clinical benefit.
- Pediatric arm and expansion part only: For participants in Cohort C: Participants with AML who have relapsed according to I 02 or have recurrent disease resistant or intolerant to available therapies.

Exclusion criteria

-Eastern Cooperative Oncology Group (ECOG) performance status >2 (>=18 years-old). Karnovsky Scale (16-17 years-old) <50% or Lansky Scale (<16 years-old) <50%.
- Ongoing or recent (within 5 years) evidence of significant autoimmune disease that requires or required treatment with systemic immunosuppressive treatments, which may suggest a risk for immune related adverse events. The following are not exclusionary: vitiligo, childhood asthma that has resolved, residual

hypothyroidism that required only hormone replacement or psoriasis that does not require systemic treatment.
- History of an invasive malignancy that requires active therapy (adjuvant hormonal therapy is allowed) other than the one treated in this study, with the exception of resected/ablated basal or squamouscell carcinoma of the skin or carcinoma in situ of the cervix, or other local tumors considered cured by local treatment)
- Evidence of active central nervous system leukemia at the time of enrollment as evidenced by cytology or pathology. Except for participants aged 1 to 17 years, central nervous system 1 disease (CNS1) and CNS2 disease according to COG classification (41) are
allowed
-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.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	04-07-2022
Enrollment:	18
Type:	Actual

Ethics review

Approved WMO

Date:	27-01-2022

Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	16-03-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	27-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-05-2023

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	01-08-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-11-2023
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-508357-58-00
EudraCT	EUCTR2021-004287-98-NL
ClinicalTrials.gov	NCT05086315
CCMO	NL80040.041.21