An open-label dose escalation study to estimate maximum tolerated dose (MTD), identify dose-limiting toxicities (DLTs) and study pharmacokinetics following a single dose of intracranially administered temozolomide-based SI-053 as an add-on to the current standard of care (SoC), in adult patients with newly diagnosed glioblastoma (GBM).

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This study has been transitioned to CTIS with ID 2024-515128-35-00 check the CTIS register for the current data. The primary objective is:• To evaluate the safety and tolerability of a single local i.c. dose of SI-053 to establish the MTD and/or the...

Ethical review	Approved WMO
Status	Pending
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON51969

Source
ToetsingOnline

Brief title
DBP-053-01

Condition

- Other condition
- Encephalopathies
- Nervous system, skull and spine therapeutic procedures

Synonym
Brain tumor, glioblastoma

Health condition

Glioblastoma

Research involving
Human

Sponsors and support

Primary sponsor: Double Bond Pharmaceutical AB
Source(s) of monetary or material Support: Double Bond Pharmaceutical AB

Intervention

Keyword: Glioblastoma, SI-053, Temozolomide

Outcome measures

Primary outcome

• Incidence rate and the grade (severity) of dose-limiting toxicities (DLTs)

based on the occurrence of adverse events (AEs) reported according to the

National Cancer Institute (NCI) - Common Terminology Criteria for Adverse

Events (CTCAE) v 5.0.

• SI-053 related AEs and toxicity determined by evaluation of the extent of

edema (and associated use of steroids to control edema), neurological

toxicities (e.g. sudden increase in seizure activity as a result of local

inflammation), any infection (by requirement for antibiotic treatment),

additional surgery or any additional treatment that would delay the

chemoradiotherapy.

Secondary outcome

• Determination of plasma concentration of TMZ and its metabolite 5-amino-1H-imidazole-4-carboxamide (AIC) and PK parameters: peak plasma concentration (Cmax), time to reach Cmax (tmax), elimination half-life (t1/2), area under the curve from time 0 to infinity (AUC0-*), AUC-time curve over the last 24 h interval (AUC0-24), AUC from time 0 up to the last measurable concentration (AUC0-last), volume of distribution (VD), systemic clearance (CL), central compartment volume (VZ).

Study description

Background summary

TRIAL BACKGROUND:
Gliomas are the most common primary malignancies of the brain in adults and have a poor prognosis, with direct repercussions on cognition and quality of life (QOL). GBMs (Grade IV gliomas) have a 5-year survival rate of less than 5%, and 70% of patients are expected to show disease progression within 1 year. SI-053 is a novel TMZ gel formulation intended to be used for newly diagnosed GBM patients as an add-on concomitantly to the SoC treatment (including maximal safe resection followed by radiation therapy with concomitant TMZ and adjuvant chemotherapy with TMZ) or the CeTeG protocol (lomustine and TMZ plus radiation therapy).

TRIAL RATIONALE:
In conjunction with surgical resection, SI-053 will be applied intracranially (i.c.) into the cavity that is formed after tumor resection, where TMZ will be released locally into the surrounding area exposing the residual tumor cells to this alkylating chemotherapy agent. Post-operative chemoradiotherapy (including concomitant and adjuvant TMZ or following the CeTeG protocol) will be initiated at least 21 and no later than 35 days after SI-053 administration.
The purpose of this first-in-human (FIH) trial is to determine the maximum tolerated dose (MTD) and/or the recommended Phase II dose (RP2D) of SI-053 and to characterize safety, tolerability, the pharmacokinetic (PK) profile, health-related quality of life (HRQOL) and preliminary efficacy, after

administering a single i.c. dose of SI-053 in conjunction with tumor resection as an add-on to the current SoC or the CeTeG protocol, in adult subjects (>= 18 to <= 70 years of age) with newly diagnosed GBM.

Study objective

This study has been transitioned to CTIS with ID 2024-515128-35-00 check the CTIS register for the current data.

The primary objective is:
• To evaluate the safety and tolerability of a single local i.c. dose of SI-053 to establish the MTD and/or the RP2D (dose escalation) and to further evaluate safety at the RP2D (dose expansion).
The secondary objective is:
• To evaluate the PK profile of a single local i.c. dose of SI-053.

Study design

This is an open-label dose escalation and expansion trial.
The dose escalation will follow a rule-based 3 + 3 design for MTD and/or RP2D determination using increasing doses of SI-053, ranging from 25 mg to 275 mg of TMZ. Reconstitution of SI-053 will be performed under sterile conditions. The SI-053 powder will be reconstituted using 7.0 mL of sterile water for injection (WFI), followed by manual mixing with a sterile spatula and leaving to swell for at least 30 min in the vial at room temperature; the reconstituted powder cannot be refrigerated. Subjects will receive a single i.c. dose of room-tempered SI-053 gel, which will be applied onto the walls of the cavity formed after tumor resection using a sterile spatula. This will be followed by chemoradiotherapy commencing at least 21 and no later than 35 days after SI-053 administration.

Intervention

Subjects will receive treatment with SI-053 as a single intraoperative dose.

Study burden and risks

Radiotherapy to the brain can cause short term side effects such as:
• Tiredness (fatigue)
• Headaches
• Hair loss
• Skin irritation
• Feeling sickness
• Memory loss

Possible discomforts with checks or measurements during the study:

Blood collection
Taking blood samples may cause pain, bleeding, bruising or infection around the injection site.

ECG
When an ECG is taken, it is possible that the skin reacts to the electrodes (a set of sticky patches).

MRI
There is a small risk of developing an allergic reaction to the contrast agent. This reaction can be mild (itching, rash, nausea) or severe (difficulty breathing or state of shock). The contrast agent can also cause dehydration or damage the kidneys, which at worst results in kidney failure.
An MRI is magnetic. It is therefore not possible to undergo an MRI scan when you have an implanted electronic device (for example a pacemaker, cochlear implant (CI), etc.) or implanted metal or magnetic devices.
Finally, it is possible to feel claustrophobic (feeling scared of a small space) in an MRI, as you will have to lie still in a narrow space for approximately 20 minutes.

Surgery
There are risks related to the brain surgery to remove the tumor.

Contacts

Public
Double Bond Pharmaceutical AB

Virdings allé 32B
Uppsala 754 50
SE
Scientific
Double Bond Pharmaceutical AB

Virdings allé 32B
Uppsala 754 50
SE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1) Signed informed consent form (ICF) prior to the start of any trial-related procedures.
2) Subject age >= 18 years with an upper limit of 70 years.
3) In the Investigator*s opinion, subject is able and willing to comply with all trial requirements for the duration of the trial.
4) Suspected primary, newly diagnosed supratentorial GBM (Grade IV glioma per WHO guidelines) based on signs/symptoms and MRI (obtained maximally 10 days prior to surgery, using the same MRI settings as will be used for post-surgery MRI; if the MRI is older than 10 days or if it is taken at a local clinic, this has to be repeated within 10 days before the surgery), needing maximum safe resection followed by chemoradiotherapy as per institutional guidelines (Stupp protocol: radiotherapy [60 Gy total; 10 Gy per week for 6 weeks] plus concomitant TMZ [75 mg/m2 of body surface area per day; 7 days per week from first to the last day of radiotherapy], followed by six cycles of adjuvant TMZ [150 to 200 mg/m2] once daily for 5 consecutive days, followed by 23 days of no treatment prior to the next cycle; or CeTeG protocol for MGMT promoter methylated GBMs: up to six courses of lomustine [100 mg/m2 on Day 1 plus TMZ [100-200 mg/m2 per day on Days 2-6 of the 6-week course] in addition to radiotherapy [59-60 Gy], if preferred by the investigator).
5) Preliminary histological diagnosis of GBM by an intraoperative *frozen section*, analyzed during surgery is mandatory before administration of SI-053. A final diagnosis is made by histopathological and molecular analysis of the resected tumor tissue.
6) It is the surgeon*s estimation that maximum safe resection of the contrast enhancing part of the tumor with image-guided surgery is possible and it is not expected that the ventricular system will be opened during surgery. When the ventricular system is opened during surgery, no SI-053 will be administered.
7) The tumor volume as assessed by pre-surgery MRI is at least 10 mL, and the actual resection bed volume based on the surgeon*s estimation after surgery enables complete administration of a single dose of SI-053.
8) Karnofsky Performance Status (KPS) score >=70% (see Appendix II)
9) Women of childbearing potential (WOCBP) and men whose partner is of

childbearing potential must use highly effective contraceptive methods from the time of screening and for 6 months after receiving SI-053. WOCBP should have a negative serum pregnancy test β-human chorionic gonadotropin (β-HCG) at trial enrollment and within <= 72 h before SI-053 administration.
10) Subjects must have following laboratory values obtained within 2 weeks prior to enrollment.
• Acceptable liver function:
- Total bilirubin <= 1.5 x upper limit of normal (ULN) (except in the case of Gilbert*s disease)
- Albumin 3.0 - 5.5 g/dL
- Aspartate transaminase (AST) <= 2.5 x ULN
• Alanine transaminase (ALT) <= 2.5 x ULN
• Alkaline phosphatase <= 2.5 x ULN
• Acceptable kidney function:
- Creatinine clearance: <= 30 mL/min (by CKD-EPI formula)
• Acceptable hematologic status:
- Absolute neutrophil count (ANC) >= 1 500 cells/mm3
- Platelet count >= 100 000 cells/mm3
- Hemoglobin >= 10.0 g/dL
11) Subjects should have a suspected life expectancy of at least 6 months.
12) Documented negative test for HBV. For HBV serology, the determination of HbsAg and anti-HbcAg Ab is required.

Exclusion criteria

1) Prior treatment for GBM including resection or radiation therapy.
2) Contraindications to radiotherapy or TMZ chemotherapy (i.e allergy, hypersensitivity or other intolerabilities to TMZ and its excipients or hypersensitivity to dacarbazine).
3) Has a history of another primary malignancy, except for:
• Malignancy treated with curative intent and with no known active disease within 2 years prior to SI-053 administration
• Adequately treated non-invasive basal skin cancer or squamous cell skin carcinoma
• Adequately treated uterine cervical cancer stage 1B or less
4) Has clinically significant cardiac disease (as identified by electrocardiogram [ECG]), including:
• Known congestive heart failure Grade III or IV by the New York Heart Failure Association;
• Myocardial infarction within 6 months prior to signing the ICF;
• Onset of unstable angina within 6 months prior to signing the ICF.
5) Infratentorial or multifocal glioblastoma.
6) Pre-operative MRI showing ventricular invasion (defined as presence of intraventricular lesion or of intraventricular tumor mass).
7) Major surgery, other than diagnostic surgery, within 4 weeks prior to Day 1.

8) Chronic use of systemic steroid therapy (>1 month of >10 mg prednisone per day or equivalent, except topical or inhaled).
9) Any significant disease or disorder which, in the opinion of the Investigator, may either put the participant at risk because of participation in the trial, or affect the participant*s ability to participate in the trial. Presence of active and uncontrolled infections or other severe concurrent disease, which, in the opinion of the Investigator, would place the subject at undue risk or interfere with the trial.
10) Subjects who have participated in another research trial involving an investigational product within the past 12 weeks or are currently participating in another clinical trial (excluding observational studies).
11) Pregnant or lactating women.
12) Subjects unable to undergo MRI during the trial participation.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-01-2023
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	SI-053
Generic name:	-

Ethics review

Approved WMO Date:	02-09-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-12-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-06-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-03-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	CTIS2024-515128-35-00
EudraCT	EUCTR2021-000928-35-NL
ClinicalTrials.gov	NCT04967690
CCMO	NL78236.078.21