TEMOkids study (ORP-TMZ-I- b): A Population pharmacokinetic, acceptability and safety study for KIMOZO, a paediatric oral suspension of temozolomide

Published: 07-12-2021
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Primary objective:• Evaluate PK parameters of the oral suspension of temozolomide in the paediatric population aged 1 year and over.Secondary objectives:• Evaluate the safety of the oral suspension of temozolomide,• Evaluate the acceptability of the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON50808

Source
ToetsingOnline

Brief title
TEMOkids study

Condition

- Other condition

Synonym
Paediatric cancer

Health condition

pediatric cancers such as malignant glioma and also relapsed or refractory neuroblastoma, rhabdomyosarcoma, medulloblastoma, and Ewing sarcoma

Research involving
Human

Sponsors and support

Primary sponsor: ORPHELIA Pharma
Source(s) of monetary or material Support: ORPHELIA Pharma

Intervention

Keyword: Oral, Paediatric, Pharmacokinetic, Temozolomide

Outcome measures

Primary outcome

Primary endpoints:

Investigated PK parameters will be TMZ apparent clearance (CL/F), distribution volume (V/F) and absorption rate constant (Ka). These PK parameters will be used to derive key estimates of exposure such as TMZ area under the curve between 2 intakes (AUC0-t) and, if feasible, maximum concentration (Cmax) for each included subject and elimination half-life (t1/2), and the total AUC0-*.

Population PK parameters will be estimated by a population analysis performed with NONMEM (7.4). Individual Bayesian estimates of the PK parameters will be used to calculate individual AUC24, Cmax, and t1/2.

A total of 6 blood samples of 1 ml* will be drawn per patient in a single daytime hospitalisation. Blood samples will be collected in prechilled K2-EDTA tubes prior to Kimozo administration and at 0.10-0.20 (6-12 min), 0.33-0.66 (20-40 min), 0.75-1.5 (45-90 min), 2.0-3.0 and 6.0-8.0 hours post-dose. The administered dose and exact time for each sample will be recorded. Should a

patient be naïve to any prior treatment with TMZ, the pre-treatment sample is not necessary.

*a minimum of 750 µL for blood sampling is required to collect 100 µL of plasma in duplicate

Secondary outcome

Secondary endpoints:

• Acceptability

The acceptability of the oral suspension of temozolomide will be scored with a standardized assessment tool: CAST - ClinSearch Acceptability Score Test®. This tool measures 9 observational drivers of medicine acceptability.

A paper diary will be filled-in to assess palatability/acceptability of the oral suspension of temozolomide.

• Safety

Safety events recorded by the caregiver in the patient diary will be medically controlled on a monthly basis by the principal investigator before collection of data into the CRF.

Safety follow-up: 21 or 28 days (or up to the next temozolomide cycle), including buccal tolerance (at day 5 and until day 21 or 28). Patient diary will be used to collect data.

After completion, patients will be proposed to receive Kimozo as a compassionate-use treatment for 5 additional treatment cycles. Safety data will be collected during this compassionate period.

• Activity

The clinical activity of the oral suspension of temozolomide during the compassionate use period will be described according to the standard follow-up exams and tests (i.e. complete or partial response, disease progression, stable disease)

Study description

Background summary

Temozolomide (TMZ) obtained market authorization in the European Union (EU) in 1999. In adults, it is used for the treatment of newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and subsequently as monotherapy treatment. It is also indicated for the treatment of recurrent (post standard therapy) malignant glioma, such as glioblastoma multiforme or anaplastic astrocytoma, in both adults and paediatric patients above three years of age[3]. In paediatric patients, it is also used off-label to treat tumours such as rhabdomyosarcoma, medulloblastoma, sarcoma, Ewing sarcoma and relapsed or refractory neuroblastoma (NB). The efficacy and safety of the drug in NB have been demonstrated in multiple published clinical trials. Today it is considered as the mainstay of therapy and is used as such in the major ongoing clinical trials conducted in Europe and in
the USA and is recommended in major guidelines for this condition.
TMZ is a pro-drug. At physiologic pH, it spontaneously hydrolyses into 3-methyl-(triazen-1- yl)imidazole-4-carboxamide (MTIC), which spontaneously fragments into 4-amino-5-imidazole carboxamide (AIC) and methyldiazonium, the alkylating agent which transfer methyl groups to DNA nucleotides, causing a cytotoxic effect on rapidly proliferating cells.

The most commonly administered paediatric regimens of TMZ are:
• As single agent: 150 mg/m²/day for 5 days, with subsequent dose escalation to 200 mg/m²/day in the absence of significant myelosuppression, every 28 days.
• In combination with topotecan: 150 mg/m²/day for 5 days, every 28 days.
• In combination with irinotecan: 100 mg/m²/day for 5 days, every 21 days.

ORPHELIA Pharma is developing Kimozo, a new formulation of temozolomide (TMZ), intended for paediatric use from the age of one year.

Study objective

Primary objective:
• Evaluate PK parameters of the oral suspension of temozolomide in the paediatric population aged 1 year and over.

Secondary objectives:
• Evaluate the safety of the oral suspension of temozolomide,
• Evaluate the acceptability of the oral suspension of temozolomide.
• Describe the activity of the oral suspension of temozolomide over the course of a 6-month-treatment period (complete or partial response, disease progression, stable disease) according to the standard follow up exams and tests recommended for each indication

Study design

Non-randomized, international, multi-centre, open-label, singlearm study

Intervention

A total of 6 blood samples of 1 ml will be drawn per patient in a single daytime hospitalisation. Blood samples will be collected in prechilled K2-EDTA tubes prior to Kimozo administration and at 0.10-0.20 (6-12 min), 0.33-0.66 (20-40 min), 0.75-1.5 (45-90 min), 2.0-3.0 and 6.0-8.0 hours post-dose.

Study burden and risks

Risks ad benefits are described in section E 9 of the ARB form.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)
Babies and toddlers (28 days-23 months)

Inclusion criteria

Paediatric patients already receiving commercially available temozolomide-based treatment or naïve paediatric patients requiring temozolomide-based treatment as per investigator*s decision (all indications with 5-day treatment per 21- or 28-day cycle). Indications include those described in the Temodal SmPC (i.e. malignant glioma such as glioblastoma and anaplastic astrocytoma). For patients having no therapeutic alternatives, the IMP may be used in off-label indications in accordance with current treatment protocols recommended by European and International Medical Associations (e.g. SIOPEN, EPSSG, COG, European ITCC, SIOP,*). Such indications include but are not limited to primarily neuroblastoma, medulloblastoma and also rhabdomyosarcoma, or Ewing sarcoma
• Male and female patients aged 1 to less than 18 years
• Patients who have signed the informed consent or for which one, both parents or legal guardian (depending on local legislation) have signed the informed consent.
• Patients having records of coverage by a health insurance
• Life expectancy >= 3 months
• Adequate haematological function:
o haemoglobin >= 80 g/L (transfusion support authorized)
o neutrophil count >= 1.0 x 109 cells/L
o platelet count >= 100 x 109 cells/L (without transfusion support)
o in case of bone marrow involvement: neutrophils >= 0.5 x 109 cells/L and platelets >=75 x 109 cells/L
• Adequate renal function:
o Creatine clearance >= 60 mL/min.1.73m² according to the Schwartz formula [1] or its modified form
[2]

• Adequate hepatic function:
o bilirubin <=1.5 x ULN
o AST and ALT <= 2.5 x ULN (AST, ALT 5xULN in case of liver metastases)
• Lansky Score >= 70%

Exclusion criteria

• Patient treated with sodium valproate within two weeks prior to receiving Kimozo or patients who are coadministrated on day one of Kimozo administration with sodium valproate as it decreases the clearance of temozolomide.
• Patients with (naso)gastric tube administration of Kimozo
• Patients already enrolled in studies investigating temozolomide or other investigational new drugs.
• A post-menarche female with a positive blood/urine pregnancy test at inclusion.
• Known contraindication or hypersensitivity to temozolomide or any chemically close substance.
• Persons who are living in a facility by order of a court or an administrative order.
• Patients infected by a SARS-CoV-2 variant.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-09-2022
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	KIMOZO
Generic name:	TEMOZOLOMIDE

Ethics review

Approved WMO Date:	07-12-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	07-01-2022
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	25-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-10-2022
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
EudraCT	EUCTR2020-003733-38-NL
ClinicalTrials.gov	NCT04610736
CCMO	NL75513.041.21

Study results

Date completed:	23-02-2023
Actual enrolment:	1