Clinical trial results:
Pharmacokinetics of temozolomide in cerebrospinal fluid in children with malignant brain tumors - a pilot study

Summary

EudraCT number	2015-002675-19
Trial protocol	AT
Global end of trial date	23 April 2019

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	TMZ-CSF-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Spitalgasse 23, Vienna, Austria, 1090
Public contact	Assoc. Prof. Dr. Andreas Peyrl, Medical University of Vienna, Department of Pediatrics, +43 140400 32320, andreas.peyrl@meduniwien.ac.at
Scientific contact	Assoc. Prof. Dr. Andreas Peyrl, Medical University of Vienna, Department of Pediatrics, +43 140400 32320, andreas.peyrl@meduniwien.ac.at

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 July 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 April 2019
Global end of trial reached?	Yes
Global end of trial date	23 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study aimed at investigating whether measurable and clinically relevant concentrations of temozolomide are reached and maintained in CSF for continuous oral administration in pediatric patients.

Protection of trial subjects:

All patients enrolled in this study received treatment for therapeutic reasons and not for the purpose of this study. After intrathecal application of chemotherapeutic agents the patients routinely remained in care of the Department of Pediatrics, Medical University of Vienna. The responsible physicians were continuously aware about medication, new diagnostic findings, the course and the state of the disease of the patient. All therapeutic measures to optimize the benefit to patients were paramount and were not affected by study procedures. Adverse events were to be followed until they had resolved or improved. Safety variables were to be assessed and included physical examinations, laboratory evaluations, vital signs and adverse events. Monitoring for adverse events was to be performed at each visit and during follow-up.
For study purposes, no additional inconvenience or pain was caused (no additional venous puncture or punctures of the ommaya reservoir). Volume of blood collected for study purposes was strictly kept to a minimum that is known to be usually well tolerated even by smaller children.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 September 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 13
Worldwide total number of subjects	13
EEA total number of subjects	13

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	2

months)	
Children (2-11 years)	9
Adolescents (12-17 years)	2
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients up to the age of 19 years at initial diagnosis, suffering from a brain tumor and receiving temozolomide and intraventricular therapy for therapeutic reasons at the sponsors institution were asked to participate in the study. Recruitment period: 23-Nov-2015 until DATE.

Pre-assignment

Screening details:

Documented screening according to incl./excl. criteria. No screen failures during screening period. Inclusion criteria: ICF obtained, aged 3-19y, Recurrent brain tumor with leptomeningeal dissemination (or risk of), treatment with oral temozolomide and intrathecal administered chemotherapy, life expectancy >8 weeks

Period 1

Period 1 title	Single Arm PK Sample Collection (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Pharmacokinetics Arm

Arm description:

To measure concentrations of temozolomide in CSF and plasma over time after metronomic administration of oral temozolomide in children with a recurrent malignant brain tumor and leptomeningeal dissemination or risk of leptomeningeal dissemination.

Arm type	single arm study
Investigational medicinal product name	Temolozomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Treatment with oral temozolomide at a metronomic schedule (daily doses of 35-75mg/m2) for therapeutic reasons.

Number of subjects in period 1	Pharmacokinetics Arm
Started	13
Completed	13

Baseline characteristics

Reporting groups

Reporting group title	Single Arm PK Sample Collection

Reporting group description: -

Reporting group values	Single Arm PK Sample Collection	Total	
Number of subjects	13	13	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	2	2	
Children (2-11 years)	9	9	
Adolescents (12-17 years)	2	2	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	4	4	
Male	9	9	
Diagnosis			
Clinical Diagnosis			
Units: Subjects			
Recurrent medulloblastoma	6	6	
Recurrent ependymoma	5	5	
ETMR	2	2	

End points

End points reporting groups

Reporting group title	Pharmacokinetics Arm

Reporting group description:

To measure concentrations of temozolomide in CSF and plasma over time after metronomic administration of oral temozolomide in children with a recurrent malignant brain tumor and leptomeningeal dissemination or risk of leptomeningeal dissemination.

Primary: Temozolomide concentration in CSF (AUC)

End point title	Temozolomide concentration in CSF (AUC)[1]

End point description:

The time of administration of temozolomide and intrathecal therapy was defined by the patient's routine treatment schedule, independent of the study.
Intrathecal, oral and intravenous therapy with other antineoplastic drugs in multiple doses were administered exclusively according to the decision of the responsible pediatric oncologist, independently of the study.
The first study period started, as soon as an intrathecal therapy was scheduled for an included study patient. Since there are usually up to 5 intrathecal routine applications of antineoplastic drugs within one week, the duration of one study period was defined as one week (day 1-7). Patients could participate for up to 5 study periods with a maximal time period between two study periods of 3 months.

A population pharmacokinetic model was developed to quantify CSF penetration of temozolomide. Two ETMR patients were excluded from final analysis to allow for a more consistent PK modeling.

End point type	Primary

End point timeframe:

Starting as soon as an intrathecal therapy was scheduled for an included study patient until max. 5 study periods of one week with max. 3 months between study periods.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive Analysis was performed to calculate for median, range and AUC of Temozolomide in CSF/plasma.

Measured values were used to develop a population PK model of temozolomide using the nonlinear mixed-effects modeling program NONMEM (Version 7.4.2), PsN 4.8.1, and Pirana 2.9.9.
R (Version 4.0.3) was used to build figures for model evaluations and for statistical summaries.
Estimations were performed using the first-order conditional estimation algorithm (FOCE) with interaction.

End point values	Pharmacokinetics Arm			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: mg*h/L				
median (confidence interval 95%)	5.99 (2.52 to 8.21)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Temozolomide concentration in CSF (range)

End point title	Temozolomide concentration in CSF (range)

End point description:

The time of administration of temozolomide and intrathecal therapy was defined by the patient's routine treatment schedule, independent of the study.
Intrathecal, oral and intravenous therapy with other antineoplastic drugs in multiple doses were administered exclusively according to the decision of the responsible pediatric oncologist, independently of the study.
The first study period started, as soon as an intrathecal therapy was scheduled for an included study patient. Since there are usually up to 5 intrathecal routine applications of antineoplastic drugs within one week, the duration of one study period was defined as one week (day 1-7). Patients could participate for up to 5 study periods with a maximal time period between two study periods of 3 months.

A population pharmacokinetic model was developed to quantify CSF penetration of temozolomide. Two ETMR patients were excluded from final analysis to allow for a more consistent PK modeling.

End point type	Other pre-specified

End point timeframe:

Starting as soon as an intrathecal therapy was scheduled for an included study patient until max. 5 study periods of one week with max. 3 months between study periods.

End point values	Pharmacokinetics Arm			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: µg/ml				
median (full range (min-max))	0.37 (0.06 to 1.76)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

All adverse events occurring after signing the informed consent and starting before follow-up visit of the last cycle were to be recorded.

Adverse event reporting additional description:

Patients received treatment as part of their routine clinical care and not for the purpose of this study. Therefore no study related adverse events were expected.

Assessment type	Systematic

Dictionary used

Dictionary name	not applicable
Dictionary version	0

Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Patients received treatment as part of their routine clinical care and not for the purpose of this study. Therefore no study related adverse events were expected.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

small patient population, measured drug concentration serves as a surrogate parameter of the active substance, VCSF was fixed to its expected mean valueno external model validation.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35355137