



Clinical trial results:

Pharmacokinetics of temozolomide in cerebrospinal fluid in children with malignant brain tumors - a pilot study

Summary

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|--------------------------|----------------|
| 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

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|--|----|
| 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: -

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| 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

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|--------------------------------------|-------------|
| 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.

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|--|------------------|
| 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.

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

Baseline characteristics

Reporting groups

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|-----------------------|---------------------------------|
| 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)

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|---|--|
| 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.

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|----------------------------------|----------------------|--|--|--|
| 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)

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|--|---|
| End point title | Temozolomide concentration in CSF (range) |
| End point description: | |
| <p>The time of administration of temozolomide and intrathecal therapy was defined by the patient's routine treatment schedule, independent of the study.</p> <p>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.</p> <p>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.</p> <p>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.</p> | |
| End point type | Other pre-specified |
| End point timeframe: | |
| <p>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.</p> | |

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|-------------------------------|----------------------|--|--|--|
| 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.

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| Assessment type | Systematic |
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Dictionary used

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| Dictionary name | not applicable |
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| Dictionary version | 0 |
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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.

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| small patient population, measured drug concentration serves as a surrogate parameter of the active substance, VCSF was fixed to its expected mean value no external model validation. |
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Notes:

Online references

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