# EU Clinical Trials Register

## Clinical trial results:
## Feasibility and effects on markers in spinal fluid in persons with early Alzheimer's disease when treated with Valaciklovir - open Fas II pilot study (VALZ-Pilot)

### Summary

| | |
|---|---|
| EudraCT number | 2016-002317-22 |
| Trial protocol | SE |
| Global end of trial date | 14 June 2021 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 25 December 2021 |
| First version publication date | 25 December 2021 |

### Trial information

#### Trial identification

| | |
|---|---|
| Sponsor protocol code | VALZ-Pilot |

#### Additional study identifiers

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

Notes:

#### Sponsors

| | |
|---|---|
| Sponsor organisation name | Region Västerbotten |
| Sponsor organisation address | Umeå University hospital, Umeå, Sweden, |
| Public contact | Hugo Lövheim, Umeå University hospital - Geriatric centre, 0046 907850000, hugo.lovheim@umu.se |
| Scientific contact | Hugo Lövheim, Umeå University hospital - Geriatric centre, 0046 907850000, hugo.lovheim@umu.se |

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 | 01 November 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 11 March 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 June 2021 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Primary objectives in this study are to evaluate change in the measured markers for Alzheimer's disease between first and second measurement (before and after 28 days of treatment with Valaciklovir), and to evaluate if [18F]-FHBG-PET/CT can be used to show replicating HSV in the brain at early Alzheimer's disease.

Another primary objective is to evaluate safety and feasibility for the thorough examinations and treatment.

Protection of trial subjects:

The study participant were followed from first dose of studymedication and up to 30 days after after last dose of studymedication both by study visits and by phone calls. Inclusions and exclusion criterias were carefully reviewed. Before start of study drug the protocol stated that bloodsamples were taken in order to exclude patients in risk.
If the patient experienced any adverse events during the study these events were carefully evaluated and if necessary the patient was taken of study drug.

| | |
|---|---|
| Background therapy: - | |
| Evidence for comparator: - | |
| Actual start date of recruitment | 14 December 2016 |
| 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 | Sweden: 73 |
| Worldwide total number of subjects | 73 |
| EEA total number of subjects | 73 |

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 months) | 0 |

| | |
|---|---|
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 68 |
| 85 years and over | 5 |

## Subject disposition

### Recruitment

Recruitment details:

Patients were recruited via advertisement i local newspapers and via ordinary doctors visits at geriatric center in Umeå, Skellefteå and Uppsala.

### Pre-assignment

Screening details:

In total 136 patients were screened for participating in the study and 73 patients were enrolled in the study.

### Period 1

| Period 1 title | Baseline |
|---|---|
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

### Arms

| Arm title | Baseline period |
|---|---|

Arm description:

Before starting studydrug treatment all patients went through a baseline period which included bloodtesting and exams to evaluate if the patient was eligible to start study drug.

| Arm type | Inclusion period |
|---|---|
| Investigational medicinal product name | 9-[4-^{18}F-Fluoro- 3(hydroxymethyl)butyl]guaine |
| Investigational medicinal product code | PR2 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Single bolus injection at two occasions, total dose 3.5 MBq/kg

| Number of subjects in period 1 | Baseline period |
|---|---|
| Started | 73 |
| Study treatment | 33 |
| Completed | 33 |
| Not completed | 40 |
|     Physician decision according to protocol | 40 |

### Period 2

| Period 2 title | Study treatment |
|---|---|
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

**Arms**

| Arm title | Study site A and B |
|---|---|

Arm description:

All patients enrolled into study site A and B were treated with study drug valaciclovir (n=33).
A subgroup from studisite A were treated with [18F]-FHBG-PET/CT  to evaluate if [18F]-FHBG-PET/CT can be used to show replicating HSV in the brain.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Valaciklovir |
| Investigational medicinal product code | PR1 |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

First 7 days 500mg x 3/day, if tolerated an increased dose of 1000 mg x3/day was done at day 7 and this dose were keept until study completion (day 28).

| | |
|---|---|
| Investigational medicinal product name | 9-[4-^{18}F-Fluoro- 3(hydroxymethyl)butyl]guaine |
| Investigational medicinal product code | PR2 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Single bolus injection at two occasions, total dose 3.5 MBq/kg

| Number of subjects in period 2 | Study site A and B |
|---|---|
| Started | 33 |
| Completed | 33 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Baseline |
|---|---|

Reporting group description:

Baseline characteristics are reported for all enrolled patients regardless study site A or B since all patients went though the same baseline procedures.

| Reporting group values | Baseline | Total | |
|---|---|---|---|
| Number of subjects | 73 | 73 | |
| Age categorical | | | |
| All patients enrolled in the studie were elderly patients. | | | |
| 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) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 68 | 68 | |
| 85 years and over | 5 | 5 | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 35 | 35 | |
| Male | 38 | 38 | |

### Subject analysis sets

| Subject analysis set title | [18F]-FHBG-PET/CT |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

A subgroup from study site A (n=9) were asked to evaluate if [18F]- FHBG-PET/CT can be used to show replicating HSV in the brain at early Alzheimer's disease.

| Subject analysis set title | Administrative group for single arm study |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Because this is a single arm study this subject analysis set is done only for administrative reasons. There are no patients to report in this group however the system does not allow a subject analysis set, number of subjects to be zero.

| Reporting group values | [18F]-FHBG-PET/CT | Administrative group for single arm study | |
|---|---|---|---|
| Number of subjects | 9 | 1 | |
| Age categorical | | | |
| All patients enrolled in the studie were elderly patients. | | | |
| Units: Subjects | | | |
| In utero | 0 | | |

| | | | |
|---|---|---|---|
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 0 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 0 | | |
| From 65-84 years | 9 | | |
| 85 years and over | 0 | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 4 | | |
| Male | 5 | | |

# End points

## End points reporting groups

| Reporting group title | Baseline period |
|---|---|

Reporting group description:

Before starting studydrug treatment all patients went through a baseline period which included bloodtesting and exams to evaluate if the patient was eligible to start study drug.

| Reporting group title | Study site A and B |
|---|---|

Reporting group description:

All patients enrolled into study site A and B were treated with study drug valaciclovir (n=33).
A subgroup from studisite A were treated with [18F]-FHBG-PET/CT to evaluate if [18F]-FHBG-PET/CT can be used to show replicating HSV in the brain.

| Subject analysis set title | [18F]-FHBG-PET/CT |
|---|---|
| Subject analysis set type | Safety analysis |

Subject analysis set description:

A subgroup from study site A (n=9) were asked to evaluate if [18F]- FHBG-PET/CT can be used to show replicating HSV in the brain at early Alzheimer's disease.

| Subject analysis set title | Administrative group for single arm study |
|---|---|
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

Because this is a single arm study this subject analysis set is done only for administrative reasons. There are no patients to report in this group however the system does not allow a subject analysis set, number of subjects to be zero.

## Primary: To evaluate change in brain damage markers total-Tau for Alzheimer's disease between first and second measurement (before and after 28 days of treatment with Valaciklovir)

| End point title | To evaluate change in brain damage markers total-Tau for Alzheimer's disease between first and second measurement (before and after 28 days of treatment with Valaciklovir) |
|---|---|

End point description:

To evaluate change in brain damage markers total-Tau for Alzheimer's disease between first and second measurement (before and after 28 days of treatment with Valaciklovir)

| End point type | Primary |
|---|---|

End point timeframe:

Evaluates by comparing first and second measurement day 1 and day 28.

| End point values | Study site A and B | Administrative group for single arm study | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 33 | 1 | | |
| Units: units | 33 | 1 | | |

## Statistical analyses

| Statistical analysis title | Statistical differences between two measurements |
|---|---|

Statistical analysis description:

Statistical differences between two measurements are analyzeded with intention to treat. Simple statistical tests to compare paired values (e.g. paired t-test) will be used to compare the level of markers in spinal fluid before and after treatment, and to evaluate other outcome measures. Each individual is it´s own control.

| Comparison groups | Study site A and B v Administrative group for single arm study |
|---|---|
| Number of subjects included in analysis | 34 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.653 [1] |
| Method | t-test, 2-sided |

Notes:

[1] - t-tau before and after (mean +- SD): 720.8 ± 342.8 och 727.7 ± 326.6 pg/mL

## Primary: Feasibility

| End point title | Feasibility |
|---|---|

End point description:

Is treatment with Valaciklovir 1500 mg/day or 3000 mg/day feasible  in elderly patients with Alzheimer's disease?
Is [18F]-FHBG-PET/CT a feasible examination in patients with Alzheimer's disease

| End point type | Primary |
|---|---|

End point timeframe:

Evaluates at v 2, v3, v4, v5 and v6, there will also be two telephone calls between v 3 and v4 where adverse events will be recorded.

| End point values | Study site A and B | Administrative group for single arm study | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 33 | 1 | | |
| Units: units | | | | |
| number (not applicable) | 33 | 1 | | |

## Statistical analyses

| Statistical analysis title | CSF acyclovir koncentration |
|---|---|

Statistical analysis description:

"The intervention's feasibility and by assessing the CSF acyclovir concentration on intervention day 28."

| Comparison groups | Study site A and B v Administrative group for single arm study |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 34 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority[2] |
| Parameter estimate | Mean difference (final values) |
| Point estimate | 5.29 |
| Confidence interval | |
|     level | 95 % |
|     sides | 2-sided |
|     lower limit | 4.47 |
|     upper limit | 6.11 |
| Variability estimate | Standard deviation |
| Dispersion value | 2.31 |

Notes:

[2] - CSF acyclovir konc = mean 5.29 ± 2.31 µmol/L.

## Primary: To evaluate change in brain damage markers NFL (Neorofilament light chain) for Alzheimer's disease between first and second measurement (before and after 28 days of treatment with Valaciklovir)

| | |
|---|---|
| End point title | To evaluate change in brain damage markers NFL (Neorofilament light chain) for Alzheimer's disease between first and second measurement (before and after 28 days of treatment with Valaciklovir) |

End point description:

To evaluate change in brain damage markers NFL (Neorofilament light chain) for Alzheimer's disease between first and second measurement (before and after 28 days of treatment with Valaciklovir)

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Evaluates by comparing first and second measurement day 1 and day 28.

| **End point values** | Study site A and B | Administrative group for single arm study | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 33 | 1 | | |
| Units: units | 33 | 1 | | |

## Statistical analyses

| **Statistical analysis title** | Statistical differences between two measurements |
|---|---|

Statistical analysis description:

Diffrence in NFL before and after treatment with Valaciclovir. Each individual is it´s own control.

| Comparison groups | Study site A and B v Administrative group for single arm study |
|---|---|

| | |
|---|---|
| Number of subjects included in analysis | 34 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| P-value | = 0.52 [3] |
| Method | t-test, 2-sided |

Notes:

[3] - NFL before and after (mean +- SD): 1768.8 ± 680.4 och 1816.3 ± 702.4 pg/mL

## Primary: Safety

| | |
|---|---|
| End point title | Safety[4] |

End point description:

Is treatment with Valaciklovir 1500 mg/day or 3000 mg/day safe and tolerated in elderly patients with Alzheimer's disease and is [18F]-FHBG-PET/CT a safe examination in patients with Alzheimer's disease? Fourteen AEs in 11 participants and two SAEs in one participant were reported. Ten AEs and no SAE in six participants (18.2% of all) were considered to be related to the valacyclovir intervention (fatigue, headache [n = 2 each]; thirst, nausea, loose stools, mild depressive symptoms, mild tremor, polyuria [n = 1 each]). One AE (panic attack) related to the [18F]FHBG PET/CT intervention occurred."
The serum creatinine did not change significantly during the intervention, but seven participants experienced temporary creatinine increases > 10%; all of these participants' creatinine levels had normalized at the time of subsequent medical records reviews."

| | |
|---|---|
| End point type | Primary |

End point timeframe:

Evaluates at v 2, v3, v4, v5 and v6, there will also be two telephone calls between v 3 and v4 where adverse events will be recorded.

Notes:

[4] - 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: This is a one armed study with only one group to analyse.

| **End point values** | Study site A and B | Administrative group for single arm study | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Subject analysis set | | |
| Number of subjects analysed | 33 | 1 | | |
| Units: units | | | | |
| number (not applicable) | 33 | 1 | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Can[18F]- FHBG-PET/CT be used to show replicating HSV in the brain at early Alzheimer's disease.

| | |
|---|---|
| End point title | Can[18F]- FHBG-PET/CT be used to show replicating HSV in the brain at early Alzheimer's disease. |

End point description:

Secondary objectives, concerning a subgroup were to evaluate if [18F]- FHBG-PET/CT can be used to show replicating HSV in the brain at early Alzheimer's disease.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Before start with study drug and after 28 days of treatment.

| End point values | [18F]-FHBG-PET/CT | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 9 | | | |
| Units: units | | | | |
| number (not applicable) | 9 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Evaluate biomarkers in CSF and MMSE-SR before and after treatment with Valaciklovir

| End point title | Evaluate biomarkers in CSF and MMSE-SR before and after treatment with Valaciklovir |
|---|---|

End point description:

Secondary objectives were also to evaluate biomarkers in CSF and MMSE-SR before and after treatment with Valaciklovir and to evaluate the concentration of Aciklovir and the breakdown product CMMG in plasma and CSF when treating elderly persons with Alzheimer's disease.

| End point type | Secondary |
|---|---|

End point timeframe:

Before start with study drug and after 28 days of treatment.

| End point values | Study site A and B | | | |
|---|---|---|---|---|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 33 | | | |
| Units: units | 33 | | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: To investigate if [18F]-FHBG is accumulated in the areas of the brain that are affected in early Alzheimer's disease and if [18F]-FHBG-PET/CT can be used to demonstrate the effect of Valaciklovir

| End point title | To investigate if [18F]-FHBG is accumulated in the areas of the brain that are affected in early Alzheimer's disease and if [18F]-FHBG-PET/CT can be used to demonstrate the effect of Valaciklovir |
|---|---|

End point description:

Another secondary objective, concerning a subgroup (study site A), is to investigate if [18F]-FHBG is accumulated in the areas of the brain that are affected in early Alzheimer's disease and if [18F]-FHBG-PET/CT can be used to demonstrate the effect of Valaciklovir and identify individuals that have an extra

good effect by the treatment.

| End point type | Secondary |
|---|---|

End point timeframe:

Before start with study drug and after 28 days of treatment.

| End point values | [18F]-FHBG-PET/CT | | | |
|---|---|---|---|---|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 9 | | | |
| Units: units | | | | |
| number (not applicable) | 9 | | | |

## Statistical analyses

No statistical analyses for this end point

# Adverse events

## Adverse events information

Timeframe for reporting adverse events:

From the time of first dose study treatment (both Valaciklovir and [18F]-FHBG) until 30 days after last dose study drug.

Adverse event reporting additional description:

Known complications of the underlying disease (Alzheimer's) are not considered complications and will not be reported as AE and SAE.

| Assessment type | Non-systematic |
|---|---|

## Dictionary used

| Dictionary name | CTCAE |
|---|---|
| Dictionary version | 5.0 |

## Reporting groups

| Reporting group title | All patients signed informed concent |
|---|---|

Reporting group description:

Deviating laboratory findings (ex clinical, haematological and urine specimens) or other abnormal findings assessed by the investigator to be clinically significant will be recorded as AE or SAE if they meet the definition of an AE or SAE and occur within the following AE reporting time frames:
All AEs are registered from the time when the study participant receives the first dose of study medicine ([18F] FHBG) site type A and Valtrex at site, until 30 days after the end of treatment with Valtrex; or 30 days after the second PET / CT scan.

| Serious adverse events | All patients signed informed concent | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
|     subjects affected / exposed | 1 / 33 (3.03%) | | |
|     number of deaths (all causes) | 0 | | |
|     number of deaths resulting from adverse events | 0 | | |
| Cardiac disorders | | | |
|   Myocardial infarction | | | |
|     subjects affected / exposed | 1 / 33 (3.03%) | | |
|     occurrences causally related to treatment / all | 0 / 1 | | |
|     deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
|   Duodenal ulcus | | | |
|     alternative dictionary used: CTCAE 5.0 | | | |
|     subjects affected / exposed | 1 / 33 (3.03%) | | |
|     occurrences causally related to treatment / all | 0 / 1 | | |
|     deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | All patients signed informed concent | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 33 (33.33%) | | |
| Nervous system disorders | | | |
| Paresthesia leg | Additional description: Numbness weakness in leg after lumbar puncture | | |
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences (all) | 2 | | |
| Headache | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences (all) | 2 | | |
| Fatigue | | | |
| subjects affected / exposed | 2 / 33 (6.06%) | | |
| occurrences (all) | 2 | | |
| Tremor mild | | | |
| alternative dictionary used: CTCAE 5.0 | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences (all) | 1 | | |
| Loose stools | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences (all) | 1 | | |
| Psychiatric disorders | | | |
| Panic attack | Additional description: related to the [18F]FHBG PET/CT intervention | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences (all) | 1 | | |
| Mild depressive mood | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Neck pain | | | |
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences (all) | 1 | | |
| Back pain | Additional description: Back pain after lumbar puncture | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 33 (3.03%) | | |
| occurrences (all) | 1 | | |
| **Metabolism and nutrition disorders** | | | |
|   Thirst | | | |
|     alternative dictionary used: CTCAE 5.0 | | | |
|     subjects affected / exposed | 1 / 33 (3.03%) | | |
|     occurrences (all) | 1 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol?  Yes

| Date | Amendment |
|---|---|
| 24 July 2018 | All outcome measures related to the [18F] -FHBG-PET / CT examinations have been changed to secondary outcome measures. Minimum number who will undergo the study according to protocol, study site A has been specified for at least 14 study participants.<br>The amendment also inculdes change in the number of study sites with the addition of a study site at Skellefteå Hospital and the University Hospital in Uppsala. Due to the availability of performing [18F]-FHBG-PET/CT examinations, the study is carried out at the two new study sites according to a somewhat simplified procedure with only three visits, according to the revised protocol. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial?  No

### Limitations and caveats

 None reported

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