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