Clinical trial results:
A Phase I/II, 2-Arm, Open Label, Single Centre Study to Investigate the Safety and Effect of Oral GABA Therapy on -cell Regeneration in Type 1-diabetes Patients

Summary

EudraCT number	2018-001115-73
Trial protocol	SE
Global end of trial date	27 September 2022

Results information

Result version number	v1 (current)
This version publication date	12 October 2023
First version publication date	12 October 2023

Trial information

Trial identification

Sponsor protocol code	Regenerate-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03635437
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Uppsala University Hospital
Sponsor organisation address	Akademiska sjukhuset , Uppsala, Sweden, 75185
Public contact	Per-Ola Carlsson, Uppsala University Hospital, 46 18 471 44 25,
Scientific contact	Per-Ola Carlsson, Uppsala University Hospital, 46 18 471 44 25 ,

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	05 May 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 September 2022
Global end of trial reached?	Yes
Global end of trial date	27 September 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the acute and long-term safety of oral GABA treatment.

Protection of trial subjects:

In the first dose-escalation part of the study, 6 patients were treated with 200 mg, 600 mg and 1200 mg GABA. The IDMC reviewed the safety data for the first patient before allowing the following five patients to begin the dose-escalation steps. After all patients had completed the dose-escalation study, the IDMC again reviewed the data to ensure safe continuation of the main study where patients were randomized to one of three treatment arms receiving a daily dose of 200 mg GABA, 600 mg GABA or 600 mg GABA + 0.5 mg alprazolam. Safety parameters, plasma concentration of GABA, insulin and glucose tolerance was evaluated for each patient.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 October 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 35
Worldwide total number of subjects	35
EEA total number of subjects	35

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)	35
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Male patients with type 1 diabetes at Uppsala University Hospital, Sweden, diagnosed ≥ 5 years at the time of screening were given information about the study and asked to participate in the trial.

Pre-assignment

Screening details:

A total of 49 patients were screened for inclusion in the Main study, of which 12 were excluded due to a screen failure and 2 because of other reasons (difficult to find appropriate blood vessels and not possible to participate due to work).

Period 1

Period 1 title	Before treatment with GABA
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

The study was an open label trial, so no blinding or code breaking procedures were needed.

Arms

Are arms mutually exclusive?	Yes
Arm title	200 mg GABA

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Remygen (GABA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

200 mg, once daily taken together with food

Arm title	600 mg GABA

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Remygen (GABA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg, once daily taken together with food

Arm title	600 mg GABA + 0.5 mg alprazolam

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Remygen (GABA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details: 600 mg, once daily taken together with food	
Investigational medicinal product name	Alprazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 0.5 mg, once daily, taken together with food.	

Number of subjects in period 1	200 mg GABA	600 mg GABA	600 mg GABA + 0.5 mg alprazolam
Started	13	11	11
Completed	13	11	9
Not completed	0	0	2
Consent withdrawn by subject	-	-	2

Period 2	
Period 2 title	Treatment with GABA
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded
Blinding implementation details: The study was an open label trial, so no blinding or code breaking procedures were needed.	

Arms	
Are arms mutually exclusive?	Yes
Arm title	200 mg GABA
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Remygen (GABA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 200 mg, once daily taken together with food	
Arm title	600 mg GABA
Arm description: -	
Arm type	Experimental

Investigational medicinal product name	Remygen (GABA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg, once daily taken together with food

Arm title	600 mg GABA + 0.5 mg alprazolam

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Remygen (GABA)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

600 mg, once daily taken together with food

Investigational medicinal product name	Alprazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

0.5 mg, once daily, taken together with food.

Number of subjects in period 2	200 mg GABA	600 mg GABA	600 mg GABA + 0.5 mg alprazolam
Started	13	11	9
Completed	12	7	7
Not completed	1	4	2
Physician decision	-	1	-
Consent withdrawn by subject	-	2	-
Adverse event, non-fatal	1	-	1
Unable to attend all study visits.	-	1	-
Lost to follow-up	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	200 mg GABA
Reporting group description: -	
Reporting group title	600 mg GABA
Reporting group description: -	
Reporting group title	600 mg GABA + 0.5 mg alprazolam
Reporting group description: -	

Reporting group values	200 mg GABA	600 mg GABA	600 mg GABA + 0.5 mg alprazolam
Number of subjects	13	11	11
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
arithmetic mean	33.5	31.1	27.4
standard deviation	± 5.3	± 7.6	± 7.3
Gender categorical Units: Subjects			
Female	0	0	0
Male	13	11	11

Reporting group values	Total		
Number of subjects	35		
Age categorical 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	0		
85 years and over	0		

Age continuous Units: years arithmetic mean standard deviation	- 		
Gender categorical Units: Subjects			
Female	0		
Male	35		

End points

End points reporting groups

Reporting group title	200 mg GABA
Reporting group description: -	
Reporting group title	600 mg GABA
Reporting group description: -	
Reporting group title	600 mg GABA + 0.5 mg alprazolam
Reporting group description: -	
Reporting group title	200 mg GABA
Reporting group description: -	
Reporting group title	600 mg GABA
Reporting group description: -	
Reporting group title	600 mg GABA + 0.5 mg alprazolam
Reporting group description: -	

Primary: Safety endpoint: Number of AEs

End point title	Safety endpoint: Number of AEs[1]
End point description:	
Number of AEs probably or possibly related to the study treatment.	
End point type	Primary
End point timeframe:	
From start of treatment until one month after end of treatment.	

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 according to protocol.

End point values	200 mg GABA	600 mg GABA	600 mg GABA + 0.5 mg alprazolam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	11	9	
Units: Number of events	14	20	25	

Statistical analyses

No statistical analyses for this end point

Primary: Safety endpoint: Number of SAEs

End point title	Safety endpoint: Number of SAEs[2]
End point description:	
Number of SAEs probably or possibly related to the study treatment.	
End point type	Primary
End point timeframe:	
From start of treatment until one month after end of treatment.	

Notes:

[2] - 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 according to protocol.

End point values	200 mg GABA	600 mg GABA	600 mg GABA + 0.5 mg alprazolam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	11	9	
Units: Number of events	1	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Change in vital signs from baseline: weight

End point title	Change in vital signs from baseline: weight[3]

End point description:

End point type	Primary

End point timeframe:

Change from baseline to Day 210 of treatment

Notes:

[3] - 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 according to protocol.

End point values	200 mg GABA	600 mg GABA	600 mg GABA + 0.5 mg alprazolam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	7	7	
Units: kg				
arithmetic mean (standard deviation)	1.2 (± 1.5)	-0.3 (± 3.8)	0.2 (± 3.7)	

Statistical analyses

No statistical analyses for this end point

Primary: Change in vital signs from baseline: diastolic blood pressure

End point title	Change in vital signs from baseline: diastolic blood pressure[4]

End point description:

End point type	Primary

End point timeframe:

Change from baseline to Day 180 of treatment

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: Descriptive analysis according to protocol.

End point values	200 mg GABA	600 mg GABA	600 mg GABA + 0.5 mg alprazolam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	8	7	
Units: mmHg				
arithmetic mean (standard deviation)	-0.9 (± 7.7)	-3.0 (± 11.8)	-4.7 (± 9.8)	

Statistical analyses

No statistical analyses for this end point

Primary: Change in vital signs from baseline: systolic blood pressure

End point title	Change in vital signs from baseline: systolic blood pressure[5]

End point description:

End point type	Primary

End point timeframe:

Change from baseline to Day 180 of treatment

Notes:

[5] - 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 according to protocol.

End point values	200 mg GABA	600 mg GABA	600 mg GABA + 0.5 mg alprazolam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	8	7	
Units: mmHg				
arithmetic mean (standard deviation)	0.9 (± 11.7)	-8.1 (± 12.5)	-6.7 (± 9.6)	

Statistical analyses

No statistical analyses for this end point

Primary: Change in laboratory parameters from baseline: WBC

End point title	Change in laboratory parameters from baseline: WBC[6]

End point description:

End point type	Primary

End point timeframe:

Change from baseline to Day 210 of treatment

Notes:

[6] - 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 according to protocol.

End point values	200 mg GABA	600 mg GABA	600 mg GABA + 0.5 mg alprazolam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	12	7	7	
Units: 10^9/L				
arithmetic mean (standard deviation)	0.07 (± 0.89)	-0.8 (± 0.73)	0.1 (± 0.94)	

Statistical analyses

No statistical analyses for this end point

Primary: Physical examination

End point title	Physical examination[7]

End point description:

The physical examination included: General appearance, skin, mouth, throat, cardiovascular system, abdomen, lymphatic glands, and neurological/musculoskeletal (incl. reflexes).

End point type	Primary

End point timeframe:

Percentage of patients with normal physical examination at baseline who had a normal physical examination at Day 210 of treatment

Notes:

[7] - 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 according to protocol.

End point values	200 mg GABA	600 mg GABA	600 mg GABA + 0.5 mg alprazolam	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	11	7	7	
Units: % of patients	100	100	100	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of treatment until one month after end of treatment.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	200 mg GABA
Reporting group description: -	
Reporting group title	600 mg GABA
Reporting group description: -	
Reporting group title	600 mg GABA + 0.5 mg alprazolam
Reporting group description: -	

Serious adverse events	200 mg GABA	600 mg GABA	600 mg GABA + 0.5 mg alprazolam
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 13 (15.38%)	0 / 11 (0.00%)	0 / 9 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Drug-induced liver injury			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	200 mg GABA	600 mg GABA	600 mg GABA + 0.5 mg alprazolam
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 13 (53.85%)	7 / 11 (63.64%)	9 / 9 (100.00%)
Investigations			
Alanine aminotransferase increased			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 13 (0.00%)	1 / 11 (9.09%)	2 / 9 (22.22%)
occurrences (all)	0	1	2
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 13 (23.08%)	3 / 11 (27.27%)	3 / 9 (33.33%)
occurrences (all)	6	7	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 13 (0.00%)	1 / 11 (9.09%)	3 / 9 (33.33%)
occurrences (all)	0	1	4
Headache			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Hypoaesthesia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Paraesthesia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Restless legs syndrome			
subjects affected / exposed	0 / 13 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Discomfort			
subjects affected / exposed	0 / 13 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1
Fatigue			
subjects affected / exposed	0 / 13 (0.00%)	1 / 11 (9.09%)	5 / 9 (55.56%)
occurrences (all)	0	1	7
Flushing			

subjects affected / exposed	1 / 13 (7.69%)	1 / 11 (9.09%)	1 / 9 (11.11%)
occurrences (all)	1	2	1
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 13 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	2 / 13 (15.38%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	2	0	1
Nausea			
subjects affected / exposed	0 / 13 (0.00%)	2 / 11 (18.18%)	1 / 9 (11.11%)
occurrences (all)	0	3	1
Vomiting			
subjects affected / exposed	1 / 13 (7.69%)	1 / 11 (9.09%)	1 / 9 (11.11%)
occurrences (all)	1	1	1
Abdominal pain upper			
subjects affected / exposed	0 / 13 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 11 (9.09%)	0 / 9 (0.00%)
occurrences (all)	0	1	0
Epistaxis			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	0 / 9 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 13 (0.00%)	0 / 11 (0.00%)	1 / 9 (11.11%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 May 2019	- Addition of the exclusion criteria: 1. Females of child-bearing potential 7. Increased plasma concentrations of alanine aminotransferase (>0.75 µkatl/l for females or >1.1 µkat/l for males) and/or aspartate aminotransferase (>0.60 µkat/l for females or >0.75µkat/l for males). 18. Participation in other clinical trials with a new chemical entity within 3 months or 5 half-lives of the new chemical entity, whatever longest. - Addition of further information regarding GABA sampling - The trial is no longer labeled "first in human" - Addition of a third arm to the main study that would receive a high dose of GABA (600 mg) in combination with 0.5 mg Alprazolam for 3 months. - Addition of 12 patients to the main study population
24 August 2020	- Addition of genotyping for HLA. - Liver function will be tested in 1- to 2-week intervals after start of study treatment - A hypoglycemic clamp will be performed twice after the 6-month treatment period

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34635547