Clinical trial results:
A 24 Week, Phase IIa, Double blind, Randomized, Parallel Group, Placebo-controlled, Proof of Concept Study to Assess the Efficacy and Safety of Two Doses of 5 Aminolevulinic Acid Co-administered with Sodium Ferrous Citrate in Adult Patients with Type 2 Diabetes Mellitus

Summary

EudraCT number	2017-004944-39
Trial protocol	EE HU PL RO
Global end of trial date	17 February 2020

Results information

Result version number	v1 (current)
This version publication date	04 December 2021
First version publication date	04 December 2021

Trial information

Trial identification

Sponsor protocol code	NPJ005-DM2-0522

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	neopharma Japan
Sponsor organisation address	2nd Floor, PMO Kojimachi, Kojimachi 6-2-6, Chiyoda-ku, Tokyo, Japan, 102-0083
Public contact	Clinical Trial Information Desk, neopharma Japan Co., Ltd., npjprd@neopharmajp.com
Scientific contact	Clinical Trial Information Desk, neopharma Japan Co., Ltd., npjprd@neopharmajp.com

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	16 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 February 2020
Global end of trial reached?	Yes
Global end of trial date	17 February 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the change from Baseline in Glycated hemoglobin (HbA1c) up to Week 24 between each dose combination of 5 aminolevulinic acid/sodium ferrous citrate (5 ALA/SFC) and placebo.

Protection of trial subjects:

Patients were enrolled in the study only after providing informed consent, and undergoing inclusion and exclusion assessments.
Rescue therapy for patients in either treatment arm with prandial insulin or oral antidiabetic (OAD) therapy was offered per Investigator’s discretion and in consultation with Medical Monitor from randomization until end of the study, depending on fasting blood glucose values.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 April 2018
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	Poland: 43
Country: Number of subjects enrolled	Estonia: 42
Country: Number of subjects enrolled	Hungary: 41
Country: Number of subjects enrolled	Romania: 46
Country: Number of subjects enrolled	Ukraine: 46
Worldwide total number of subjects	218
EEA total number of subjects	172

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)	130
From 65 to 84 years	88
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

218 patients were enrolled at 74 sites in Hungary, Poland, Estonia, Romania and Ukraine from 31-May-2018 to 17-Feb-2020.

Pre-assignment

Screening details:

434 potential patients underwent a screening period of maximally 2 weeks. Eligible patients enrolled with current OAD monotherapy underwent a 4-week Washout period followed by a 2-week single-blinded Placebo run-in period before entering the 24-week Treatment period.

Period 1

Period 1 title	Treatment period (24 weeks) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Carer, Subject

Blinding implementation details:

The appearance, including packaging and labeling of the study treatment (capsules, packaging) was the same for 5-ALA/SFC and the placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	5-ALA-HCl 150 mg/SFC 118 mg

Arm description:

The patients received 5-ALA/SFC at a dose of 150 mg/118 mg (1 capsule each BID), for a total daily dose of 300 mg/236 mg for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	5-aminolevulinic acid hydrochloride/sodium ferrous citrate (5-ALA-HCl/SFC)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

5-ALA/SFC was administered orally at a dose of 150 mg/119 mg (1 capsule each BID), for a total daily dose of 300 mg/236 mg at least 8 hours apart in the morning and evening, after the meal, for 24 weeks.

Arm title	5-ALA-HCl 50 mg/SFC 39 mg

Arm description:

The patients received 5-ALA/SFC at a dose of 50 mg/39 mg (1 capsule each BID), for a total daily dose of 100 mg/78 mg for 24 weeks.

Arm type	Experimental
Investigational medicinal product name	5-aminolevulinic acid hydrochloride/sodium ferrous citrate (5-ALA-HCl/SFC)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

5-ALA/SFC was administered orally at a dose of 50 mg/39 mg (1 capsule each BID), for a total daily dose of 100 mg/78 mg at least 8 hours apart in the morning and evening, after the meal, for 24 weeks.

Arm title	Placebo

Arm description:

The patients received an equal number of matching placebo capsules (BID) for 24 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Matching placebo capsules were administered in the same manner as the test product.

Number of subjects in period 1	5-ALA-HCl 150 mg/SFC 118 mg	5-ALA-HCl 50 mg/SFC 39 mg	Placebo
Started	72	73	73
Completed	63	56	60
Not completed	9	17	13
Consent withdrawn by subject	2	4	3
Adverse event, non-fatal	2	4	2
Other	-	-	1
Rescue Criteria Met	4	8	6
Use of Prohibited Medication	1	1	-
Noncompliance with protocol	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	5-ALA-HCl 150 mg/SFC 118 mg
Reporting group description:	
The patients received 5-ALA/SFC at a dose of 150 mg/118 mg (1 capsule each BID), for a total daily dose of 300 mg/236 mg for 24 weeks.	
Reporting group title	5-ALA-HCl 50 mg/SFC 39 mg
Reporting group description:	
The patients received 5-ALA/SFC at a dose of 50 mg/39 mg (1 capsule each BID), for a total daily dose of 100 mg/78 mg for 24 weeks.	
Reporting group title	Placebo
Reporting group description:	
The patients received an equal number of matching placebo capsules (BID) for 24 weeks.	

Reporting group values	5-ALA-HCl 150 mg/SFC 118 mg	5-ALA-HCl 50 mg/SFC 39 mg	Placebo
Number of subjects	72	73	73
Age categorical Units: Subjects			
< 65 years	42	43	45
≥ 65 years	30	30	28
Age continuous Units: years			
arithmetic mean	60.2	61.6	59.4
standard deviation	± 9.48	± 8.16	± 9.53
Gender categorical Units: Subjects			
Female	41	39	40
Male	31	34	33
Ethnicity Units: Subjects			
Not Hispanic or Latino	72	73	73
Race Units: Subjects			
White	72	73	73
Oral antidiabetic mono therapy Units: Subjects			
Yes	45	46	46
No	27	27	27
Treatment-Free Status Units: Subjects			
Yes	27	27	27
No	45	46	46
Complication related T2DM Units: Subjects			
Yes	8	8	7
No	64	65	66
HbA1c Units: Subjects			

< 8%	55	57	54
≥ 8%	17	16	19

Height			
Units: cm			
arithmetic mean	167.17	168.46	168.67
standard deviation	± 9.264	± 8.947	± 9.293
Weight			
Units: kg			
arithmetic mean	91.74	91.50	94.07
standard deviation	± 14.894	± 16.602	± 15.477
BMI			
Units: kg/m2			
arithmetic mean	32.76	32.10	32.96
standard deviation	± 4.102	± 4.283	± 4.057
Waist Circumference			
Units: cm			
arithmetic mean	107.7	107.6	108.4
standard deviation	± 13.04	± 12.85	± 11.61
Systolic blood pressure			
Units: mmHg			
arithmetic mean	133.0	131.8	133.7
standard deviation	± 10.32	± 13.47	± 11.22
Diastolic blood pressure			
Units: mmHg			
arithmetic mean	78.0	78.3	79.2
standard deviation	± 7.01	± 8.42	± 7.89
HbA1c			
Units: percent			
arithmetic mean	7.34	7.37	7.49
standard deviation	± 0.698	± 0.875	± 0.757
Duration of T2DM			
Units: years			
arithmetic mean	4.94	6.21	6.83
standard deviation	± 4.695	± 5.051	± 5.717
Fasting C-peptide			
Units: nmol/L			
arithmetic mean	1.045	0.968	0.920
standard deviation	± 0.5062	± 0.4234	± 0.3573
Fasting Plasma Glucose			
Units: mmol/L			
arithmetic mean	8.70	8.90	9.18
standard deviation	± 1.996	± 2.200	± 1.989
eGFR			
Units: ml/min/1.73m2			
arithmetic mean	94.71	91.87	94.21
standard deviation	± 22.552	± 20.969	± 20.061
Serum Zinc			
The threshold of serum zinc ≥ lower level was 9.2 µmol/L (range: 9.2 to 19.9 µmol/L)			
Units: µg/dL			
arithmetic mean	15.29	14.74	14.10

standard deviation	± 3.678	± 4.360	± 2.957
CGM			
Units: mg/dL			
arithmetic mean	116.7	126.4	113.8
standard deviation	± 70.92	± 71.93	± 68.62

Reporting group values	Total		
Number of subjects	218		
Age categorical			
Units: Subjects			
< 65 years	130		
≥ 65 years	88		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender categorical			
Units: Subjects			
Female	120		
Male	98		
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	218		
Race			
Units: Subjects			
White	218		
Oral antidiabetic mono therapy			
Units: Subjects			
Yes	137		
No	81		
Treatment-Free Status			
Units: Subjects			
Yes	81		
No	137		
Complication related T2DM			
Units: Subjects			
Yes	23		
No	195		
HbA1c			
Units: Subjects			
< 8%	166		
≥ 8%	52		
Height			
Units: cm			
arithmetic mean			
standard deviation	-		
Weight			
Units: kg			
arithmetic mean			
standard deviation	-		
BMI			

Units: kg/m2 arithmetic mean standard deviation	- -		
Waist Circumference Units: cm arithmetic mean standard deviation	- -		
Systolic blood pressure Units: mmHg arithmetic mean standard deviation	- -		
Diastolic blood pressure Units: mmHg arithmetic mean standard deviation	- -		
HbA1c Units: percent arithmetic mean standard deviation	- -		
Duration of T2DM Units: years arithmetic mean standard deviation	- -		
Fasting C-peptide Units: nmol/L arithmetic mean standard deviation	- -		
Fasting Plasma Glucose Units: mmol/L arithmetic mean standard deviation	- -		
eGFR Units: ml/min/1.73m2 arithmetic mean standard deviation	- -		
Serum Zinc			
The threshold of serum zinc ≥ lower level was 9.2 µmol/L (range: 9.2 to 19.9 µmol/L)			
Units: µg/dL arithmetic mean standard deviation	- -		
CGM Units: mg/dL arithmetic mean standard deviation	- -		

End points

End points reporting groups

Reporting group title	5-ALA-HCl 150 mg/SFC 118 mg
Reporting group description:	
The patients received 5-ALA/SFC at a dose of 150 mg/118 mg (1 capsule each BID), for a total daily dose of 300 mg/236 mg for 24 weeks.	
Reporting group title	5-ALA-HCl 50 mg/SFC 39 mg
Reporting group description:	
The patients received 5-ALA/SFC at a dose of 50 mg/39 mg (1 capsule each BID), for a total daily dose of 100 mg/78 mg for 24 weeks.	
Reporting group title	Placebo
Reporting group description:	
The patients received an equal number of matching placebo capsules (BID) for 24 weeks.	

Primary: Change from baseline in HbA1c to Week 24

End point title	Change from baseline in HbA1c to Week 24
End point description:	
End point type	Primary
End point timeframe:	
From baseline to Week 24	

End point values	5-ALA-HCl 150 mg/SFC 118 mg	5-ALA-HCl 50 mg/SFC 39 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	71	70	
Units: percent				
least squares mean (standard error)	-0.27 (± 0.076)	-0.01 (± 0.080)	0.00 (± 0.078)	

Statistical analyses

Statistical analysis title	Primary efficacy
Statistical analysis description:	
The evaluation of mean change from Baseline in HbA1c compared to Placebo will be done using the Placebo Multiple Imputation (pMI) method followed by analysis using an Analysis of Covariance (ANCOVA) model with Full Analysis Set data.	
Comparison groups	5-ALA-HCl 150 mg/SFC 118 mg v 5-ALA-HCl 50 mg/SFC 39 mg v Placebo

Number of subjects included in analysis	213
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	ANCOVA

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent AEs (TEAEs) were defined as AEs that first occurred or worsened in severity after the first administration of the study medication, until end of the study.

Adverse event reporting additional description:

An Adverse Event was any untoward medical occurrence in a patient or subject, temporally associated with the use of study treatment, whether or not considered related to the study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	5-ALA/SFC 150 mg/118 mg
Reporting group description: -	
Reporting group title	5-ALA/SFC 50 mg/39 mg
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	5-ALA/SFC 150 mg/118 mg	5-ALA/SFC 50 mg/39 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 72 (4.17%)	2 / 73 (2.74%)	2 / 73 (2.74%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	1 / 72 (1.39%)	0 / 73 (0.00%)	0 / 73 (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
Parathyroid tumour benign			
subjects affected / exposed	0 / 72 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute coronary syndrome			

subjects affected / exposed	1 / 72 (1.39%)	0 / 73 (0.00%)	0 / 73 (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
Cardiac failure			
subjects affected / exposed	0 / 72 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 72 (0.00%)	0 / 73 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Oedematous pancreatitis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 73 (0.00%)	0 / 73 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 72 (1.39%)	0 / 73 (0.00%)	0 / 73 (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
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 73 (0.00%)	1 / 73 (1.37%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	5-ALA/SFC 150 mg/118 mg	5-ALA/SFC 50 mg/39 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 72 (63.89%)	48 / 73 (65.75%)	44 / 73 (60.27%)
Investigations			
Blood glucose increased			
subjects affected / exposed	1 / 72 (1.39%)	3 / 73 (4.11%)	0 / 73 (0.00%)
occurrences (all)	1	3	0
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	2 / 72 (2.78%)	0 / 73 (0.00%)	2 / 73 (2.74%)
occurrences (all)	2	0	2
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 72 (1.39%)	0 / 73 (0.00%)	2 / 73 (2.74%)
occurrences (all)	1	0	2
Alanine aminotransferase increased			
subjects affected / exposed	2 / 72 (2.78%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	2	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 72 (2.78%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	3	0	0
Blood pressure increased			
subjects affected / exposed	0 / 72 (0.00%)	2 / 73 (2.74%)	0 / 73 (0.00%)
occurrences (all)	0	2	0
Hyperkalaemia			
subjects affected / exposed	2 / 72 (2.78%)	2 / 73 (2.74%)	4 / 73 (5.48%)
occurrences (all)	2	2	4
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 72 (1.39%)	0 / 73 (0.00%)	2 / 73 (2.74%)
occurrences (all)	1	0	2
Headache			
subjects affected / exposed	3 / 72 (4.17%)	1 / 73 (1.37%)	0 / 73 (0.00%)
occurrences (all)	5	1	0
Hypoaesthesia			
subjects affected / exposed	0 / 72 (0.00%)	2 / 73 (2.74%)	0 / 73 (0.00%)
occurrences (all)	0	2	0

Sciatica			
subjects affected / exposed	2 / 72 (2.78%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	2	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 72 (4.17%)	2 / 73 (2.74%)	2 / 73 (2.74%)
occurrences (all)	7	2	2
Muscle spasms			
subjects affected / exposed	2 / 72 (2.78%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 72 (1.39%)	4 / 73 (5.48%)	3 / 73 (4.11%)
occurrences (all)	1	4	3
Bronchitis			
subjects affected / exposed	2 / 72 (2.78%)	4 / 73 (5.48%)	1 / 73 (1.37%)
occurrences (all)	2	4	1
Upper respiratory tract infection			
subjects affected / exposed	3 / 72 (4.17%)	2 / 73 (2.74%)	1 / 73 (1.37%)
occurrences (all)	4	2	1
Pharyngitis			
subjects affected / exposed	1 / 72 (1.39%)	2 / 73 (2.74%)	1 / 73 (1.37%)
occurrences (all)	1	2	1
Urinary tract infection			
subjects affected / exposed	1 / 72 (1.39%)	1 / 73 (1.37%)	2 / 73 (2.74%)
occurrences (all)	1	1	3
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 72 (0.00%)	2 / 73 (2.74%)	2 / 73 (2.74%)
occurrences (all)	0	2	2
Pneumonia			
subjects affected / exposed	0 / 72 (0.00%)	2 / 73 (2.74%)	0 / 73 (0.00%)
occurrences (all)	0	2	0
Rhinitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 73 (0.00%)	2 / 73 (2.74%)
occurrences (all)	0	0	2
Viral pharyngitis			

subjects affected / exposed	2 / 72 (2.78%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	15 / 72 (20.83%)	17 / 73 (23.29%)	18 / 73 (24.66%)
occurrences (all)	46	47	36
Hypoglycaemia			
subjects affected / exposed	5 / 72 (6.94%)	1 / 73 (1.37%)	2 / 73 (2.74%)
occurrences (all)	7	1	3
Hyperlipidaemia			
subjects affected / exposed	0 / 72 (0.00%)	2 / 73 (2.74%)	0 / 73 (0.00%)
occurrences (all)	0	2	0
Hypocalcaemia			
subjects affected / exposed	2 / 72 (2.78%)	0 / 73 (0.00%)	0 / 73 (0.00%)
occurrences (all)	2	0	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 March 2018	Inclusion and exclusion criteria was amended as a result of the feedback received from VHP.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported