

**Clinical trial results:****A 24-week, Phase IIa, Double blind, Randomized, Parallel Group, Placebo controlled, Exploratory Study to Evaluate the Efficacy and Safety of 5 Aminolevulinic Acid Co-administered with Sodium Ferrous Citrate Compared with Placebo in the Treatment of Adult Type 2 Diabetes Mellitus Patients who have not Achieved Adequate Glycaemic Control with Maximum Tolerated Dose of Metformin Daily or Sulfonylurea****Summary**

EudraCT number	2017-004959-23
Trial protocol	HU PL
Global end of trial date	11 March 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-DM2-0521
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**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, npjprd@neopharmajp.com
Scientific contact	Clinical Trial Information Desk, neopharma Japan, 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	11 March 2020
Global end of trial reached?	Yes
Global end of trial date	11 March 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 5 aminolevulinic acid/sodium ferrous citrate (5 ALA/SFC) plus metformin (or sulfonylurea [SU]) and placebo plus metformin (or SU).

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 other than Metformin or Sulfonylurea 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:

At time of enrollment, patients were treated with a stable maximum tolerated dose (MTD) of metformin (immediate release and extended release) of at least 1500 mg daily or Sulfonylurea (SU) of at least half the maximum dose as per local label, for at least 12 weeks prior to screening visit. Background therapy with metformin or SU remained on the same dose for the duration of the study for both the treatment arms indicated.

Evidence for comparator: -

Actual start date of recruitment	25 October 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: 51
Country: Number of subjects enrolled	Hungary: 31
Country: Number of subjects enrolled	Ukraine: 19
Worldwide total number of subjects	101
EEA total number of subjects	82

Notes:

#### Subjects enrolled per age group

In utero	0
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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)	60
From 65 to 84 years	41
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

101 patients were enrolled at 18 sites in Hungary, Poland and Ukraine from 25-Oct-2018 to 11-Mar-2020.

### Pre-assignment

Screening details:

174 potential patients underwent a screening period of maximally 4 weeks during which all inclusion/exclusion were checked. 101 patients were randomized to either arm of 5 ALA/SFC 50 mg/39 mg orally twice daily (BID) or a matching placebo in a 2:1 ratio.

### 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	Subject, Investigator, Monitor, Data analyst, Carer

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
<b>Arm title</b>	5-ALA-HCl 50 mg/SFC 39 mg + MET/SU

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.

<b>Arm title</b>	Placebo + MET/SU
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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.

<b>Number of subjects in period 1</b>	<b>5-ALA-HCl 50 mg/SFC 39 mg + MET/SU</b>	<b>Placebo + MET/SU</b>
Started	68	33
Completed	55	29
Not completed	13	4
Adverse event, serious fatal	1	-
Consent withdrawn by subject	2	-
Adverse event, non-fatal	5	1
Other	-	1
Rescue Criteria Met	3	2
Use of Prohibited Medication	1	-
Noncompliance with protocol	1	-

## Baseline characteristics

### Reporting groups

Reporting group title	5-ALA-HCl 50 mg/SFC 39 mg + MET/SU
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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 + MET/SU
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Reporting group description:

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

Reporting group values	5-ALA-HCl 50 mg/SFC 39 mg + MET/SU	Placebo + MET/SU	Total
Number of subjects	68	33	101
Age categorical			
Units: Subjects			
< 65 years	43	17	60
≥ 65 years	25	16	41
Age continuous			
Units: years			
arithmetic mean	63.4	61.2	-
standard deviation	± 6.76	± 9.45	-
Gender categorical			
Units: Subjects			
Female	27	16	43
Male	41	17	58
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	68	33	101
Race			
Units: Subjects			
White	68	33	101
Complication related T2DM (Y/N)			
Units: Subjects			
Yes	19	7	26
No	49	26	75
Background medication			
Units: Subjects			
Metformin	64	31	95
Sulfonylurea	4	2	6
HbA1c			
Units: Subjects			
< 8%	48	24	72
≥ 8%	20	9	29
Height			
Units: cm			
arithmetic mean	168.71	169.52	-
standard deviation	± 8.743	± 9.501	-
Weight			

Units: kg			
arithmetic mean	91.28	93.11	-
standard deviation	± 16.238	± 18.341	-
BMI			
Units: kg/m <sup>2</sup>			
arithmetic mean	31.94	32.16	-
standard deviation	± 4.182	± 4.282	-
HbA1c			
Units: percent			
arithmetic mean	7.61	7.44	-
standard deviation	± 0.768	± 0.716	-
Duration of T2DM			
Units: years			
arithmetic mean	8.61	7.96	-
standard deviation	± 5.937	± 5.143	-
Fasting plasma glucose			
Units: mmol/L			
arithmetic mean	9.00	9.16	-
standard deviation	± 2.190	± 2.145	-
Waist circumference			
Units: cm			
arithmetic mean	106.9	108.1	-
standard deviation	± 11.65	± 11.63	-
Systolic blood pressure			
Units: mm Hg			
arithmetic mean	137.8	133.8	-
standard deviation	± 11.34	± 9.79	-
Diastolic blood pressure			
Units: mm Hg			
arithmetic mean	80.4	78.0	-
standard deviation	± 8.23	± 7.26	-
Fructosamine levels			
Units: µmol/L			
arithmetic mean	286.1	278.3	-
standard deviation	± 36.76	± 38.53	-
Serum zinc (≥ lower level)			
The threshold of serum zinc ≥ lower level was 9.2 µmol/L (range: 9.2 to 19.9 µmol/L)			
Units: µmol/L			
arithmetic mean	13.87	15.05	-
standard deviation	± 3.006	± 4.472	-
Fasting C-peptide			
Units: nmol/L			
arithmetic mean	0.947	0.983	-
standard deviation	± 0.4039	± 0.2837	-
eGFR			
Units: mL/min/1.73 m <sup>2</sup>			
arithmetic mean	87.97	89.14	-
standard deviation	± 23.318	± 23.193	-
CGM			
Units: mg/dL			
arithmetic mean	98.3	96.7	-
standard deviation	± 80.23	± 65.06	-



## End points

### End points reporting groups

Reporting group title	5-ALA-HCl 50 mg/SFC 39 mg + MET/SU
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 + MET/SU
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 50 mg/SFC 39 mg + MET/SU	Placebo + MET/SU		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	32		
Units: percent				
least squares mean (standard error)	-0.12 ( $\pm$ 0.079)	-0.12 ( $\pm$ 0.107)		

### Statistical analyses

Statistical analysis title	Primary efficacy
Statistical analysis description: Change from baseline HbA1c was analyzed based on Mixed Model for Repeated Measures with treatment, visit as fixed factors, treatment*visit as interaction effects and baseline HbA1c as covariate.	
Comparison groups	Placebo + MET/SU v 5-ALA-HCl 50 mg/SFC 39 mg + MET/SU
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	< 0.05
Method	Mixed models analysis

## 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
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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### Reporting groups

Reporting group title	5-ALA-HCl 50 mg/SFC 39 mg + MET/SU
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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 + MET/SU
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Reporting group description:

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

Serious adverse events	5-ALA-HCl 50 mg/SFC 39 mg + MET/SU	Placebo + MET/SU	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 68 (5.88%)	1 / 33 (3.03%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	1	0	
Cardiac disorders			
Cardiac failure chronic			
subjects affected / exposed	1 / 68 (1.47%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 68 (1.47%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Dizziness			

subjects affected / exposed	1 / 68 (1.47%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 68 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pyelonephritis			
subjects affected / exposed	1 / 68 (1.47%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	5-ALA-HCl 50 mg/SFC 39 mg + MET/SU	Placebo + MET/SU	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 68 (69.12%)	22 / 33 (66.67%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	6 / 68 (8.82%)	1 / 33 (3.03%)	
occurrences (all)	6	1	
Blood pressure fluctuation			
subjects affected / exposed	0 / 68 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 68 (0.00%)	1 / 33 (3.03%)	
occurrences (all)	0	1	

Investigations Blood thyroid stimulating hormone decreased subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	1 / 33 (3.03%) 1	
Cardiac disorders Atrioventricular block first degree subjects affected / exposed occurrences (all)  Tachycardia subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1  1 / 68 (1.47%) 1	1 / 33 (3.03%) 1  1 / 33 (3.03%) 1	
Nervous system disorders Dizziness subjects affected / exposed occurrences (all)  Headache subjects affected / exposed occurrences (all)  Sciatica subjects affected / exposed occurrences (all)  Transient ischaemic attack subjects affected / exposed occurrences (all)	2 / 68 (2.94%) 2  2 / 68 (2.94%) 3  0 / 68 (0.00%) 0  0 / 68 (0.00%) 0	0 / 33 (0.00%) 0  0 / 33 (0.00%) 0  1 / 33 (3.03%) 1  1 / 33 (3.03%) 1	
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	1 / 33 (3.03%) 1	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)  Abdominal pain subjects affected / exposed occurrences (all)  Nausea	6 / 68 (8.82%) 6  4 / 68 (5.88%) 5	1 / 33 (3.03%) 1  0 / 33 (0.00%) 0	

subjects affected / exposed occurrences (all)	3 / 68 (4.41%) 4	0 / 33 (0.00%) 0	
Abdominal pain upper subjects affected / exposed occurrences (all)	2 / 68 (2.94%) 2	0 / 33 (0.00%) 0	
Dyspepsia subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	1 / 33 (3.03%) 1	
Noninfective sialoadenitis subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	1 / 33 (3.03%) 1	
<b>Skin and subcutaneous tissue disorders</b>			
Urticaria subjects affected / exposed occurrences (all)	2 / 68 (2.94%) 3	0 / 33 (0.00%) 0	
Dermatitis subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	1 / 33 (3.03%) 1	
Rash pruritic subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	1 / 33 (3.03%) 1	
<b>Renal and urinary disorders</b>			
Proteinuria subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	1 / 33 (3.03%) 1	
Urinary tract inflammation subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	1 / 33 (3.03%) 1	
<b>Endocrine disorders</b>			
Hypothyroidism subjects affected / exposed occurrences (all)	2 / 68 (2.94%) 2	0 / 33 (0.00%) 0	
Thyroid mass subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	1 / 33 (3.03%) 1	
<b>Musculoskeletal and connective tissue disorders</b>			

Back pain subjects affected / exposed occurrences (all)	3 / 68 (4.41%) 6	2 / 33 (6.06%) 2	
Arthralgia subjects affected / exposed occurrences (all)	2 / 68 (2.94%) 2	0 / 33 (0.00%) 0	
Pain in extremity subjects affected / exposed occurrences (all)	2 / 68 (2.94%) 2	0 / 33 (0.00%) 0	
Spinal pain subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	2 / 33 (6.06%) 2	
Infections and infestations			
Nasopharyngitis subjects affected / exposed occurrences (all)	6 / 68 (8.82%) 7	4 / 33 (12.12%) 5	
Pharyngitis subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	2 / 33 (6.06%) 2	
Influenza subjects affected / exposed occurrences (all)	1 / 68 (1.47%) 1	1 / 33 (3.03%) 1	
Metabolism and nutrition disorders			
Hyperglycaemia subjects affected / exposed occurrences (all)	21 / 68 (30.88%) 74	10 / 33 (30.30%) 33	
Hypoglycaemia subjects affected / exposed occurrences (all)	5 / 68 (7.35%) 11	3 / 33 (9.09%) 6	
Obesity subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	1 / 33 (3.03%) 1	
Overweight subjects affected / exposed occurrences (all)	0 / 68 (0.00%) 0	1 / 33 (3.03%) 1	



## 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:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported