Clinical trial results:
Multicenter, double-blind, parallel-group, randomised, 48 weeks, dose-ranging, placebo-controlled phase II trial to evaluate efficacy, safety and tolerability of multiple subcutaneous (s.c.) doses of BI456906 in patients with non-alcoholic steatohepatitis (NASH) and fibrosis

Summary

EudraCT number	2020-002723-11
Trial protocol	FR BE NL PT CZ DE HU AT GR PL IT
Global end of trial date	21 December 2023

Results information

Result version number	v1 (current)
This version publication date	02 January 2025
First version publication date	02 January 2025

Trial information

Trial identification

Sponsor protocol code	1404-0043

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04771273
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim, Call Center, Boehringer Ingelheim, 001 18002430127, clintriage.rdg@boehringer-ingelheim.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	02 February 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 November 2023
Global end of trial reached?	Yes
Global end of trial date	21 December 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary trial objectives were to demonstrate a non-flat dose response curve, to evaluate the size of the treatment effect (using the absolute difference in proportions of patients with NASH and fibrosis that show histological improvement between Survodutide [BI 456906] and placebo treatment at Week 48), and to characterize the dose-response relationship.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all subjects as required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 July 2021
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	China: 58
Country: Number of subjects enrolled	Hong Kong: 14
Country: Number of subjects enrolled	Japan: 77
Country: Number of subjects enrolled	Korea, Republic of: 10
Country: Number of subjects enrolled	Taiwan: 13
Country: Number of subjects enrolled	Austria: 7
Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Czechia: 8
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 43
Country: Number of subjects enrolled	Greece: 11
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Italy: 22
Country: Number of subjects enrolled	Netherlands: 11
Country: Number of subjects enrolled	Poland: 78
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Spain: 27
Country: Number of subjects enrolled	United Kingdom: 26

Country: Number of subjects enrolled	Canada: 17
Country: Number of subjects enrolled	United States: 632
Country: Number of subjects enrolled	Australia: 17
Country: Number of subjects enrolled	Israel: 12
Country: Number of subjects enrolled	Malaysia: 16
Country: Number of subjects enrolled	New Zealand: 13
Country: Number of subjects enrolled	Singapore: 13
Worldwide total number of subjects	1153
EEA total number of subjects	235

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)	937
From 65 to 84 years	216
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This was a trial in patients with non-alcoholic steatohepatitis (NASH).
Main parameters for inclusion of patients and for evaluation of treatment response were based on the histological evaluation from the liver biopsy and non-invasive imaging modalities.

Pre-assignment

Screening details:

All subjects were screened for eligibility prior to participation in the trial. Patients who met the eligibility criteria at an initial screening visit had a second screening visit for biopsy to confirm their eligibility, if no sufficient material from a historical biopsy within the 6 months prior to randomisation was available.

Period 1

Period 1 title	Randomisation period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Blinding implementation details:

This trial has a double-blind design across dose groups. Patients, investigators, central reviewers, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial (except for an interim analysis which was performed for internal planning purposes by an independent team within the sponsor) remained blinded with regard to the randomised treatment assignments until after the main database lock.

Arms

Are arms mutually exclusive?	Yes
Arm title	Survodutide 2.4 mg - planned maintenance treatment

Arm description:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3). were to be administered once weekly, subcutaneously a solution for injection of survodutide at a starting dose of 0.3 milligrams (mg) followed by a dose escalation up to the maintenance dose of 2.4 mg of survodutide.
The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period).
Patients not tolerating the assigned dose due to gastrointestinal adverse events had the option of a dose adjustment which could lead to a maintenance dose lower than the dose the patient was randomized to.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Survodutide 4.8 mg - planned maintenance treatment

Arm description:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3). were to be administered once weekly, subcutaneously a solution for injection of survodutide at a starting dose of 0.3 milligrams (mg) followed by a dose escalation up to the maintenance dose of 4.8 mg of survodutide.
The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period).
Patients not tolerating the assigned dose due to gastrointestinal adverse events had the option of a dose adjustment which could lead to a maintenance dose lower than the dose the patient was randomized to.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Survodutide 6.0 mg - planned maintenance treatment

Arm description:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3). were to be administered once weekly, subcutaneously a solution for injection of survodutide at a starting dose of 0.3 milligrams (mg) followed by a dose

escalation up to the maintenance dose of 6.0 mg of survodutide.
The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period).
Patients not tolerating the assigned dose due to gastrointestinal adverse events had the option of a dose adjustment which could lead to a maintenance dose lower than the dose the patient was randomized to.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo - planned maintenance treatment

Arm description:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3). were administered once weekly, subcutaneously a solution for injection of placebo matching survodutide. The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Survodutide 2.4 mg - planned maintenance treatment	Survodutide 4.8 mg - planned maintenance treatment	Survodutide 6.0 mg - planned maintenance treatment
Started	73	73	75
Completed	73	72	74
Not completed	0	1	1
Not treated	-	1	1

Number of subjects in period 1	Placebo - planned maintenance treatment
Started	74
Completed	74
Not completed	0
Not treated	-

Period 2

Period 2 title	Dose Escalation + Maintenance Periods
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Blinding implementation details:

This trial has a double-blind design across dose groups. Patients, investigators, central reviewers, and everyone involved in trial conduct or analysis or with any other interest in this double-blind trial (except for an interim analysis which was performed for internal planning purposes by an independent team within the sponsor) remained blinded with regard to the randomised treatment assignments until after the main database lock.

Arms

Are arms mutually exclusive?	Yes

Arm title	Survodutide 2.4 mg - planned maintenance treatment

Arm description:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3) were to be administered once weekly, subcutaneously a solution for injection of survodutide at a starting dose of 0.3 milligrams (mg) followed by a dose escalation up to the maintenance dose of 2.4 mg of survodutide.
The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period).
Patients not tolerating the assigned dose due to gastrointestinal adverse events had the option of a dose adjustment which could lead to a maintenance dose lower than the dose the patient was randomized to.

Arm type	Experimental
Investigational medicinal product name	Survodutide
Investigational medicinal product code	
Other name	BI 456906
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3) were to be administered once weekly, subcutaneously a solution for injection of survodutide at a starting dose of 0.3 milligrams (mg) followed by a dose escalation up to the maintenance dose of 2.4 mg of survodutide.

Arm title	Survodutide 4.8 mg - planned maintenance treatment

Arm description:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3) were to be administered once weekly, subcutaneously a solution for injection of survodutide at a starting dose of 0.3 milligrams (mg) followed by a dose escalation up to the maintenance dose of 4.8 mg of survodutide.
The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period).
Patients not tolerating the assigned dose due to gastrointestinal adverse events had the option of a dose adjustment which could lead to a maintenance dose lower than the dose the patient was randomized to.

Arm type	Experimental
Investigational medicinal product name	Survodutide
Investigational medicinal product code	
Other name	BI 456906
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3). were to be administered once weekly, subcutaneously a solution for injection of survodutide at a starting dose of 0.3 milligrams (mg) followed by a dose escalation up to the maintenance dose of 4.8 mg of survodutide.

Arm title	Survodutide 6.0 mg - planned maintenance treatment

Arm description:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3) were to be administered once weekly, subcutaneously a solution for injection of survodutide at a starting dose of 0.3 milligrams (mg) followed by a dose escalation up to the maintenance dose of 6.0 mg of survodutide.
The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period).
Patients not tolerating the assigned dose due to gastrointestinal adverse events had the option of a dose adjustment which could lead to a maintenance dose lower than the dose the patient was randomized to.

Arm type	Experimental
Investigational medicinal product name	Survodutide
Investigational medicinal product code	
Other name	BI 456906
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3). were to be administered once weekly, subcutaneously a solution for injection of survodutide at a starting dose of 0.3 milligrams (mg) followed by a dose escalation up to the maintenance dose of 6.0 mg of survodutide.

Arm title	Placebo - planned maintenance treatment

Arm description:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3) were administered once weekly, subcutaneously a solution for injection of placebo matching survodutide. The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period).

Arm type	Placebo
Investigational medicinal product name	Placebo to match BI 456906
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3). were administered once weekly, subcutaneously a solution for injection of placebo matching survodutide.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: In this period the subjects who were randomized in this trial are reported. The baseline characteristics are not reported for the randomized subjects but for the treated subjects.

Number of subjects in period 2[2]	Survodutide 2.4 mg - planned maintenance treatment	Survodutide 4.8 mg - planned maintenance treatment	Survodutide 6.0 mg - planned maintenance treatment
Started	73	72	74
Completed	53	55	49
Not completed	20	17	25
Other reasons than listed	6	2	2
Adverse event, non-fatal	12	14	17
Perceived lack of efficacy	-	-	-
Burden of study procedures	2	-	-
Change of residence	-	1	3
Protocol deviation	-	-	3

Number of subjects in period 2[2]	Placebo - planned maintenance treatment
Started	74
Completed	64
Not completed	10
Other reasons than listed	4
Adverse event, non-fatal	2
Perceived lack of efficacy	2
Burden of study procedures	-

Change of residence	1
Protocol deviation	1

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Out of 1153 subjects screened only 293 subjects were treated.

Baseline characteristics

Reporting groups	
Reporting group title	Survodutide 2.4 mg - planned maintenance treatment
Reporting group description:	
Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3) were to be administered once weekly, subcutaneously a solution for injection of survodutide at a starting dose of 0.3 milligrams (mg) followed by a dose escalation up to the maintenance dose of 2.4 mg of survodutide. The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period). Patients not tolerating the assigned dose due to gastrointestinal adverse events had the option of a dose adjustment which could lead to a maintenance dose lower than the dose the patient was randomized to.	
Reporting group title	Survodutide 4.8 mg - planned maintenance treatment
Reporting group description:	
Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3) were to be administered once weekly, subcutaneously a solution for injection of survodutide at a starting dose of 0.3 milligrams (mg) followed by a dose escalation up to the maintenance dose of 4.8 mg of survodutide. The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period). Patients not tolerating the assigned dose due to gastrointestinal adverse events had the option of a dose adjustment which could lead to a maintenance dose lower than the dose the patient was randomized to.	
Reporting group title	Survodutide 6.0 mg - planned maintenance treatment
Reporting group description:	
Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3) were to be administered once weekly, subcutaneously a solution for injection of survodutide at a starting dose of 0.3 milligrams (mg) followed by a dose escalation up to the maintenance dose of 6.0 mg of survodutide. The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period). Patients not tolerating the assigned dose due to gastrointestinal adverse events had the option of a dose adjustment which could lead to a maintenance dose lower than the dose the patient was randomized to.	
Reporting group title	Placebo - planned maintenance treatment
Reporting group description:	
Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3) were administered once weekly, subcutaneously a solution for injection of placebo matching survodutide. The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period).	

Reporting group values	Survodutide 2.4 mg - planned maintenance treatment	Survodutide 4.8 mg - planned maintenance treatment	Survodutide 6.0 mg - planned maintenance treatment
Number of subjects	73	72	74
Age categorical			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0

Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	60	62	62
From 65-84 years	13	10	12
85 years and over	0	0	0
Age Continuous			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: years			
arithmetic mean	49.6	50.2	50.4
standard deviation	± 13.7	± 12.9	± 13.1
Sex: Female, Male			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Participants			
Female	36	34	41
Male	37	38	33
Ethnicity (NIH/OMB)			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Hispanic or Latino	14	19	26
Not Hispanic or Latino	59	53	48
Unknown or Not Reported	0	0	0
Race (NIH/OMB)			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	24	22	17
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	3	0
White	46	47	56
More than one race	1	0	0
Unknown or Not Reported	0	0	0
Number of participants at each category of liver fibrosis stage at baseline			
Number of participants at each category of liver fibrosis stage at baseline is reported. The total score for the fibrosis stage ranges from 0 to 4 with higher score indication worsening of the disease and the stages of fibrosis based on their location are the following: - 1A Zone 3, perisinusoidal, delicate; - 1B Zone 3, perisinuosoidal, dense; - 1C Portal, periportal only; - 2 Zone 3, perisinusoidal + portal, periportal only; - 3 Bridging fibrosis; - 4 Cirrhosis.			
Units: Subjects			
Stage 1A	0	3	3
Stage 1B	17	7	14
Stage 1C	3	3	6
Stage 2	30	36	24
Stage 3	23	23	27
Number of participants in each category			

of diabetes at baseline			
Number of participants at each category of diabetes at baseline is reported. The reported categories of diabetes stratification are the following: Yes, No. Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Diabetes = No	44	43	44
Diabetes = Yes	29	29	30
Number of patients in each category of NAS score			
The non-alcoholic fatty liver disease (NAFLD) activity score (NAS) is the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. The reported categories of NAS score range are: 0; 1; 2; 3; 4; 5; 6; 7; 8. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
NAS total score = 0	0	0	0
NAS total score = 1	0	0	0
NAS total score = 2	0	0	0
NAS total score = 3	0	0	0
NAS total score = 4	21	20	26
NAS total score = 5	27	21	17
NAS total score = 6	17	22	26
NAS total score = 7	8	8	5
NAS total score = 8	0	1	0
Number of patients in each category of the NAS sub-score steatosis			
The NAS represents the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. Number of patients in each category of the score range for steatosis is reported. Treated set - planned maintenance treatment. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Steatosis total score = 0	0	0	0
Steatosis total score = 1	6	0	1
Steatosis total score = 2	38	38	49
Steatosis total score = 3	29	34	24
Number of patients in each category of the NAS sub-scores (ballooning)			
The NAS represents the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. Number of patients in each category of the score range for ballooning is reported. Treated set - planned maintenance treatment. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Ballooning total score = 0	0	0	0
Ballooning total score = 1	55	55	53
Ballooning total score = 2	18	17	21
Number of patients in each category of the NAS sub-score lobular inflammation			
The NAS represents the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3)			

and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. Number of patients in each category of the score range for lobular inflammation is reported. Treated set - planned maintenance treatment. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Lobular inflammation score = 0	0	0	0
Lobular inflammation score = 1	32	31	36
Lobular inflammation score = 2	38	40	36
Lobular inflammation score = 3	3	1	2
The non-alcoholic fatty liver disease (NAFLD) activity score (NAS) at baseline			
The NAS represents the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. Treated set - planned maintenance treatment. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: score on a scale			
arithmetic mean	5.2	5.3	5.1
standard deviation	± 1.0	± 1.1	± 1.0

Reporting group values	Placebo - planned maintenance treatment	Total	
Number of subjects	74	293	
Age categorical			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
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)	64	248	
From 65-84 years	10	45	
85 years and over	0	0	
Age Continuous			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: years			
arithmetic mean	53.0		
standard deviation	± 11.5	-	
Sex: Female, Male			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Participants			
Female	44	155	

Male	30	138	

Ethnicity (NIH/OMB)			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Hispanic or Latino	22	81	
Not Hispanic or Latino	52	212	
Unknown or Not Reported	0	0	
Race (NIH/OMB)			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
American Indian or Alaska Native	0	1	
Asian	17	80	
Native Hawaiian or Other Pacific Islander	1	1	
Black or African American	0	5	
White	56	205	
More than one race	0	1	
Unknown or Not Reported	0	0	
Number of participants at each category of liver fibrosis stage at baseline			
Number of participants at each category of liver fibrosis stage at baseline is reported. The total score for the fibrosis stage ranges from 0 to 4 with higher score indication worsening of the disease and the stages of fibrosis based on their location are the following: - 1A Zone 3, perisinusoidal, delicate; - 1B Zone 3, perisinuosoidal, dense; - 1C Portal, periportal only; - 2 Zone 3, perisinusoidal + portal, periportal only; - 3 Bridging fibrosis; - 4 Cirrhosis.			
Units: Subjects			
Stage 1A	2	8	
Stage 1B	9	47	
Stage 1C	3	15	
Stage 2	30	120	
Stage 3	30	103	
Number of participants in each category of diabetes at baseline			
Number of participants at each category of diabetes at baseline is reported. The reported categories of diabetes stratification are the following: Yes, No. Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Diabetes = No	45	176	
Diabetes = Yes	29	117	
Number of patients in each category of NAS score			
The non-alcoholic fatty liver disease (NAFLD) activity score (NAS) is the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. The reported categories of NAS score range are: 0; 1; 2; 3; 4; 5; 6; 7; 8. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle"			

on any maintenance dose.			
Units: Subjects			
NAS total score = 0	0	0	
NAS total score = 1	0	0	
NAS total score = 2	0	0	
NAS total score = 3	0	0	
NAS total score = 4	22	89	
NAS total score = 5	28	93	
NAS total score = 6	8	73	
NAS total score = 7	16	37	
NAS total score = 8	0	1	
Number of patients in each category of the NAS sub-score steatosis			
The NAS represents the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. Number of patients in each category of the score range for steatosis is reported. Treated set - planned maintenance treatment. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Steatosis total score = 0	0	0	
Steatosis total score = 1	3	10	
Steatosis total score = 2	43	168	
Steatosis total score = 3	28	115	
Number of patients in each category of the NAS sub-scores (ballooning)			
The NAS represents the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. Number of patients in each category of the score range for ballooning is reported. Treated set - planned maintenance treatment. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Ballooning total score = 0	0	0	
Ballooning total score = 1	49	212	
Ballooning total score = 2	25	81	
Number of patients in each category of the NAS sub-score lobular inflammation			
The NAS represents the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. Number of patients in each category of the score range for lobular inflammation is reported. Treated set - planned maintenance treatment. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Lobular inflammation score = 0	0	0	
Lobular inflammation score = 1	37	136	
Lobular inflammation score = 2	32	146	
Lobular inflammation score = 3	5	11	
The non-alcoholic fatty liver disease (NAFLD) activity score (NAS) at baseline			
The NAS represents the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. Treated set - planned maintenance treatment. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the			

maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: score on a scale			
arithmetic mean	5.2		
standard deviation	± 1.1	-	

Subject analysis sets

Subject analysis set title	Survodutide 2.4 mg - actual maintenance treatment
Subject analysis set type	Full analysis

Subject analysis set description:

This arm includes patients who were treated with 2.4 mg of survodutide administered weekly at the start of the maintenance period, for patients who reached the maintenance period, regardless of whether this was the randomised (planned) dose or not, and regardless of whether the patient stayed on that dose throughout the maintenance period.
This arm includes also those patients for whom the next maintenance dose up from the dose at treatment discontinuation was 2.4 mg of survodutide administered weekly, for patients who discontinued treatment prior to the maintenance period, regardless of the reason for the treatment discontinuation.

Subject analysis set title	Survodutide 4.8 mg - actual maintenance treatment
Subject analysis set type	Full analysis

Subject analysis set description:

This arm includes patients who were treated with 4.8 mg of survodutide administered weekly at the start of the maintenance period, for patients who reached the maintenance period, regardless of whether this was the randomised (planned) dose or not, and regardless of whether the patient stayed on that dose throughout the maintenance period.
This arm includes also those patients for whom the next maintenance dose up from the dose at treatment discontinuation was 4.8 mg of survodutide administered weekly, for patients who discontinued treatment prior to the maintenance period, regardless of the reason for the treatment discontinuation.

Subject analysis set title	Survodutide 6.0 mg - actual maintenance treatment
Subject analysis set type	Full analysis

Subject analysis set description:

This arm includes patients who were treated with 6.0 mg of survodutide administered weekly at the start of the maintenance period, for patients who reached the maintenance period, regardless of whether this was the randomised (planned) dose or not, and regardless of whether the patient stayed on that dose throughout the maintenance period.
This arm includes also those patients for whom the next maintenance dose up from the dose at treatment discontinuation was 6.0 mg of survodutide administered weekly, for patients who discontinued treatment prior to the maintenance period, regardless of the reason for the treatment discontinuation.

Subject analysis set title	Placebo - actual maintenance treatment
Subject analysis set type	Full analysis

Subject analysis set description:

This arm includes patients who were treated with placebo matching survodutide administered weekly at the start of the maintenance period, for patients who reached the maintenance period, regardless of whether this was the randomised (planned) dose or not, and regardless of whether the patient stayed on that dose throughout the maintenance period.
This arm includes also those patients who were receiving placebo matching survodutide administered weekly and who discontinued treatment prior to the maintenance period, regardless of the reason for the treatment discontinuation.

Reporting group values	Survodutide 2.4 mg - actual maintenance treatment	Survodutide 4.8 mg - actual maintenance treatment	Survodutide 6.0 mg - actual maintenance treatment
Number of subjects	93	69	52
Age categorical			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			

Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	76	60	45
From 65-84 years	17	9	7
85 years and over	0	0	0
Age Continuous			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: years			
arithmetic mean	50.6	49.5	49.9
standard deviation	± 13.5	± 12.9	± 12.8
Sex: Female, Male			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Participants			
Female	49	31	29
Male	44	38	23
Ethnicity (NIH/OMB)			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Hispanic or Latino	20	17	21
Not Hispanic or Latino	73	52	31
Unknown or Not Reported	0	0	0
Race (NIH/OMB)			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	27	22	12
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	3	0
White	63	44	39
More than one race	1	0	0
Unknown or Not Reported	0	0	0
Number of participants at each category of liver fibrosis stage at baseline			
Number of participants at each category of liver fibrosis stage at baseline is reported. The total score for the fibrosis stage ranges from 0 to 4 with higher score indication worsening of the disease and the stages of fibrosis based on their location are the following: - 1A Zone 3, perisinusoidal, delicate; - 1B Zone 3, perisinuosoidal, dense; - 1C Portal, periportal only; - 2 Zone 3, perisinusoidal + portal,			

periportal only; - 3 Bridging fibrosis; - 4 Cirrhosis.			
Units: Subjects			
Stage 1A	0	3	3
Stage 1B	16	9	11
Stage 1C	5	3	4
Stage 2	42	30	16
Stage 3	30	24	18
Number of participants in each category of diabetes at baseline			
Number of participants at each category of diabetes at baseline is reported. The reported categories of diabetes stratification are the following: Yes, No. Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Diabetes = No	54	40	34
Diabetes = Yes	39	29	18
Number of patients in each category of NAS score			
The non-alcoholic fatty liver disease (NAFLD) activity score (NAS) is the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. The reported categories of NAS score range are: 0; 1; 2; 3; 4; 5; 6; 7; 8. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
NAS total score = 0	0	0	0
NAS total score = 1	0	0	0
NAS total score = 2	0	0	0
NAS total score = 3	0	0	0
NAS total score = 4	27	19	19
NAS total score = 5	34	19	12
NAS total score = 6	23	22	17
NAS total score = 7	9	8	4
NAS total score = 8	0	1	0
Number of patients in each category of the NAS sub-score steatosis			
The NAS represents the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. Number of patients in each category of the score range for steatosis is reported. Treated set - planned maintenance treatment. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Steatosis total score = 0	0	0	0
Steatosis total score = 1	6	0	1
Steatosis total score = 2	49	39	33
Steatosis total score = 3	38	30	18
Number of patients in each category of the NAS sub-scores (ballooning)			
The NAS represents the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. Number of patients in each category of the score range for ballooning is reported. Treated set - planned maintenance treatment. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the			

maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Ballooning total score = 0	0	0	0
Ballooning total score = 1	70	50	39
Ballooning total score = 2	23	19	13
Number of patients in each category of the NAS sub-score lobular inflammation			
The NAS represents the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. Number of patients in each category of the score range for lobular inflammation is reported. Treated set - planned maintenance treatment. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Lobular inflammation score = 0	0	0	0
Lobular inflammation score = 1	43	28	26
Lobular inflammation score = 2	48	40	24
Lobular inflammation score = 3	2	1	2
The non-alcoholic fatty liver disease (NAFLD) activity score (NAS) at baseline			
The NAS represents the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. Treated set - planned maintenance treatment. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: score on a scale			
arithmetic mean	5.2	5.3	5.1
standard deviation	± 1.0	± 1.1	± 1.0

Reporting group values	Placebo - actual maintenance treatment		
Number of subjects	79		
Age categorical			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
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)	67		
From 65-84 years	12		
85 years and over	0		
Age Continuous			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: years			

arithmetic mean	52.8		
standard deviation	± 11.9		

Sex: Female, Male			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Participants			
Female	46		
Male	33		
Ethnicity (NIH/OMB)			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Hispanic or Latino	23		
Not Hispanic or Latino	56		
Unknown or Not Reported	0		
Race (NIH/OMB)			
Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
American Indian or Alaska Native	19		
Asian	0		
Native Hawaiian or Other Pacific Islander	1		
Black or African American	0		
White	59		
More than one race	0		
Unknown or Not Reported	0		
Number of participants at each category of liver fibrosis stage at baseline			
Number of participants at each category of liver fibrosis stage at baseline is reported. The total score for the fibrosis stage ranges from 0 to 4 with higher score indication worsening of the disease and the stages of fibrosis based on their location are the following: - 1A Zone 3, perisinusoidal, delicate; - 1B Zone 3, perisinuosoidal, dense; - 1C Portal, periportal only; - 2 Zone 3, perisinusoidal + portal, periportal only; - 3 Bridging fibrosis; - 4 Cirrhosis.			
Units: Subjects			
Stage 1A	2		
Stage 1B	11		
Stage 1C	3		
Stage 2	32		
Stage 3	31		
Number of participants in each category of diabetes at baseline			
Number of participants at each category of diabetes at baseline is reported. The reported categories of diabetes stratification are the following: Yes, No. Treated set - planned maintenance treatment: included all patients that were administered survodutide or placebo matching survodutide. Patients are analyzed according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Diabetes = No	48		

Diabetes = Yes	31		
Number of patients in each category of NAS score			
The non-alcoholic fatty liver disease (NAFLD) activity score (NAS) is the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. The reported categories of NAS score range are: 0; 1; 2; 3; 4; 5; 6; 7; 8. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
NAS total score = 0	0		
NAS total score = 1	0		
NAS total score = 2	0		
NAS total score = 3	0		
NAS total score = 4	24		
NAS total score = 5	28		
NAS total score = 6	11		
NAS total score = 7	16		
NAS total score = 8	0		
Number of patients in each category of the NAS sub-score steatosis			
The NAS represents the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. Number of patients in each category of the score range for steatosis is reported. Treated set - planned maintenance treatment. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Steatosis total score = 0	0		
Steatosis total score = 1	3		
Steatosis total score = 2	47		
Steatosis total score = 3	29		
Number of patients in each category of the NAS sub-scores (ballooning)			
The NAS represents the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. Number of patients in each category of the score range for ballooning is reported. Treated set - planned maintenance treatment. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Ballooning total score = 0	0		
Ballooning total score = 1	53		
Ballooning total score = 2	26		
Number of patients in each category of the NAS sub-score lobular inflammation			
The NAS represents the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. Number of patients in each category of the score range for lobular inflammation is reported. Treated set - planned maintenance treatment. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: Subjects			
Lobular inflammation score = 0	0		
Lobular inflammation score = 1	39		

Lobular inflammation score = 2	34		
Lobular inflammation score = 3	6		

The non-alcoholic fatty liver disease (NAFLD) activity score (NAS) at baseline			
The NAS represents the sum of subscores for steatosis (scored 0-3), lobular inflammation (scored 0-3) and ballooning (scored 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease. Treated set - planned maintenance treatment. Patients are analyzed according to the planned maintenance dose strength they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.			
Units: score on a scale			
arithmetic mean	5.2		
standard deviation	± 1.1		

End points reporting groups

Reporting group title	Survodutide 2.4 mg - planned maintenance treatment

Reporting group description:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3). were to be administered once weekly, subcutaneously a solution for injection of survodutide at a starting dose of 0.3 milligrams (mg) followed by a dose escalation up to the maintenance dose of 2.4 mg of survodutide.
The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period).
Patients not tolerating the assigned dose due to gastrointestinal adverse events had the option of a dose adjustment which could lead to a maintenance dose lower than the dose the patient was randomized to.

Reporting group title	Survodutide 4.8 mg - planned maintenance treatment

Reporting group description:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3). were to be administered once weekly, subcutaneously a solution for injection of survodutide at a starting dose of 0.3 milligrams (mg) followed by a dose escalation up to the maintenance dose of 4.8 mg of survodutide.
The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period).
Patients not tolerating the assigned dose due to gastrointestinal adverse events had the option of a dose adjustment which could lead to a maintenance dose lower than the dose the patient was randomized to.

Reporting group title	Survodutide 6.0 mg - planned maintenance treatment

Reporting group description:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3). were to be administered once weekly, subcutaneously a solution for injection of survodutide at a starting dose of 0.3 milligrams (mg) followed by a dose escalation up to the maintenance dose of 6.0 mg of survodutide.
The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period).
Patients not tolerating the assigned dose due to gastrointestinal adverse events had the option of a dose adjustment which could lead to a maintenance dose lower than the dose the patient was randomized to.

Reporting group title	Placebo - planned maintenance treatment

Reporting group description:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3). were administered once weekly, subcutaneously a solution for injection of placebo matching survodutide. The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period).

Reporting group title	Survodutide 2.4 mg - planned maintenance treatment

Reporting group description:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3) were to be administered once weekly, subcutaneously a solution for injection of survodutide at a starting dose of 0.3 milligrams (mg) followed by a dose escalation up to the maintenance dose of 2.4 mg of survodutide.
The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period).
Patients not tolerating the assigned dose due to gastrointestinal adverse events had the option of a dose adjustment which could lead to a maintenance dose lower than the dose the patient was randomized to.

Reporting group title	Survodutide 4.8 mg - planned maintenance treatment

Reporting group description:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3) were to be administered once weekly, subcutaneously a solution for injection of survodutide at a starting dose of 0.3 milligrams (mg) followed by a dose escalation up to the maintenance dose of 4.8 mg of survodutide.
The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period).
Patients not tolerating the assigned dose due to gastrointestinal adverse events had the option of a dose adjustment which could lead to a maintenance dose lower than the dose the patient was randomized to.

Reporting group title	Survodutide 6.0 mg - planned maintenance treatment

Reporting group description:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3) were to be administered once weekly, subcutaneously a solution for injection of survodutide at a starting dose of 0.3 milligrams (mg) followed by a dose escalation up to the maintenance dose of 6.0 mg of survodutide.
The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period).
Patients not tolerating the assigned dose due to gastrointestinal adverse events had the option of a dose adjustment which could lead to a maintenance dose lower than the dose the patient was randomized to.

Reporting group title	Placebo - planned maintenance treatment

Reporting group description:

Patients with non-alcoholic steatohepatitis (NASH) with non-alcoholic fatty liver disease (NAFLD) activity score (NAS) ≥4 and fibrosis stage 1-3 (F1-F3) were administered once weekly, subcutaneously a solution for injection of placebo matching survodutide. The total treatment duration was 48 weeks (consisting of up to 24 weeks dose escalation period and at least 24 weeks maintenance period).

Subject analysis set title	Survodutide 2.4 mg - actual maintenance treatment
Subject analysis set type	Full analysis

Subject analysis set description:

This arm includes patients who were treated with 2.4 mg of survodutide administered weekly at the start of the maintenance period, for patients who reached the maintenance period, regardless of whether this was the randomised (planned) dose or not, and regardless of whether the patient stayed on that dose throughout the maintenance period.
This arm includes also those patients for whom the next maintenance dose up from the dose at treatment discontinuation was 2.4 mg of survodutide administered weekly, for patients who discontinued treatment prior to the maintenance period, regardless of the reason for the treatment discontinuation.

Subject analysis set title	Survodutide 4.8 mg - actual maintenance treatment
Subject analysis set type	Full analysis

Subject analysis set description:

This arm includes patients who were treated with 4.8 mg of survodutide administered weekly at the start of the maintenance period, for patients who reached the maintenance period, regardless of whether this was the randomised (planned) dose or not, and regardless of whether the patient stayed on that dose throughout the maintenance period.
This arm includes also those patients for whom the next maintenance dose up from the dose at treatment discontinuation was 4.8 mg of survodutide administered weekly, for patients who discontinued treatment prior to the maintenance period, regardless of the reason for the treatment discontinuation.

Subject analysis set title	Survodutide 6.0 mg - actual maintenance treatment
Subject analysis set type	Full analysis

Subject analysis set description:

This arm includes patients who were treated with 6.0 mg of survodutide administered weekly at the start of the maintenance period, for patients who reached the maintenance period, regardless of whether this was the randomised (planned) dose or not, and regardless of whether the patient stayed on that dose throughout the maintenance period.
This arm includes also those patients for whom the next maintenance dose up from the dose at treatment discontinuation was 6.0 mg of survodutide administered weekly, for patients who discontinued treatment prior to the maintenance period, regardless of the reason for the treatment discontinuation.

Subject analysis set title	Placebo - actual maintenance treatment
Subject analysis set type	Full analysis

Subject analysis set description:

This arm includes patients who were treated with placebo matching survodutide administered weekly at the start of the maintenance period, for patients who reached the maintenance period, regardless of whether this was the randomised (planned) dose or not, and regardless of whether the patient stayed on that dose throughout the maintenance period.
This arm includes also those patients who were receiving placebo matching survodutide administered weekly and who discontinued treatment prior to the maintenance period, regardless of the reason for the treatment discontinuation.

Primary: Improvement (yes/ no) from baseline in liver histological findings based on liver biopsy after 48 weeks of treatment in patients with NASH (NAS ≥ 4, fibrosis F1-F3) - actual maintenance treatment

End point title	Improvement (yes/ no) from baseline in liver histological findings based on liver biopsy after 48 weeks of treatment in patients with NASH (NAS ≥ 4, fibrosis F1-F3) - actual maintenance treatment

End point description:

Percentage of patients who had an improvement from baseline in liver histological findings based on liver biopsy after 48 weeks of treatment is reported. Percentages were rounded to one decimal place.
Improvement in histological findings was defined as a composite of improvement in NASH and no worsening of fibrosis.
Improvement in non-alcoholic steatohepatitis (NASH) was defined as decrease of at least 2 points in non-alcoholic fatty liver disease (NAFLD) activity score (NAS) with at least 1 point decrease in NAS subscore of either lobular inflammation or ballooning.
Patients without post-baseline data were considered non-responders.
Patients are analyzed according to the actual treatment they received at the start of the dose maintenance period (for patients who reached the maintenance period) or the next maintenance dose up from the dose at treatment discontinuation (for patients who discontinued treatment prior to the maintenance period).

End point type	Primary

End point timeframe:

At baseline and at 48 weeks.

End point values	Survodutide 2.4 mg - actual maintenance treatment	Survodutide 4.8 mg - actual maintenance treatment	Survodutide 6.0 mg - actual maintenance treatment	Placebo - actual maintenance treatment
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	93	69	52	79
Units: Percentage of participants				
number (not applicable)	38.7	63.8	55.8	15.2

Statistical analyses

Statistical analysis title	Logistic regression-2.4 mg Survodutide vs. Placebo

Statistical analysis description:

The logistic regression model included actual treatment, presence of diabetes of any type and Baseline Fibrosis Score. Firth’s penalized regression was used.
The logistic regression model included all 293 treated subjects, not just those allocated to the two compared treatment groups.

Comparison groups	Survodutide 2.4 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.001 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.47

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.66
upper limit	7.25

Notes:

[1] - No confirmatory hypothesis testing was performed.
Odds Ratio of "Survodutide 2.4 mg" vs. "Placebo".
[2] - The p−value reported is considered nominal.

Statistical analysis title	Logistic regression-4.8 mg Survodutide vs. Placebo

Statistical analysis description:

The logistic regression model included actual treatment, presence of diabetes of any type and Baseline Fibrosis Score. Firth’s penalized regression was used.
The logistic regression model included all 293 treated subjects, not just those allocated to the two compared treatment groups.

Comparison groups	Survodutide 4.8 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	< 0.0001 [4]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	9.52
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.35
upper limit	20.85

Notes:

[3] - No confirmatory hypothesis testing was performed.
Odds Ratio of "Survodutide 4.8 mg" vs. "Placebo".
[4] - The p−value reported is considered nominal.

Statistical analysis title	Logistic regression-6.0 mg Survodutide vs. Placebo

Statistical analysis description:

The logistic regression model included actual treatment, presence of diabetes of any type and Baseline Fibrosis Score. Firth’s penalized regression was used.
The logistic regression model included all 293 treated subjects, not just those allocated to the two compared treatment groups.

Comparison groups	Survodutide 6.0 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.0001 [6]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	7.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.1
upper limit	16.16

Notes:

[5] - No confirmatory hypothesis testing was performed.

Odds Ratio of "Survodutide 6.0 mg" vs. "Placebo".
[6] - The p−value reported is considered nominal.

Statistical analysis title	MCP-Mod linear model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).

Comparison groups	Survodutide 2.4 mg - actual maintenance treatment v Survodutide 4.8 mg - actual maintenance treatment v Survodutide 6.0 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	< 0.0001
Method	MCP-Mod linear model fit

Notes:

[7] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept, and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors.
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.
Linear model fit assumption.

Statistical analysis title	MCP-Mod exponential-1 model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).

Comparison groups	Survodutide 2.4 mg - actual maintenance treatment v Survodutide 4.8 mg - actual maintenance treatment v Survodutide 6.0 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	< 0.0001
Method	MCP-Mod exponential-1 model fit

Notes:

[8] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept, and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors.
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.
MCP-Mod exponential-1 model assumption: 25% of maximum effect is achieved at dose 3.0 mg.

Statistical analysis title	MCP-Mod exponential-2 model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).

Comparison groups	Survodutide 2.4 mg - actual maintenance treatment v Survodutide 4.8 mg - actual maintenance treatment v Survodutide 6.0 mg - actual maintenance treatment v Placebo

	- actual maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.0008
Method	MCP-Mod exponential -2 model fit

Notes:

[9] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors.
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.
MCP-Mod exponential-2 model assumption: 5% of maximum effect is achieved at dose 3.0 mg.

Statistical analysis title	MCP-Mod Emax1 model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).

Comparison groups	Survodutide 2.4 mg - actual maintenance treatment v Survodutide 4.8 mg - actual maintenance treatment v Survodutide 6.0 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	< 0.0001
Method	MCP-Mod Emax1 model fit

Notes:

[10] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors.
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.
MCP-Mod Emax1 model assumption: 50% of maximum effect is achieved at dose 3.0 mg.

Statistical analysis title	MCP-Mod Emax2 model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).

Comparison groups	Survodutide 2.4 mg - actual maintenance treatment v Survodutide 4.8 mg - actual maintenance treatment v Survodutide 6.0 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	< 0.0001
Method	MCP-Mod Emax2 model fit

Notes:

[11] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors.
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.
MCP-Mod Emax2 model assumption: 80% of maximum effect is achieved at dose 3.0 mg.

Statistical analysis title	MCP-Mod quadratic model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).

Comparison groups	Survodutide 2.4 mg - actual maintenance treatment v Survodutide 4.8 mg - actual maintenance treatment v Survodutide 6.0 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	< 0.0001
Method	MCP-Mod quadratic model fit

Notes:

[12] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors.
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.
MCP-Mod quadratic model assumption: Maximum effect is achieved at dose 4.8 mg.

Primary: Improvement (yes/ no) from baseline in liver histological findings based on liver biopsy after 48 weeks of treatment in patients with NASH (NAS ≥ 4, fibrosis F1-F3) - planned maintenance treatment

End point title	Improvement (yes/ no) from baseline in liver histological findings based on liver biopsy after 48 weeks of treatment in patients with NASH (NAS ≥ 4, fibrosis F1-F3) - planned maintenance treatment

End point description:

Percentage of patients who had an improvement from baseline in liver histological findings based on liver biopsy after 48 weeks of treatment is reported. Percentages were rounded to one decimal place.
Improvement in histological findings was defined as a composite of improvement in non-alcoholic steatohepatitis (NASH) and no worsening of fibrosis.
Improvement in NASH was defined as decrease of at least 2 points in non-alcoholic fatty liver disease (NAFLD) activity score (NAS) with at least 1 point decrease in NAS subscore of either lobular inflammation or ballooning.
Patients without post-baseline data were considered non-responders.
Patients are analyzed for this endpoint according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.

End point type	Primary

End point timeframe:

At baseline and after 48 weeks of treatment.

End point values	Survodutide 2.4 mg - planned maintenance treatment	Survodutide 4.8 mg - planned maintenance treatment	Survodutide 6.0 mg - planned maintenance treatment	Placebo - planned maintenance treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73	72	74	74
Units: percentage of participants				
number (not applicable)	46.6	62.5	43.2	13.5

Statistical analyses

Statistical analysis title	Logistic regression-2.4 mg Survodutide vs. Placebo

Statistical analysis description:

The logistic regression model includes planned treatment, presence of diabetes of any type and Baseline Fibrosis Score. Firth’s penalized regression was used.
The logistic regression model included all 293 treated subjects, not just those allocated to the two compared treatment groups.

Comparison groups	Survodutide 2.4 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	< 0.0001 [14]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.46
upper limit	12.28

Notes:

[13] - No confirmatory hypothesis testing was performed.
Odds Ratio of "Survodutide 2.4 mg" vs. "Placebo".
[14] - The p−value reported is considered nominal.

Statistical analysis title	Logistic regression-6.0 mg Survodutide vs. Placebo

Statistical analysis description:

The logistic regression model includes planned treatment, presence of diabetes of any type and Baseline Fibrosis Score. Firth’s penalized regression was used.
The logistic regression model included all 293 treated subjects, not just those allocated to the two compared treatment groups.

Comparison groups	Survodutide 6.0 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.0001 [16]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	4.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.18
upper limit	10.91

Notes:

[15] - No confirmatory hypothesis testing was performed.
Odds Ratio of "Survodutide 6.0 mg" vs. "Placebo".
[16] - The p−value reported is considered nominal.

Statistical analysis title	MCP-Mod linear model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).

Comparison groups	Survodutide 2.4 mg - planned maintenance treatment v Survodutide 4.8 mg - planned maintenance treatment v Survodutide 6.0 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.0001
Method	MCP-Mod linear model fit

Notes:

[17] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors.
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.
Linear model fit assumption.

Statistical analysis title	Logistic regression-4.8 mg Survodutide vs. Placebo

Statistical analysis description:

The logistic regression model includes planned treatment, presence of diabetes of any type and Baseline Fibrosis Score. Firth’s penalized regression was used.
The logistic regression model included all 293 treated subjects, not just those allocated to the two compared treatment groups.

Comparison groups	Survodutide 4.8 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	< 0.0001 [19]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	10.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.49
upper limit	22.87

Notes:

[18] - No confirmatory hypothesis testing was performed.
Odds Ratio of "Survodutide 4.8 mg" vs. "Placebo".
[19] - The p−value reported is considered nominal.

Statistical analysis title	MCP-Mod exponential-1 model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1,

Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).

Comparison groups	Survodutide 2.4 mg - planned maintenance treatment v Survodutide 4.8 mg - planned maintenance treatment v Survodutide 6.0 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.0115
Method	MCP-Mod exponential-1 model fit

Notes:

[20] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept, and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors.
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.
Model assumption: 25% of maximum effect is achieved at dose 3.0 mg.

Statistical analysis title	MCP-Mod exponential-2 model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).

Comparison groups	Survodutide 2.4 mg - planned maintenance treatment v Survodutide 4.8 mg - planned maintenance treatment v Survodutide 6.0 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.2204
Method	MCP-Mod exponential-2 model fit

Notes:

[21] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept, and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors.
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.
Model assumption: 5% of maximum effect is achieved at dose 3.0 mg.

Statistical analysis title	MCP-Mod Emax1 model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).

Comparison groups	Survodutide 2.4 mg - planned maintenance treatment v Survodutide 4.8 mg - planned maintenance treatment v Survodutide 6.0 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	< 0.0001
Method	MCP-Mod Emax1 model fit

Notes:

[22] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept, and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors.

P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.
Model assumption: 50% of maximum effect is achieved at dose 3.0 mg.

Statistical analysis title	MCP-Mod Emax2 model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).

Comparison groups	Survodutide 2.4 mg - planned maintenance treatment v Survodutide 4.8 mg - planned maintenance treatment v Survodutide 6.0 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	< 0.0001
Method	MCP-Mod Emax2 model fit

Notes:

[23] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors.
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.
Model assumption: 80% of maximum effect is achieved at dose 3.0 mg.

Statistical analysis title	MCP-Mod quadratic model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the Multiple Comparison Procedure - Modelling (MCP-Mod) approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).

Comparison groups	Survodutide 2.4 mg - planned maintenance treatment v Survodutide 4.8 mg - planned maintenance treatment v Survodutide 6.0 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[24]
P-value	< 0.0001
Method	MCP-Mod quadratic model fit

Notes:

[24] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept, and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors.
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.
Model assumption: Maximum effect is achieved at dose 4.8 mg.

Secondary: Improvement of liver fat content (yes/ no) defined as at least 30% relative reduction in liver fat content after 48 weeks of treatment compared to baseline assessed by MRI-PDFF - actual maintenance treatment

End point title	Improvement of liver fat content (yes/ no) defined as at least 30% relative reduction in liver fat content after 48 weeks of treatment compared to baseline assessed by MRI-PDFF - actual maintenance treatment

End point description:

Percentage of participants with improvement in liver fat content is reported. Improvement in liver fat content was defined as percentage reduction from baseline of ≥30% in liver fat content after 48 weeks

of treatment compared to baseline. Percentages were rounded to one decimal place.
Liver fat content was assessed by Magnetic Resonance Imaging - Proton Density Fat Fraction (MRI-PDFF).
Patients without post-baseline values were imputed as non-responders.
Treated set - actual maintenance treatment. Patients are analyzed according to the actual treatment they received at the start of the dose maintenance period (for patients who reached the maintenance period) or the next maintenance dose up from the dose at treatment discontinuation (for patients who discontinued treatment prior to the maintenance period).
Number of patients analyzed reflects the number of patients included in the analysis model.

End point type	Secondary

End point timeframe:

At baseline and after 48 weeks.

End point values	Survodutide 2.4 mg - actual maintenance treatment	Survodutide 4.8 mg - actual maintenance treatment	Survodutide 6.0 mg - actual maintenance treatment	Placebo - actual maintenance treatment
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	93	69	52	79
Units: Percentage of participants				
number (not applicable)	50.5	66.7	76.9	16.5

Statistical analyses

Statistical analysis title	Logistic regression-2.4 mg Survodutide vs. Placebo

Statistical analysis description:

The logistic regression model included actual treatment, presence of diabetes of any type, baseline liver fat content and baseline fibrosis score. Firth’s penalized regression was used.
The logistic regression model included all 293 treated subjects, not just those allocated to the two compared treatment groups.

Comparison groups	Survodutide 2.4 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	other[25]
P-value	< 0.0001 [26]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	5.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.47
upper limit	10.4

Notes:

[25] - No confirmatory hypothesis testing was performed.
Odds Ratio of "Survodutide 2.4 mg" vs. "Placebo".
[26] - The p−value reported is considered nominal.

Statistical analysis title	Logistic regression-6.0 mg Survodutide vs. Placebo

Statistical analysis description:

The logistic regression model included actual treatment, presence of diabetes of any type, baseline liver fat content and baseline fibrosis score. Firth's penalized regression was used.
The logistic regression model included all 293 treated subjects, not just those allocated to the two compared treatment groups.

Comparison groups	Survodutide 6.0 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	other[27]
P-value	< 0.0001 [28]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	16.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	6.69
upper limit	38.73

Notes:

[27] - No confirmatory hypothesis testing was performed.
Odds Ratio of "Survodutide 6.0 mg" vs. "Placebo".
[28] - The p−value reported is considered nominal.

Statistical analysis title	MCP-Mod linear model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.

Comparison groups	Survodutide 2.4 mg - actual maintenance treatment v Survodutide 4.8 mg - actual maintenance treatment v Survodutide 6.0 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[29]
P-value	< 0.0001
Method	MCP-Mod linear model fit

Notes:

[29] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors, and baseline liver fat content (assessed by MRI-PDFF) as a continuous linear covariate.
Linear model fit assumption.

Statistical analysis title	MCP-Mod quadratic model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.

Comparison groups	Survodutide 2.4 mg - actual maintenance treatment v Survodutide 4.8 mg - actual maintenance treatment v Survodutide 6.0 mg - actual maintenance treatment v Placebo

	- actual maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[30]
P-value	< 0.0001
Method	MCP-Mod quadratic model fit

Notes:

[30] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors, and baseline liver fat content (assessed by MRI-PDFF) as a continuous linear covariate.
MCP-Mod quadratic model assumption: Maximum effect is achieved at dose 4.8 mg.

Statistical analysis title	MCP-Mod exponential-2 model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.

Comparison groups	Survodutide 2.4 mg - actual maintenance treatment v Survodutide 4.8 mg - actual maintenance treatment v Survodutide 6.0 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[31]
P-value	< 0.0001
Method	MCP-Mod exponential-2 model fit

Notes:

[31] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept, and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors, and baseline liver fat content (assessed by MRI-PDFF) as a continuous linear covariate.
MCP-Mod exponential-2 model assumption: 5% of maximum effect achieved at dose 3.0 mg.

Statistical analysis title	MCP-Mod Emax1 model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.

Comparison groups	Survodutide 2.4 mg - actual maintenance treatment v Survodutide 4.8 mg - actual maintenance treatment v Survodutide 6.0 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[32]
P-value	< 0.0001
Method	MCP-Mod Emax1 model fit

Notes:

[32] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors, and baseline liver fat content (assessed by MRI-PDFF) as a continuous linear covariate.
MCP-Mod Emax1 model assumption: 50% of maximum effect is achieved at dose 3.0 mg.

Statistical analysis title	MCP-Mod Emax2 model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.

Comparison groups	Survodutide 2.4 mg - actual maintenance treatment v Survodutide 4.8 mg - actual maintenance treatment v Survodutide 6.0 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[33]
P-value	< 0.0001
Method	MCP-Mod Emax2 model fit

Notes:

[33] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept, and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors, and baseline liver fat content (assessed by MRI-PDFF) as a continuous linear covariate.
MCP-Mod Emax2 model assumption: 80% of maximum effect is achieved at dose 3.0 mg.

Statistical analysis title	Logistic regression-4.8 mg Survodutide vs. Placebo

Statistical analysis description:

The logistic regression model included actual treatment, presence of diabetes of any type, baseline liver fat content and baseline fibrosis score. Firth’s penalized regression was used.
The logistic regression model included all 293 treated subjects, not just those allocated to the two compared treatment groups.

Comparison groups	Survodutide 4.8 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	other[34]
P-value	< 0.0001 [35]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	9.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.36
upper limit	20.51

Notes:

[34] - No confirmatory hypothesis testing was performed.
Odds Ratio of "Survodutide 4.8 mg" vs. "Placebo".
[35] - The p−value reported is considered nominal.

Statistical analysis title	MCP-Mod exponential-1 model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the

type I error (one-sided alpha of 0.050).
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.

Comparison groups	Survodutide 2.4 mg - actual maintenance treatment v Survodutide 4.8 mg - actual maintenance treatment v Survodutide 6.0 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[36]
P-value	< 0.0001
Method	MCP-Mod exponential-1 model fit

Notes:

[36] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept, and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors, and baseline liver fat content (assessed by MRI-PDFF) as a continuous linear covariate.
MCP-Mod exponential-1 model assumption: 25% of maximum effect is achieved at dose 3.0 mg.

Secondary: Improvement of liver fat content (yes/ no) defined as at least 30% relative reduction in liver fat content after 48 weeks of treatment compared to baseline assessed by MRI-PDFF - planned maintenance treatment

End point title	Improvement of liver fat content (yes/ no) defined as at least 30% relative reduction in liver fat content after 48 weeks of treatment compared to baseline assessed by MRI-PDFF - planned maintenance treatment

End point description:

Percentage of participants with improvement in liver fat content is reported. Improvement in liver fat content was defined as percentage reduction from baseline of ≥30% in liver fat content after 48 weeks of treatment compared to baseline.
Liver fat content was assessed by Magnetic Resonance Imaging - Proton Density Fat Fraction (MRI-PDFF).
Patients without post-baseline values were imputed as non-responders.
Patients are analyzed for this endpoint according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.

End point type	Secondary

End point timeframe:

At baseline and at 48 weeks.

End point values	Survodutide 2.4 mg - planned maintenance treatment	Survodutide 4.8 mg - planned maintenance treatment	Survodutide 6.0 mg - planned maintenance treatment	Placebo - planned maintenance treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73	72	74	74
Units: Percentage of participants				
number (not applicable)	63.0	66.7	56.8	13.5

Statistical analyses

Statistical analysis title	MCP-Mod linear model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.

Comparison groups	Survodutide 2.4 mg - planned maintenance treatment v Survodutide 4.8 mg - planned maintenance treatment v Survodutide 6.0 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[37]
P-value	< 0.0001
Method	MCP-Mod linear model fit

Notes:

[37] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept, and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors, and baseline liver fat content (assessed by MRI-PDFF) as a continuous linear covariate.
Linear model fit assumption.

Statistical analysis title	Logistic regression-6.0 mg Survodutide vs. Placebo

Statistical analysis description:

The logistic regression model included planned treatment, presence of diabetes of any type, baseline liver fat content and baseline fibrosis score. Firth’s penalized regression was used.
The logistic regression model included all 293 treated subjects, not just those allocated to the two compared treatment groups.

Comparison groups	Survodutide 6.0 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	other[38]
P-value	< 0.0001 [39]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	8.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.66
upper limit	18.5

Notes:

[38] - No confirmatory hypothesis testing was performed.
Odds Ratio of "Survodutide 6.0 mg" vs. "Placebo".
[39] - The p−value reported is considered nominal.

Statistical analysis title	Logistic regression-4.8 mg Survodutide vs. Placebo

Statistical analysis description:

The logistic regression model included planned treatment, presence of diabetes of any type, baseline liver fat content and baseline fibrosis score. Firth’s penalized regression was used.
The logistic regression model included all 293 treated subjects, not just those allocated to the two compared treatment groups.

Comparison groups	Survodutide 4.8 mg - planned maintenance treatment v Placebo - planned maintenance treatment

Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other[40]
P-value	< 0.0001 [41]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	12.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.3
upper limit	27.45

Notes:

[40] - No confirmatory hypothesis testing was performed.
Odds Ratio of "Survodutide 4.8 mg" vs. "Placebo".
[41] - The p−value reported is considered nominal.

Statistical analysis title	Logistic regression-2.4 mg Survodutide vs. Placebo

Statistical analysis description:

The logistic regression model included planned treatment, presence of diabetes of any type, baseline liver fat content and baseline fibrosis score. Firth’s penalized regression was used.
The logistic regression model included all 293 treated subjects, not just those allocated to the two compared treatment groups.

Comparison groups	Survodutide 2.4 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[42]
P-value	< 0.0001 [43]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	10.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.6
upper limit	23.45

Notes:

[42] - No confirmatory hypothesis testing was performed.
Odds Ratio of "Survodutide 2.4 mg" vs. "Placebo".
[43] - The p−value reported is considered nominal.

Statistical analysis title	MCP-Mod Emax2 model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.

Comparison groups	Survodutide 2.4 mg - planned maintenance treatment v Survodutide 4.8 mg - planned maintenance treatment v Survodutide 6.0 mg - planned maintenance treatment v Placebo - planned maintenance treatment

Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[44]
P-value	< 0.0001
Method	MCP-Mod Emax2 model fit

Notes:

[44] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors, and baseline liver fat content (assessed by MRI-PDFF) as a continuous linear covariate.
MCP-Mod Emax2 model assumption: 80% of maximum effect is achieved at dose 3.0 mg.

Statistical analysis title	MCP-Mod Emax1 model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.

Comparison groups	Survodutide 2.4 mg - planned maintenance treatment v Survodutide 4.8 mg - planned maintenance treatment v Survodutide 6.0 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[45]
P-value	< 0.0001
Method	MCP-Mod Emax1 model fit

Notes:

[45] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors, and baseline liver fat content (assessed by MRI-PDFF) as a continuous linear covariate.
MCP-Mod Emax1 model assumption: 50% of maximum effect is achieved at dose 3.0 mg.

Statistical analysis title	MCP-Mod exponential-2 model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.

Comparison groups	Survodutide 2.4 mg - planned maintenance treatment v Survodutide 4.8 mg - planned maintenance treatment v Survodutide 6.0 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[46]
P-value	= 0.0925
Method	MCP-Mod exponential-2 model fit

Notes:

[46] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors, and baseline liver fat content (assessed by MRI-PDFF) as a continuous linear covariate.
MCP-Mod exponential-2 model assumption: 5% of maximum effect is achieved at dose 3.0 mg.

Statistical analysis title	MCP-Mod quadratic model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.

Comparison groups	Survodutide 2.4 mg - planned maintenance treatment v Survodutide 4.8 mg - planned maintenance treatment v Survodutide 6.0 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[47]
P-value	< 0.0001
Method	MCP-Mod quadratic model fit

Notes:

[47] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept, and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors, and baseline liver fat content (assessed by MRI-PDFF) as a continuous linear covariate.
MCP-Mod quadratic model assumption: Maximum effect is achieved at dose 4.8 mg.

Statistical analysis title	MCP-Mod exponential-1 model fit

Statistical analysis description:

A flat vs. non-flat dose-response relationship across the 3 doses of survodutide and placebo was tested using the MCP-Mod approach which evaluated simultaneously 6 different plausible dose-response patterns (linear, exponential1, exponential2, Emax1, Emax2, quadratic) while keeping full control of the type I error (one-sided alpha of 0.050).
P-values from the contrast tests corresponding to each dose response pattern evaluated were adjusted for the multiple comparisons performed.

Comparison groups	Survodutide 2.4 mg - planned maintenance treatment v Survodutide 4.8 mg - planned maintenance treatment v Survodutide 6.0 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	293
Analysis specification	Pre-specified
Analysis type	other[48]
P-value	= 0.0031
Method	MCP-Mod exponential-1 model fit

Notes:

[48] - Logistic regression estimates were used as input for the MCP-Mod. The logistic regression model was fitted without an intercept and included presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3] and the dose group as factors, and baseline liver fat content (assessed by MRI-PDFF) as a continuous linear covariate.
MCP-Mod exponential-1 model assumption: 25% of maximum effect is achieved at dose 3.0 mg.

Secondary: Absolute change of liver fat content from baseline after 48 weeks of treatment assessed by MRI-PDFF - actual maintenance treatment

End point title	Absolute change of liver fat content from baseline after 48 weeks of treatment assessed by MRI-PDFF - actual maintenance treatment

End point description:

Absolute change of liver fat content (percentage [%]) from baseline after 48 weeks of treatment is reported. Liver fat content was assessed by Magnetic Resonance Imaging - Proton Density Fat Fraction (MRI-PDFF).
Least Squares Mean (Standard error) were calculated from mixed-effect model for repeated measures (MMRM) including fixed effects for baseline liver fat content (%) as a continuous linear covariate, and treatment, presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3], visit, treatment by visit interaction and baseline by visit interaction as factors.

Patients are analyzed according to the actual treatment they received at the start of the dose maintenance period (for patients who reached the maintenance period) or the next maintenance dose up from the dose at treatment discontinuation
(for patients who discontinued treatment prior to the maintenance period). Number of patients analyzed reflects the number of patients included in the analysis model.

End point type	Secondary

End point timeframe:

MMRM included measurements from baseline and at Week 28 and at Week 48 after first drug administration. MMRM estimates of absolute change from baseline to Week 48 is reported.

End point values	Survodutide 2.4 mg - actual maintenance treatment	Survodutide 4.8 mg - actual maintenance treatment	Survodutide 6.0 mg - actual maintenance treatment	Placebo - actual maintenance treatment
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	60	51	73
Units: percentage of liver fat content				
least squares mean (confidence interval 95%)	-10.48 (-11.92 to -9.04)	-12.80 (-14.32 to -11.28)	-12.96 (-14.62 to -11.30)	-1.89 (-3.26 to -0.51)

Statistical analyses

Statistical analysis title	MMRM - 2.4 mg Survodutide vs. Placebo

Statistical analysis description:

Least Squares Mean differences and 95% confidence interval were calculated from mixed-effect model for repeated measures (MMRM) including fixed effects for baseline liver fat content (%) as a continuous linear covariate, and treatment, presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3], visit, treatment by visit interaction and baseline by visit interaction as factors.

Comparison groups	Survodutide 2.4 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	other[49]
P-value	< 0.0001 [50]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-8.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.59
upper limit	-6.6

Notes:

[49] - No confirmatory hypothesis testing was performed.
The number of subjects in this analysis included all the subjects for an MMRM analysis, in which all subjects contribute to variability and covariance matrix estimates, even if not part of the pairwise comparison being presented, i.e.,252 subjects.
Mean Difference (Net) was calculated as: Least Squares Mean of "Survodutide 2.4 mg"- Least Squares Mean of "Placebo".

[50] - The p−value reported is considered nominal.

Statistical analysis title	MMRM - 6.0 mg Survodutide vs. Placebo

Statistical analysis description:

Least Squares Mean differences and 95% confidence interval were calculated from mixed-effect model for repeated measures (MMRM) including fixed effects for baseline liver fat content (%) as a continuous linear covariate, and treatment, presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3], visit, treatment by visit interaction and baseline by visit interaction as factors.

Comparison groups	Survodutide 6.0 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other[51]
P-value	< 0.0001 [52]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-11.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13.23
upper limit	-8.92

Notes:

[51] - No confirmatory hypothesis testing was performed.

The number of subjects in this analysis included all the subjects for an MMRM analysis, in which all subjects contribute to variability and covariance matrix estimates, even if not part of the pairwise comparison being presented, i.e.,252 subjects.
Mean Difference (Net) was calculated as: Least Squares Mean of "Survodutide 6.0 mg"- Least Squares Mean of "Placebo".

[52] - The p−value reported is considered nominal.

Statistical analysis title	MMRM - 4.8 mg Survodutide vs. Placebo

Statistical analysis description:

Least Squares Mean differences and 95% confidence interval were calculated from mixed-effect model for repeated measures (MMRM) including fixed effects for baseline liver fat content (%) as a continuous linear covariate, and treatment, presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3], visit, treatment by visit interaction and baseline by visit interaction as factors.

Comparison groups	Survodutide 4.8 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other[53]
P-value	< 0.0001 [54]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-10.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.96
upper limit	-8.86

Notes:

[53] - No confirmatory hypothesis testing was performed.
The number of subjects in this analysis included all the subjects for an MMRM analysis, in which all subjects contribute to variability and covariance matrix estimates, even if not part of the pairwise comparison being presented, i.e.,252 subjects.
Mean Difference (Net) was calculated as: Least Squares Mean of "Survodutide 4.8 mg"- Least Squares Mean of "Placebo".

[54] - The p−value reported is considered nominal.

Secondary: Absolute change of liver fat content from baseline after 48 weeks of treatment assessed by MRI-PDFF - planned maintenance treatment

End point title	Absolute change of liver fat content from baseline after 48 weeks of treatment assessed by MRI-PDFF - planned maintenance treatment

End point description:

Absolute change of liver fat content from baseline after 48 weeks of treatment is reported. Liver fat content was assessed by Magnetic Resonance Imaging - Proton Density Fat Fraction (MRI-PDFF). Least Squares Mean (Standard error) were calculated from mixed-effect model for repeated measures (MMRM) including fixed effects for baseline liver fat content (%) as a continuous linear covariate, and treatment, presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3], visit, treatment by visit interaction and baseline by visit interaction as factors.
Patients are analyzed for this endpoint according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose. Number of patients analyzed reflects the number of patients included in the analysis model.

End point type	Secondary

End point timeframe:

MMRM included measurements from baseline and at Week 28 and at Week 48 after first drug administration. MMRM estimates of absolute change from baseline to Week 48 is reported.

End point values	Survodutide 2.4 mg - planned maintenance treatment	Survodutide 4.8 mg - planned maintenance treatment	Survodutide 6.0 mg - planned maintenance treatment	Placebo - planned maintenance treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61	64	58	69
Units: percentage of liver fat content				
least squares mean (confidence interval 95%)	-10.73 (-12.25 to -9.22)	-12.40 (-13.90 to -10.91)	-12.48 (-14.06 to -10.89)	-1.61 (-3.04 to -0.19)

Statistical analyses

Statistical analysis title	MMRM - 2.4 mg Survodutide vs. Placebo

Statistical analysis description:

Least Squares Mean differences and 95% confidence interval were calculated from mixed-effect model for repeated measures (MMRM) including fixed effects for baseline liver fat content (%) as a continuous linear covariate, and treatment, presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3], visit, treatment by visit interaction and baseline by visit interaction as factors.

Comparison groups	Survodutide 2.4 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other[55]
P-value	< 0.0001 [56]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-9.12

Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.21
upper limit	-7.03

Notes:

[55] - No confirmatory hypothesis testing was performed.

The number of subjects "in this analysis" included all the subjects for an MMRM analysis, in which all subjects contribute to variability and covariance matrix estimates, even if not part of the pairwise comparison being presented, i.e.,252 subjects.
Mean Difference (Net) was calculated as: Least Squares Mean of "Survodutide 2.4 mg"- Least Squares Mean of "Placebo".
[56] - The p−value reported is considered nominal.

Statistical analysis title	MMRM - 6.0 mg Survodutide vs. Placebo

Statistical analysis description:

Least Squares Mean differences and 95% confidence interval were calculated from mixed-effect model for repeated measures (MMRM) including fixed effects for baseline liver fat content (%) as a continuous linear covariate, and treatment, presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3], visit, treatment by visit interaction and baseline by visit interaction as factors.

Comparison groups	Survodutide 6.0 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	other[57]
P-value	< 0.0001 [58]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-10.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-13
upper limit	-8.73

Notes:

[57] - No confirmatory hypothesis testing was performed.

The number of subjects "in this analysis" included all the subjects for an MMRM analysis, in which all subjects contribute to variability and covariance matrix estimates, even if not part of the pairwise comparison being presented, i.e.,252 subjects.
Mean Difference (Net) was calculated as: Least Squares Mean of "Survodutide 6.0 mg"- Least Squares Mean of "Placebo".
[58] - The p−value reported is considered nominal.

Statistical analysis title	MMRM - 4.8 mg Survodutide vs. Placebo

Statistical analysis description:

Least Squares Mean differences and 95% confidence interval were calculated from mixed-effect model for repeated measures (MMRM) including fixed effects for baseline liver fat content (%) as a continuous linear covariate, and treatment, presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3], visit, treatment by visit interaction and baseline by visit interaction as factors.

Comparison groups	Survodutide 4.8 mg - planned maintenance treatment v Placebo - planned maintenance treatment

Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other[59]
P-value	< 0.0001 [60]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-10.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.85
upper limit	-8.73

Notes:

[59] - No confirmatory hypothesis testing was performed.

The number of subjects "in this analysis" included all the subjects for an MMRM analysis, in which all subjects contribute to variability and covariance matrix estimates, even if not part of the pairwise comparison being presented, i.e.,252 subjects.
Mean Difference (Net) was calculated as: Least Squares Mean of "Survodutide 4.8 mg"- Least Squares Mean of "Placebo".

[60] - The p−value reported is considered nominal.

Secondary: Percent change of liver fat content from baseline after 48 weeks of treatment assessed by MRI-PDFF - actual maintenance treatment

End point title	Percent change of liver fat content from baseline after 48 weeks of treatment assessed by MRI-PDFF - actual maintenance treatment

End point description:

Percent change of liver fat content (percentage [%]) from baseline after 48 weeks of treatment is reported. Liver fat content was assessed by Magnetic Resonance Imaging - Proton Density Fat Fraction (MRI-PDFF).
Least Squares Mean (Standard error) were calculated from mixed-effect model for repeated measures (MMRM) including fixed effects for baseline liver fat content (%) as a continuous linear covariate, and treatment, presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3], visit, treatment by visit interaction and baseline by visit interaction as factors.

Patients are analyzed according to the actual treatment they received at the start of the dose maintenance period (for patients who reached the maintenance period) or the next maintenance dose up from the dose at treatment discontinuation (for patients who discontinued treatment prior to the maintenance period). Number of patients analyzed reflects the number of patients included in the analysis model.

End point type	Secondary

End point timeframe:

MMRM included measurements from baseline and at Week 28 and at Week 48 after first drug administration. MMRM estimates of percent change from baseline to Week 48 is reported.

End point values	Survodutide 2.4 mg - actual maintenance treatment	Survodutide 4.8 mg - actual maintenance treatment	Survodutide 6.0 mg - actual maintenance treatment	Placebo - actual maintenance treatment
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	68	60	51	73
Units: percent change of liver fat content				
least squares mean (confidence interval 95%)	-50.92 (-58.05 to -43.80)	-62.79 (-70.26 to -55.32)	-64.30 (-72.48 to -56.12)	-7.28 (-14.06 to -0.50)

Statistical analyses

Statistical analysis title	MMRM - 2.4 mg Survodutide vs. Placebo

Statistical analysis description:

Least Squares Mean differences and 95% confidence interval were calculated from mixed-effect model for repeated measures (MMRM) including fixed effects for baseline liver fat content (%) as a continuous linear covariate, and treatment, presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3], visit, treatment by visit interaction and baseline by visit interaction as factors.

Comparison groups	Survodutide 2.4 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	other[61]
P-value	< 0.0001 [62]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-43.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	-53.49
upper limit	-33.79

Notes:

[61] - No confirmatory hypothesis testing was performed.

The number of subjects in this analysis included all the subjects for an MMRM analysis, in which all subjects contribute to variability and covariance matrix estimates, even if not part of the pairwise comparison being presented, i.e.,252 subjects.
Mean Difference (Net) was calculated as: Least Squares Mean of "Survodutide 2.4 mg"- Least Squares Mean of "Placebo".
[62] - The p−value reported is considered nominal.

Statistical analysis title	MMRM - 4.8 mg Survodutide vs. Placebo

Statistical analysis description:

Least Squares Mean differences and 95% confidence interval were calculated from mixed-effect model for repeated measures (MMRM) including fixed effects for baseline liver fat content (%) as a continuous linear covariate, and treatment, presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3], visit, treatment by visit interaction and baseline by visit interaction as factors.

Comparison groups	Survodutide 4.8 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other[63]
P-value	< 0.0001 [64]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-55.52

Confidence interval	
level	95 %
sides	2-sided
lower limit	-65.61
upper limit	-45.42

Notes:

[63] - No confirmatory hypothesis testing was performed.

The number of subjects in this analysis included all the subjects for an MMRM analysis, in which all subjects contribute to variability and covariance matrix estimates, even if not part of the pairwise comparison being presented, i.e.,252 subjects.
Mean Difference (Net) was calculated as: Least Squares Mean of "Survodutide 4.8 mg"- Least Squares Mean of "Placebo".
[64] - The p−value reported is considered nominal.

Statistical analysis title	MMRM - 6.0 mg Survodutide vs. Placebo

Statistical analysis description:

Least Squares Mean differences and 95% confidence interval were calculated from mixed-effect model for repeated measures (MMRM) including fixed effects for baseline liver fat content (%) as a continuous linear covariate, and treatment, presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3], visit, treatment by visit interaction and baseline by visit interaction as factors.

Comparison groups	Survodutide 6.0 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	124
Analysis specification	Pre-specified
Analysis type	other[65]
P-value	< 0.0001 [66]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-57.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-67.66
upper limit	-46.39

Notes:

[65] - No confirmatory hypothesis testing was performed.

The number of subjects in this analysis included all the subjects for an MMRM analysis, in which all subjects contribute to variability and covariance matrix estimates, even if not part of the pairwise comparison being presented, i.e.,252 subjects.
Mean Difference (Net) was calculated as: Least Squares Mean of "Survodutide 6.0 mg"- Least Squares Mean of "Placebo".
[66] - The p−value reported is considered nominal.

Secondary: Percent change of liver fat content from baseline after 48 weeks of treatment assessed by MRI-PDFF - planned maintenance treatment

End point title	Percent change of liver fat content from baseline after 48 weeks of treatment assessed by MRI-PDFF - planned maintenance treatment

End point description:

Percent change of liver fat content (percentage [%]) from baseline after 48 weeks of treatment is reported. Liver fat content was assessed by Magnetic Resonance Imaging - Proton Density Fat Fraction (MRI-PDFF).
Least Squares Mean (Standard error) were calculated from mixed-effect model for repeated measures (MMRM) including fixed effects for baseline liver fat content (%) as a continuous linear covariate, and treatment, presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3], visit, treatment by visit interaction and baseline by visit interaction as factors.
Patients are analyzed for this endpoint according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at

all, and therefore did not "settle" on any maintenance dose. Only patients which were included in the analysis model of this endpoint are reported.

End point type	Secondary

End point timeframe:

MMRM included measurements from baseline and at Week 28 and at Week 48 after first drug administration. MMRM estimates of percent change from baseline to Week 48 is reported.

End point values	Survodutide 2.4 mg - planned maintenance treatment	Survodutide 4.8 mg - planned maintenance treatment	Survodutide 6.0 mg - planned maintenance treatment	Placebo - planned maintenance treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	61	64	58	69
Units: percent change of liver fat content				
least squares mean (confidence interval 95%)	-52.20 (-59.66 to -44.75)	-60.82 (-68.16 to -53.48)	-61.97 (-69.78 to -54.16)	-5.71 (-12.70 to 1.28)

Statistical analyses

Statistical analysis title	MMRM - 2.4 mg Survodutide vs. Placebo

Statistical analysis description:

Least Squares Mean differences and 95% confidence interval were calculated from mixed-effect model for repeated measures (MMRM) including fixed effects for baseline liver fat content (%) as a continuous linear covariate, and treatment, presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3], visit, treatment by visit interaction and baseline by visit interaction as factors.

Comparison groups	Survodutide 2.4 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other[67]
P-value	< 0.0001 [68]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-46.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-56.74
upper limit	-36.25

Notes:

[67] - No confirmatory hypothesis testing was performed.

The number of subjects in this analysis included all the subjects for an MMRM analysis, in which all subjects contribute to variability and covariance matrix estimates, even if not part of the pairwise comparison being presented, i.e.,252 subjects.
Mean Difference (Net) was calculated as: Least Squares Mean of "Survodutide 2.4 mg"- Least Squares Mean of "Placebo".

[68] - The p−value reported is considered nominal.

Statistical analysis title	MMRM - 4.8 mg Survodutide vs. Placebo

Statistical analysis description:

Least Squares Mean differences and 95% confidence interval were calculated from mixed-effect model for repeated measures (MMRM) including fixed effects for baseline liver fat content (%) as a continuous linear covariate, and treatment, presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3], visit, treatment by visit interaction and baseline by visit interaction as factors.

Comparison groups	Survodutide 4.8 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	other[69]
P-value	< 0.0001 [70]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-55.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	-65.25
upper limit	-44.98

Notes:

[69] - No confirmatory hypothesis testing was performed.
The number of subjects in this analysis included all the subjects for an MMRM analysis, in which all subjects contribute to variability and covariance matrix estimates, even if not part of the pairwise comparison being presented, i.e.,252 subjects.
Mean Difference (Net) was calculated as: Least Squares Mean of "Survodutide 4.8 mg"- Least Squares Mean of "Placebo".
[70] - The p−value reported is considered nominal.

Statistical analysis title	MMRM - 6.0 mg Survodutide vs. Placebo

Statistical analysis description:

Least Squares Mean differences and 95% confidence interval were calculated from mixed-effect model for repeated measures (MMRM) including fixed effects for baseline liver fat content (%) as a continuous linear covariate, and treatment, presence of diabetes of any type [yes, no], baseline fibrosis score [F1, F2, F3], visit, treatment by visit interaction and baseline by visit interaction as factors.

Comparison groups	Survodutide 6.0 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	other[71]
P-value	< 0.0001 [72]
Method	MMRM
Parameter estimate	Mean difference (net)
Point estimate	-56.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	-66.76
upper limit	-45.77

Notes:

[71] - No confirmatory hypothesis testing was performed.
The number of subjects in this analysis included all the subjects for an MMRM analysis, in which all subjects contribute to variability and covariance matrix estimates, even if not part of the pairwise comparison being presented, i.e.,252 subjects.
Mean Difference (Net) was calculated as: Least Squares Mean of "Survodutide 6.0 mg"- Least Squares Mean of "Placebo".
[72] - The p−value reported is considered nominal.

Secondary: Improvement of fibrosis (yes/ no) defined as at least one stage decrease in fibrosis stage after 48 weeks of treatment assessed by liver biopsy - actual maintenance treatment

End point title	Improvement of fibrosis (yes/ no) defined as at least one stage decrease in fibrosis stage after 48 weeks of treatment assessed by liver biopsy - actual maintenance treatment

End point description:

Percentage of participants with improvement of liver fibrosis is reported.
Improvement of fibrosis was defined as at least one stage decrease in fibrosis stage after 48 weeks of treatment assessed by liver biopsy.
The total score for the fibrosis stage ranges from 0 to 4 with higher score indication worsening of the disease and the stages of fibrosis based on their location are the following:

- 1A Zone 3, perisinusoidal, delicate;
- 1B Zone 3, perisinuosoidal, dense;
- 1C Portal, periportal only;
- 2 Zone 3, perisinusoidal + portal, periportal only;
- 3 Bridging fibrosis;
- 4 Cirrhosis.

For analysis purposes no distinction was made between stages 1A, 1B and 1C.

Patients are analyzed according to the actual treatment they received at the start of the dose maintenance period (for patients who reached the maintenance period) or the next maintenance dose up from the dose at treatment discontinuation (for patients who discontinued treatment prior to the maintenance period).

End point type	Secondary

End point timeframe:

At baseline and after 48 weeks of treatment.

End point values	Survodutide 2.4 mg - actual maintenance treatment	Survodutide 4.8 mg - actual maintenance treatment	Survodutide 6.0 mg - actual maintenance treatment	Placebo - actual maintenance treatment
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	93	69	52	79
Units: Percentage of participants				
number (not applicable)	30.1	34.8	44.2	21.5

Statistical analyses

Statistical analysis title	Logistic regression-2.4 mg Survodutide vs. Placebo

Statistical analysis description:

The logistic regression model included actual treatment, presence of diabetes of any type and baseline fibrosis score. Firth‘s penalized regression was used.
The logistic regression model included all 293 treated subjects, not just those allocated to the two compared treatment groups.

Comparison groups	Survodutide 2.4 mg - actual maintenance treatment v Placebo - actual maintenance treatment

Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	other[73]
P-value	= 0.1894 [74]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.79
upper limit	3.26

Notes:

[73] - No confirmatory hypothesis testing was performed.
Odds Ratio of "Survodutide 2.4 mg" vs. "Placebo".
[74] - The p−value reported is considered nominal.

Statistical analysis title	Logistic regression-6.0 mg Survodutide vs. Placebo

Statistical analysis description:

The logistic regression model included actual treatment, presence of diabetes of any type and baseline fibrosis score. Firth‘s penalized regression was used.
The logistic regression model included all 293 treated subjects, not just those allocated to the two compared treatment groups.

Comparison groups	Survodutide 6.0 mg - actual maintenance treatment v Placebo - actual maintenance treatment
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	other[75]
P-value	= 0.0028 [76]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.52
upper limit	7.45

Notes:

[75] - No confirmatory hypothesis testing was performed.
Odds Ratio of "Survodutide 6.0 mg" vs. "Placebo".
[76] - The p−value reported is considered nominal.

Statistical analysis title	Logistic regression-4.8 mg Survodutide vs. Placebo

Statistical analysis description:

The logistic regression model included actual treatment, presence of diabetes of any type and baseline fibrosis score. Firth‘s penalized regression was used.
The logistic regression model included all 293 treated subjects, not just those allocated to the two compared treatment groups.

Comparison groups	Survodutide 4.8 mg - actual maintenance treatment v Placebo - actual maintenance treatment

Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	other[77]
P-value	= 0.0685 [78]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	4.2

Notes:

[77] - No confirmatory hypothesis testing was performed.
Odds Ratio of "Survodutide 4.8 mg" vs. "Placebo".
[78] - The p−value reported is considered nominal.

Secondary: Improvement of fibrosis (yes/ no) defined as at least one stage decrease in fibrosis stage after 48 weeks of treatment assessed by liver biopsy - planned maintenance treatment

End point title	Improvement of fibrosis (yes/ no) defined as at least one stage decrease in fibrosis stage after 48 weeks of treatment assessed by liver biopsy - planned maintenance treatment

End point description:

Percentage of participants with improvement of liver fibrosis is reported.
Improvement of fibrosis was defined as at least one stage decrease in fibrosis stage after 48 weeks of treatment assessed by liver biopsy.
The total score for the fibrosis stage ranges from 0 to 4 with higher score indication worsening of the disease and the stages of fibrosis based on their location are the following:

- 1A Zone 3, perisinusoidal, delicate;
- 1B Zone 3, perisinuosoidal, dense;
- 1C Portal, periportal only;
- 2 Zone 3, perisinusoidal + portal, periportal only;
- 3 Bridging fibrosis;
- 4 Cirrhosis.

For analysis purposes no distinction was made between stages 1A, 1B and 1C.

Patients are analyzed for this endpoint according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.

End point type	Secondary

End point timeframe:

At baseline and after 48 weeks of treatment.

End point values	Survodutide 2.4 mg - planned maintenance treatment	Survodutide 4.8 mg - planned maintenance treatment	Survodutide 6.0 mg - planned maintenance treatment	Placebo - planned maintenance treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	73	72	74	74
Units: Percentage of participants				
number (not applicable)	34.2	36.1	33.8	21.6

Statistical analyses

Statistical analysis title	Logistic regression-2.4 mg Survodutide vs. Placebo

Statistical analysis description:

The logistic regression model included planned treatment, presence of diabetes of any type and baseline fibrosis score. Firth‘s penalized regression was used.
The logistic regression model included all 293 treated subjects, not just those allocated to the two compared treatment groups.

Comparison groups	Survodutide 2.4 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[79]
P-value	= 0.0663 [80]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	4.27

Notes:

[79] - No confirmatory hypothesis testing was performed.
Odds Ratio of "Survodutide 2.4 mg" vs. "Placebo".
[80] - The p−value reported is considered nominal.

Statistical analysis title	Logistic regression-4.8 mg Survodutide vs. Placebo

Statistical analysis description:

The logistic regression model included planned treatment, presence of diabetes of any type and baseline fibrosis score. Firth‘s penalized regression was used.
The logistic regression model included all 293 treated subjects, not just those allocated to the two compared treatment groups.

Comparison groups	Survodutide 4.8 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	other[81]
P-value	= 0.0672 [82]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	4.23

Notes:

[81] - No confirmatory hypothesis testing was performed.
Odds Ratio of "Survodutide 4.8 mg" vs. "Placebo".
[82] - The p−value reported is considered nominal.

Statistical analysis title	Logistic regression-6.0 mg Survodutide vs. Placebo

Statistical analysis description:

The logistic regression model included planned treatment, presence of diabetes of any type and baseline fibrosis score. Firth‘s penalized regression was used.
The logistic regression model included all 293 treated subjects, not just those allocated to the two compared treatment groups.

Comparison groups	Survodutide 6.0 mg - planned maintenance treatment v Placebo - planned maintenance treatment
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	other[83]
P-value	= 0.0512 [84]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.11
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	4.46

Notes:

[83] - No confirmatory hypothesis testing was performed.
Odds Ratio of "Survodutide 6.0 mg" vs. "Placebo".
[84] - The p−value reported is considered nominal.

Secondary: Absolute change from baseline in NAS after 48 weeks of treatment assessed by liver biopsy - actual maintenance treatment

End point title	Absolute change from baseline in NAS after 48 weeks of treatment assessed by liver biopsy - actual maintenance treatment

End point description:

Absolute change from baseline in NAS after 48 weeks of treatment assessed by liver biopsy is reported. The non-alcoholic fatty liver disease (NAFLD) activity score (NAS) represents the sum of subscores for steatosis (scored from 0-3), lobular inflammation (scored from 0-3) and ballooning (scored from 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease.

Patients are analyzed according to the actual treatment they received at the start of the dose maintenance period (for patients who reached the maintenance period) or the next maintenance dose up from the dose at treatment discontinuation (for patients who discontinued treatment prior to the maintenance period). Number of patients analyzed reflects the number of patients included in the analysis model.

End point type	Secondary

End point timeframe:

At baseline and 48 weeks of treatment.

End point values	Survodutide 2.4 mg - actual maintenance treatment	Survodutide 4.8 mg - actual maintenance treatment	Survodutide 6.0 mg - actual maintenance treatment	Placebo - actual maintenance treatment
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	56	53	44	66
Units: units on a scale				
arithmetic mean (standard deviation)	-2.8 (± 1.8)	-3.2 (± 1.8)	-3.3 (± 2.0)	-0.4 (± 1.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Absolute change from baseline in NAS after 48 weeks of treatment assessed by liver biopsy - planned maintenance treatment

End point title	Absolute change from baseline in NAS after 48 weeks of treatment assessed by liver biopsy - planned maintenance treatment

End point description:

Absolute change from baseline in NAS after 48 weeks of treatment assessed by liver biopsy is reported. The non-alcoholic fatty liver disease (NAFLD) activity score (NAS) represents the sum of subscores for steatosis (scored from 0-3), lobular inflammation (scored from 0-3) and ballooning (scored from 0-2), and the total score ranges from 0 to 8 with higher scores representing worsening of the disease.
Patients are analyzed for this endpoint according to the planned treatment (planned maintenance dose strength) they were assigned at randomisation even if patients did not reach the maintenance period at all, and therefore did not "settle" on any maintenance dose.
Only patients with NAS at baseline and at 48 weeks after treatment are included in the analysis.

End point type	Secondary

End point timeframe:

At baseline and 48 weeks of treatment.

End point values	Survodutide 2.4 mg - planned maintenance treatment	Survodutide 4.8 mg - planned maintenance treatment	Survodutide 6.0 mg - planned maintenance treatment	Placebo - planned maintenance treatment
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	53	55	48	63
Units: units on a scale				
arithmetic mean (standard deviation)	-2.8 (± 1.8)	-3.2 (± 1.8)	-3.3 (± 1.9)	-0.2 (± 1.5)

Statistical analyses

No statistical analyses for this end point

Adverse events information

Timeframe for reporting adverse events:

[All-Cause Mortality], [Serious Adverse Events], [Other Adverse Events]: From first study drug administration until last study drug administration plus 28 days of residual effect period (REP), up to 365 days.

Adverse event reporting additional description:

Adverse events are reported according to the actual treatment the patents received at the start of the dose maintenance phase (for patients who reached the maintenance period) or the next maintenance dose up from the dose at treatment discontinuation (for patients who discontinued treatment prior to the maintenance period).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Survodutide 2.4 mg - actual maintenance treatment

Reporting group description:

This arm includes patients who were treated with 2.4 mg of survodutide administered weekly at the start of the maintenance period, for patients who reached the maintenance period, regardless of whether this was the randomised (planned) dose or not, and regardless of whether the patient stayed on that dose throughout the maintenance period.
This arm includes also those patients for whom the next maintenance dose up from the dose at treatment discontinuation was 2.4 mg of survodutide administered weekly, for patients who discontinued treatment prior to the maintenance period, regardless of the reason for the treatment discontinuation.

Reporting group title	Placebo

Reporting group description:

This arm includes patients who were treated with placebo matching survodutide administered weekly at the start of the maintenance period, for patients who reached the maintenance period, regardless of whether this was the randomised (planned) dose or not, and regardless of whether the patient stayed on that dose throughout the maintenance period.
This arm includes also those patients who were receiving placebo matching survodutide administered weekly and who discontinued treatment prior to the maintenance period, regardless of the reason for the treatment discontinuation.

Reporting group title	Survodutide 6.0 mg - actual maintenance treatment

Reporting group description:

This arm includes patients who were treated with 6.0 mg of survodutide administered weekly at the start of the maintenance period, for patients who reached the maintenance period, regardless of whether this was the randomised (planned) dose or not, and regardless of whether the patient stayed on that dose throughout the maintenance period.
This arm includes also those patients for whom the next maintenance dose up from the dose at treatment discontinuation was 6.0 mg of survodutide administered weekly, for patients who discontinued treatment prior to the maintenance period, regardless of the reason for the treatment discontinuation.

Reporting group title	Survodutide 4.8 mg - actual maintenance treatment

Reporting group description:

This arm includes patients who were treated with 4.8 mg of survodutide administered weekly at the start of the maintenance period, for patients who reached the maintenance period, regardless of whether this was the randomised (planned) dose or not, and regardless of whether the patient stayed on that dose throughout the maintenance period.
This arm includes also those patients for whom the next maintenance dose up from the dose at treatment discontinuation was 4.8 mg of survodutide administered weekly, for patients who discontinued treatment prior to the maintenance period, regardless of the reason for the treatment discontinuation.

Serious adverse events	Survodutide 2.4 mg - actual maintenance treatment	Placebo	Survodutide 6.0 mg - actual maintenance treatment
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 93 (5.38%)	5 / 79 (6.33%)	5 / 52 (9.62%)
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)			
Squamous cell carcinoma			
subjects affected / exposed	0 / 93 (0.00%)	0 / 79 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 93 (0.00%)	1 / 79 (1.27%)	0 / 52 (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
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 79 (0.00%)	0 / 52 (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
General disorders and administration site conditions			
Puncture site pain			
subjects affected / exposed	0 / 93 (0.00%)	1 / 79 (1.27%)	0 / 52 (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
Reproductive system and breast disorders			
Abnormal uterine bleeding			
subjects affected / exposed	1 / 93 (1.08%)	0 / 79 (0.00%)	0 / 52 (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
Respiratory, thoracic and mediastinal disorders			
Combined pulmonary fibrosis and emphysema			

subjects affected / exposed	1 / 93 (1.08%)	0 / 79 (0.00%)	0 / 52 (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
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 93 (0.00%)	1 / 79 (1.27%)	0 / 52 (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
Investigations			
Amylase increased			
subjects affected / exposed	0 / 93 (0.00%)	0 / 79 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	0 / 93 (0.00%)	0 / 79 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 93 (0.00%)	0 / 79 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lipase increased			
subjects affected / exposed	0 / 93 (0.00%)	0 / 79 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Post procedural haemorrhage			
subjects affected / exposed	0 / 93 (0.00%)	0 / 79 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 93 (0.00%)	0 / 79 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 93 (0.00%)	0 / 79 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 93 (1.08%)	0 / 79 (0.00%)	0 / 52 (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
Cerebral infarction			
subjects affected / exposed	1 / 93 (1.08%)	0 / 79 (0.00%)	0 / 52 (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
Intracranial aneurysm			
subjects affected / exposed	1 / 93 (1.08%)	0 / 79 (0.00%)	0 / 52 (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
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	0 / 93 (0.00%)	0 / 79 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Blindness transient			
subjects affected / exposed	0 / 93 (0.00%)	0 / 79 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Intestinal polyp			
subjects affected / exposed	0 / 93 (0.00%)	1 / 79 (1.27%)	0 / 52 (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
Enteritis			

subjects affected / exposed	1 / 93 (1.08%)	0 / 79 (0.00%)	0 / 52 (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			
Hepatic cirrhosis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 79 (1.27%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 79 (0.00%)	2 / 52 (3.85%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 79 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 93 (0.00%)	1 / 79 (1.27%)	0 / 52 (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
Angioedema			
subjects affected / exposed	1 / 93 (1.08%)	0 / 79 (0.00%)	0 / 52 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 93 (0.00%)	0 / 79 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	1 / 93 (1.08%)	0 / 79 (0.00%)	0 / 52 (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	1 / 93 (1.08%)	0 / 79 (0.00%)	0 / 52 (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
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 93 (0.00%)	1 / 79 (1.27%)	0 / 52 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 93 (0.00%)	0 / 79 (0.00%)	1 / 52 (1.92%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Survodutide 4.8 mg - actual maintenance treatment		
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 69 (10.14%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertensive crisis			

subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Puncture site pain			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Abnormal uterine bleeding			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Combined pulmonary fibrosis and emphysema			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Investigations			
Amylase increased			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood creatinine increased			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Glomerular filtration rate decreased			

subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lipase increased				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Post procedural haemorrhage				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Spinal compression fracture				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	1 / 69 (1.45%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Carotid artery stenosis				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cerebral infarction				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Intracranial aneurysm				
subjects affected / exposed	0 / 69 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Blindness transient			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Intestinal polyp			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Hepatic cirrhosis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholecystitis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Pruritus			

subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Angioedema			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute kidney injury			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Lumbar spinal stenosis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Survodutide 2.4 mg - actual maintenance treatment	Placebo	Survodutide 6.0 mg - actual maintenance treatment
Total subjects affected by non-serious adverse events			
subjects affected / exposed	85 / 93 (91.40%)	68 / 79 (86.08%)	49 / 52 (94.23%)
Investigations			
Lipase increased			
subjects affected / exposed	5 / 93 (5.38%)	0 / 79 (0.00%)	1 / 52 (1.92%)
occurrences (all)	7	0	1
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	0 / 93 (0.00%)	5 / 79 (6.33%)	1 / 52 (1.92%)
occurrences (all)	0	5	1
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 93 (22.58%)	13 / 79 (16.46%)	6 / 52 (11.54%)
occurrences (all)	60	25	13
Dizziness			
subjects affected / exposed	11 / 93 (11.83%)	6 / 79 (7.59%)	3 / 52 (5.77%)
occurrences (all)	17	9	4
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 93 (1.08%)	5 / 79 (6.33%)	1 / 52 (1.92%)
occurrences (all)	1	5	1
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	3 / 93 (3.23%)	5 / 79 (6.33%)	1 / 52 (1.92%)
occurrences (all)	18	17	2
Asthenia			
subjects affected / exposed	5 / 93 (5.38%)	1 / 79 (1.27%)	2 / 52 (3.85%)
occurrences (all)	6	1	2
Early satiety			
subjects affected / exposed	2 / 93 (2.15%)	1 / 79 (1.27%)	6 / 52 (11.54%)
occurrences (all)	2	1	7
Fatigue			
subjects affected / exposed	18 / 93 (19.35%)	7 / 79 (8.86%)	8 / 52 (15.38%)
occurrences (all)	56	12	12
Injection site bruising			

subjects affected / exposed	3 / 93 (3.23%)	6 / 79 (7.59%)	1 / 52 (1.92%)
occurrences (all)	4	21	5
Injection site pain			
subjects affected / exposed	3 / 93 (3.23%)	6 / 79 (7.59%)	0 / 52 (0.00%)
occurrences (all)	32	10	0
Pyrexia			
subjects affected / exposed	4 / 93 (4.30%)	5 / 79 (6.33%)	2 / 52 (3.85%)
occurrences (all)	5	5	2
Malaise			
subjects affected / exposed	2 / 93 (2.15%)	0 / 79 (0.00%)	5 / 52 (9.62%)
occurrences (all)	2	0	7
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	15 / 93 (16.13%)	7 / 79 (8.86%)	9 / 52 (17.31%)
occurrences (all)	34	8	24
Abdominal pain upper			
subjects affected / exposed	7 / 93 (7.53%)	4 / 79 (5.06%)	1 / 52 (1.92%)
occurrences (all)	13	6	4
Abdominal pain			
subjects affected / exposed	12 / 93 (12.90%)	4 / 79 (5.06%)	5 / 52 (9.62%)
occurrences (all)	15	4	5
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 93 (8.60%)	5 / 79 (6.33%)	3 / 52 (5.77%)
occurrences (all)	9	6	3
Nausea			
subjects affected / exposed	60 / 93 (64.52%)	22 / 79 (27.85%)	33 / 52 (63.46%)
occurrences (all)	225	103	175
Vomiting			
subjects affected / exposed	38 / 93 (40.86%)	6 / 79 (7.59%)	15 / 52 (28.85%)
occurrences (all)	99	16	82
Eructation			
subjects affected / exposed	12 / 93 (12.90%)	2 / 79 (2.53%)	8 / 52 (15.38%)
occurrences (all)	25	3	12
Dyspepsia			
subjects affected / exposed	14 / 93 (15.05%)	3 / 79 (3.80%)	11 / 52 (21.15%)
occurrences (all)	23	9	23

Diarrhoea			
subjects affected / exposed	38 / 93 (40.86%)	20 / 79 (25.32%)	29 / 52 (55.77%)
occurrences (all)	133	61	97
Constipation			
subjects affected / exposed	16 / 93 (17.20%)	14 / 79 (17.72%)	15 / 52 (28.85%)
occurrences (all)	27	21	29
Flatulence			
subjects affected / exposed	8 / 93 (8.60%)	4 / 79 (5.06%)	8 / 52 (15.38%)
occurrences (all)	23	6	14
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	5 / 93 (5.38%)	8 / 79 (10.13%)	2 / 52 (3.85%)
occurrences (all)	6	8	3
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 93 (1.08%)	3 / 79 (3.80%)	4 / 52 (7.69%)
occurrences (all)	1	3	5
Alopecia			
subjects affected / exposed	0 / 93 (0.00%)	0 / 79 (0.00%)	4 / 52 (7.69%)
occurrences (all)	0	0	4
Hyperhidrosis			
subjects affected / exposed	0 / 93 (0.00%)	4 / 79 (5.06%)	1 / 52 (1.92%)
occurrences (all)	0	4	1
Psychiatric disorders			
Insomnia			
subjects affected / exposed	2 / 93 (2.15%)	6 / 79 (7.59%)	0 / 52 (0.00%)
occurrences (all)	2	6	0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 93 (8.60%)	7 / 79 (8.86%)	7 / 52 (13.46%)
occurrences (all)	8	12	7
Arthralgia			
subjects affected / exposed	4 / 93 (4.30%)	12 / 79 (15.19%)	5 / 52 (9.62%)
occurrences (all)	4	15	7
Pain in extremity			

subjects affected / exposed	1 / 93 (1.08%)	5 / 79 (6.33%)	1 / 52 (1.92%)
occurrences (all)	1	6	1
Myalgia			
subjects affected / exposed	4 / 93 (4.30%)	5 / 79 (6.33%)	1 / 52 (1.92%)
occurrences (all)	4	6	1
Infections and infestations			
COVID-19			
subjects affected / exposed	19 / 93 (20.43%)	16 / 79 (20.25%)	5 / 52 (9.62%)
occurrences (all)	23	16	5
Urinary tract infection			
subjects affected / exposed	7 / 93 (7.53%)	5 / 79 (6.33%)	7 / 52 (13.46%)
occurrences (all)	8	9	8
Influenza			
subjects affected / exposed	2 / 93 (2.15%)	5 / 79 (6.33%)	2 / 52 (3.85%)
occurrences (all)	2	5	2
Nasopharyngitis			
subjects affected / exposed	6 / 93 (6.45%)	10 / 79 (12.66%)	4 / 52 (7.69%)
occurrences (all)	6	13	4
Sinusitis			
subjects affected / exposed	1 / 93 (1.08%)	5 / 79 (6.33%)	2 / 52 (3.85%)
occurrences (all)	1	5	3
Upper respiratory tract infection			
subjects affected / exposed	7 / 93 (7.53%)	3 / 79 (3.80%)	2 / 52 (3.85%)
occurrences (all)	10	4	3
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	7 / 93 (7.53%)	2 / 79 (2.53%)	1 / 52 (1.92%)
occurrences (all)	9	8	1
Hyperglycaemia			
subjects affected / exposed	1 / 93 (1.08%)	4 / 79 (5.06%)	0 / 52 (0.00%)
occurrences (all)	1	6	0
Decreased appetite			
subjects affected / exposed	20 / 93 (21.51%)	8 / 79 (10.13%)	8 / 52 (15.38%)
occurrences (all)	23	11	10

Non-serious adverse events	Survodutide 4.8 mg - actual maintenance		

	treatment		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 69 (86.96%)		
Investigations			
Lipase increased			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	10		
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	2		
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 69 (17.39%)		
occurrences (all)	22		
Dizziness			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	3		
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences (all)	5		
Asthenia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Early satiety			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	2		
Fatigue			
subjects affected / exposed	10 / 69 (14.49%)		
occurrences (all)	13		
Injection site bruising			

subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	3		
Injection site pain			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Pyrexia			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences (all)	5		
Malaise			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	10 / 69 (14.49%)		
occurrences (all)	29		
Abdominal pain upper			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	3		
Abdominal pain			
subjects affected / exposed	5 / 69 (7.25%)		
occurrences (all)	9		
Gastrooesophageal reflux disease			
subjects affected / exposed	7 / 69 (10.14%)		
occurrences (all)	13		
Nausea			
subjects affected / exposed	46 / 69 (66.67%)		
occurrences (all)	192		
Vomiting			
subjects affected / exposed	33 / 69 (47.83%)		
occurrences (all)	89		
Eructation			
subjects affected / exposed	9 / 69 (13.04%)		
occurrences (all)	35		
Dyspepsia			
subjects affected / exposed	6 / 69 (8.70%)		
occurrences (all)	10		

Diarrhoea subjects affected / exposed occurrences (all)	37 / 69 (53.62%) 170		
Constipation subjects affected / exposed occurrences (all)	12 / 69 (17.39%) 21		
Flatulence subjects affected / exposed occurrences (all)	6 / 69 (8.70%) 36		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	1 / 69 (1.45%) 1		
Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all)	3 / 69 (4.35%) 5		
Alopecia subjects affected / exposed occurrences (all)	1 / 69 (1.45%) 1		
Hyperhidrosis subjects affected / exposed occurrences (all)	0 / 69 (0.00%) 0		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	2 / 69 (2.90%) 2		
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	3 / 69 (4.35%) 4		
Arthralgia subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 13		
Pain in extremity			

subjects affected / exposed	3 / 69 (4.35%)		
occurrences (all)	3		
Myalgia			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences (all)	3		
Infections and infestations			
COVID-19			
subjects affected / exposed	15 / 69 (21.74%)		
occurrences (all)	16		
Urinary tract infection			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	2 / 69 (2.90%)		
occurrences (all)	2		
Nasopharyngitis			
subjects affected / exposed	12 / 69 (17.39%)		
occurrences (all)	13		
Sinusitis			
subjects affected / exposed	0 / 69 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	4 / 69 (5.80%)		
occurrences (all)	5		
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	3 / 69 (4.35%)		
occurrences (all)	4		
Hyperglycaemia			
subjects affected / exposed	1 / 69 (1.45%)		
occurrences (all)	1		
Decreased appetite			
subjects affected / exposed	9 / 69 (13.04%)		
occurrences (all)	10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2020	Global protocol amendment No. 1 - Part 1: Regular self-monitoring blood glucose (SMBG) measurements in type 2 diabetes mellitus (T2DM) patients on antidiabetic medication and safety measures in case of hypoglycaemic events were added at request from Health Authority. Dispensation of SMBG device was implemented as an additional safety measure. Unplanned data monitoring committee (DMC) meeting and unblinded safety assessment by DMC at the occurrence of adverse events that might lead to trial discontinuation were added at request from Health Authority regarding trial stopping criteria and process. Inclusion criterion body mass index (BMI) cut-off increased to 25 kg/m2 to homogenously include overweight patients of all ethnicities. The previous BMI cut-off included normal weight Caucasians or overweight Asians. Exclusion criteria modified: Estimated glomerular filtration rate (eGFR) cut-off increased to 60 mL/min/1.73m2 (at request from Health Authority). Exclusion of patients with history of organ transplantation except for corneal transplantation (at request from Health Authority). For patients with history of major depressive disorder in the past 2 years, the criterion "requiring inpatient treatment or escalation of care" was added for identification of patients with history of major depressive disorder.
18 December 2020	Global protocol amendment No. 1 - Part 2: Trial treatment discontinuation criteria modified: Occurrence of an adverse event (AE) Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 related to trial treatment added to the trial treatment discontinuation criteria for individual patients. Information regarding close monitoring and medical review of all AEs CTCAE Grade 3 and higher added as triggers for discontinuation of trial treatment for all patients. Minimum requirement for collection of liver biopsy specimen (i.e. size of biopsy needle, size of biopsy specimen) added to define the quality standards for an accurate histology evaluation Clarification added to exclude patients from sites in China for collection of blood samples for exploratory biomarkers, but Fib-4 index and aspartate amino transferase (AST) to platelet ratio index (APRI) were to be calculated. Guidelines for removal of individual patients in case of increased liver enzymes revised, and trial treatment discontinuation criteria defined for individual patients in the event of drug-induced liver injury, at request from Health Authority.

14 May 2021	Global protocol amendment No. 2: Cap for patients from sites in China removed: Definition of full analysis set amended to omit the reference to China. Sensitivity analysis of the primary endpoint including patients from sites in China removed. Description of interim analysis modified to include patients from sites in China. Screening period extended to 10 weeks, as central assessments might take longer than 8 weeks. Vital signs at Visit 1a became optional, as measurement at the primary site on the day of the screening biopsy might not be always possible. Requirement to perform imaging assessments at the same time of the day removed. Urine pregnancy test at Follow-Up Visit added, pregnancy test should be performed at the end of the relevant systemic exposure. Exclusion criteria modified: Fasting condition was no longer required for blood samples collection at any visit. However, serum triglycerides might be retested at fasting condition during screening if the levels at Visit 1 exceeded 500 mg/dL (5.65 mmol/L). Congestive heart failure New York Heart Association (NYHA) class III-IV added to align with trials using the same compound. Treatment discontinuation criteria modified: Torsade de Pointes and any major adverse cardiovascular events added at request from Health Authority. Clinically significant elevation of liver enzymes and tolerance issues added for completeness (this information was already mentioned in other sections). Information from toxicology studies relevant to selection of 6 mg dose added at request from Health Authority. Paper Instructions for Use, paper diary, and paper PRO questionnaires added as a backup solution in case electronic documents were not available. Option to conduct safety laboratory tests in local laboratories added to ensure trial continuity while maintaining patient safety in the event of disruptive circumstances.
24 May 2022	Global Protocol amendment No. 3 - Part 2: Sodium-Glucose Co-Transporter 2 (SGLT-2) inhibitors removed from the list of restricted concomitant medications, there are no clinical justifications for complete exclusion of T2DM patients treated with SGLT-2 inhibitors. Medications known to significantly prolong the QT/QTc interval added as restricted concomitant medications, to align with exclusion criterion #15. Requirement to repeat FibroScan® and MR imaging at re-screening removed, if the initial screening was performed within a month, to reduce burden for patients. Guidelines for removal of individual patients in case of increased liver enzymes revised, to align with the consensus guidelines including provisions for patients with Gilbert's syndrome. Note: upon submission of CTP version 4.0 dated 24 May 2022 Boehringer Ingelheim (BI) received advice from the FDA to: (1) implement non-invasive tests and/or imaging tools in non-cirrhotic subjects with low platelet count in order to exclude portal hypertension, and (2) exclude patients who recently started treatment with an SGLT-2 inhibitor. As the trial was in the final stage of recruitment and the implementation of additional tests and tools would require more time than the remaining time for recruitment, it was decided that clinical trial protocol (CTP) version 4.0 dated 24 May 2022 was not implemented.

24 May 2022	Global Protocol amendment No. 3 - Part 1: Inclusion criterion modified: liver biopsy findings should always be the primary assessment if histology and non-invasive assessments differed, as liver biopsy is more accurate in staging and grading NASH and liver fibrosis than FibroScan® and Magnetic Resonance Imaging - Proton Density Fat Fraction (MRI-PDFF). Screening period extended if logistical issues caused delays for results of liver biopsy from central vendor(s). Eligible patients could be considered for trial participation even if results were received more than 10 weeks after Visit 1 (ethical aspect). Exclusion criteria: eGFR cut-off modified to include patients with mild or moderate renal impairment, as recent findings indicated no safety concerns for these patients. Platelet count cut-off modified: liver cirrhosis was ruled out by histology, therefore patients without any sign of liver cirrhosis and a platelet count >110 x 10^9/L assumably have a non-significant risk of portal hypertension. Stopping rules of the trial modified: instead of stopping the trial treatment in all patients, enrolment of new patients was to be stopped pending DMC recommendation, as sudden stop and possible restart of the trial treatment in all patients might lead to drug tolerability issues in many patients. Criteria for Grade 3 CTCAE AEs of nausea, vomiting, diarrhoea, constipation, or anorexia specified: evaluation the CTCAE grading was put into a more clinically meaningful context to be considered for stopping enrolment of new patients and potentially stopping the trial following DMC recommendation.
04 August 2022	Global Protocol amendment No. 4: Platelet count cut-off changed back to the original level, as the trial was in the final stage of recruitment and implementation of alternative non-invasive tests and/or imaging tools for the exclusion of portal hypertension as requested by Health Authority would require more time than the remaining recruitment time. Patients recently started on SGLT-2 inhibitors excluded as recommended by Health Authority.
27 July 2023	Global Protocol amendment No. 5: Information on purpose of the interim analysis and access to unblinded data from the interim analysis modified, as data on liver fat reduction and liver benefits from this trial were essential for developing the Phase III program for Survodutide in chronic weight management.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported