Clinical trial results:
A single centre, pilot trial of YF476 in patients with chronic atrophic gastritis, hypergastrinaemia and type I gastric carcinoids

Summary

EudraCT number	2007-002916-24
Trial protocol	GB
Global end of trial date	25 February 2014

Results information

Result version number	v1 (current)
This version publication date	05 February 2021
First version publication date	05 February 2021
Summary attachment (see zip file)	07-504 SOTR (07-504 SOTR 03 Nov 2020.pdf)

Trial information

Trial identification

Sponsor protocol code	T-008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	HMR code: 07-504

Notes:

Sponsors

Sponsor organisation name	Trio Medicines Ltd
Sponsor organisation address	PO Box 53346, London, United Kingdom, NW10 7XU
Public contact	Dr Malcolm Boyce, Trio Medicines Ltd, +44 2089614130, mboyce@triomedicines.com
Scientific contact	Dr Malcolm Boyce, Trio Medicines Ltd, +44 2089614130, mboyce@triomedicines.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	25 February 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 February 2014
Global end of trial reached?	Yes
Global end of trial date	25 February 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary:
To assess if netazepide (YF476) is an effective medical treatment for type I gastric carcinoids.
Secondary:
To assess the tolerability and safety of netazepide (YF476); and
To assess the effect of netazepide (YF476) on plasma concentration and transcript profiles of biomarkers such as chromogranin A (CgA).

Protection of trial subjects:

Before the trial started, we did a risk assessment to identify and manage risks to the trial patients. We determined that the overall risk to the patients was negligible because:

1. netazepide has a good safety profile in non-clinical and clinical studies;
2. the expected netazepide exposure during the study was within the safe limits seen in non-clinical studies;
3. the safety testing and assessments were adequate based on our clinical experience of netazepide; and
4. any risks were adequately mitigated by safety assessments, and by the medical cover provided by the investigator site.

All study procedures and information given to the subjects were reviewed and approved by a research ethics committee. To minimise anxiety in the subjects and to ensure that they were fully informed about the trial, subjects were asked to read and sign an information and consent form (ICF). The ICF gave details:

1. about netazepide, including risks of taking it;
2. of inclusion and exclusion criteria;
3. of lifestyle restrictions and risks/disadvantages of taking part in the study;
4. of procedures during the study, including the amount of blood to be donated; and
5. about payment and clinical studies in general.

Background therapy:

There wasn't any background therapy.

Evidence for comparator:

No comparator was used.

Actual start date of recruitment	04 January 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 8
Worldwide total number of subjects	8
EEA total number of subjects	8

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)	3
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Screening started on 04 Jan 2011.

Pre-assignment

Screening details:

Patients, aged ≥ 18 years, deemed otherwise healthy based on medical history, physical findings, electrocardiogram (ECG) and laboratory values; that had gastric carcinoids associated with chronic atrophic gastritis (CAG) and hypergastrinaemia; who attended the outpatient clinic of the principal investigator; and could give fully-informed consent

Period 1

Period 1 title	Overall trial
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Overall enrollment and completion of all participants

Arm description:

The study was done over 12 visits: patients took a dose of netazepide (YF476) 50 mg by mouth, once daily at home, every day for 12 weeks (up to Visit 6). Patients didn't take netazepide (YF476) between Visits 6 and 8, for at least 23 weeks. Patients were then prescribed netazepide capsules at Visit 8, to take every day as before, for 52 more weeks until Visit 12. There was at least 3 weeks between each visit.

In the event, all participants attended all visits.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Overall dosing

Arm description:

The dosing and compliance of all participants in the study.

Arm type	Experimental
Investigational medicinal product name	netazepide
Investigational medicinal product code	YF476
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

At Visit 1, patients didn't receive netazepide, as they were being screened at this visit.

Between Visits 2-6, the patients took netazepide (YF476) 50 mg once daily with breakfast, apart from one patient, who accidently took 25 mg, instead of 50 mg, up until Visit 4. Patients stopped taking netazepide (YF476) between Visits 6 and 7, for 12 weeks.

Patients resumed taking netazepide (YF476) 50 mg at Visit 8, at least 23 weeks after Visit 7. Between Visits 8-12, patients took netazepide (YF476) 50 mg once daily with breakfast.

Number of subjects in period 1	Overall enrollment and completion of all participants	Overall dosing
Started	8	8
Completed	8	8

Period 2	
Period 2 title	netazepide (YF476)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	netazepide (YF476) 50 mg fed
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	netazepide 50 mg
Investigational medicinal product code	YF476
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Participants took an oral dose of netazepide (YF476) 50 mg, daily, with breakfast.

Number of subjects in period 2	netazepide (YF476) 50 mg fed
Started	8
Completed	8

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
All participants enrolled in the study.	

Reporting group values	Overall trial	Total	
Number of subjects	8	8	
Age categorical 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)	3	3	
From 65-84 years	5	5	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	65.6		
standard deviation	± 5.97	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	4	4	
Ethnicity Units: Subjects			
Asian/Indian	2	2	
Europid	6	6	
H. pylori status Units: Subjects			
Negative	8	8	
Height Units: cm			
arithmetic mean	167.4		
standard deviation	± 12.15	-	
Weight Units: kg			
arithmetic mean	87.84		
standard deviation	± 21.883	-	
Body mass index Units: kg/m^2			
arithmetic mean	31.09		
standard deviation	± 5.575	-	

End points

End points reporting groups

Reporting group title	Overall enrollment and completion of all participants

Reporting group description:

The study was done over 12 visits: patients took a dose of netazepide (YF476) 50 mg by mouth, once daily at home, every day for 12 weeks (up to Visit 6). Patients didn't take netazepide (YF476) between Visits 6 and 8, for at least 23 weeks. Patients were then prescribed netazepide capsules at Visit 8, to take every day as before, for 52 more weeks until Visit 12. There was at least 3 weeks between each visit.

In the event, all participants attended all visits.

Reporting group title	Overall dosing

Reporting group description:

The dosing and compliance of all participants in the study.

Reporting group title	netazepide (YF476) 50 mg fed

Reporting group description: -

Primary: Mean number of type 1 tumours

End point title	Mean number of type 1 tumours[1]

End point description:

At each gastroscopy a patient underwent, the number of tumours for that patient was counted.

End point type	Primary

End point timeframe:

Each patient's tumours were monitored throughout the study; patients underwent gastroscopy and gastric biopsies on Visits 2, 4, 6, 7, 8, 10 and 12.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not done.

End point values	netazepide (YF476) 50 mg fed			
Subject group type	Reporting group			
Number of subjects analysed	8[2]			
Units: tumours				
Screening	12			
Visit 4	9			
Visit 6	7			
Visit 7	7			
Visit 8	10			
Visit 10	8			
Visit 12	8			

Notes:

[2] - Except Visit 8, where n was 7.

Statistical analyses

No statistical analyses for this end point

Primary: Mean size of the largest tumour

End point title	Mean size of the largest tumour[3]

End point description:

The size of a patient's tumours was measured at each gastroscopy. A pair of standard biopsy forceps was used as an internal standard, for size correction between saved images of the tumours.

End point type	Primary

End point timeframe:

Each patient's tumours were monitored throughout the study; patients underwent gastroscopy and gastric biopsies on Visits 2, 4, 6, 7, 8, 10 and 12.

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not done.

End point values	netazepide (YF476) 50 mg fed			
Subject group type	Reporting group			
Number of subjects analysed	8[4]			
Units: mm				
number (not applicable)				
Screening	8.6			
Visit 4	6.5			
Visit 6	5.5			
Visit 7	5.1			
Visit 8	6.3			
Visit 10	3.6			
Visit 12	3.1			

Notes:

[4] - Except Visit 8, where n was 7.

Statistical analyses

No statistical analyses for this end point

Primary: Histology of tumour biopsies

End point title	Histology of tumour biopsies[5]

End point description:

Biopsies were taken at gastroscopy and were classified.

Histology classifications:
NET = neuroendocrine tumour
ECL-D = ECL-cell dysplasia
ECL-L = linear ECL-cell hyperplasia
ECL-M = micronodular ECL-cell hyperplasia

Note that these classifications are not mutually exclusive.

End point type	Primary

End point timeframe:

Each patient's tumours were monitored throughout the study; patients underwent gastroscopy and gastric biopsies on Visits 2, 4, 6, 7, 8, 10 and 12.

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analysis was not done.

End point values	netazepide (YF476) 50 mg fed			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Participants				
NET	7			
ECL-D	1			
ECL-L	1			
ECL-M	7			

Attachments (see zip file)	Histology of tumour biopsies/Histologytable.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Peak plasma concentrations of netazepide (YF476)

End point title	Peak plasma concentrations of netazepide (YF476)

End point description:

Nominal blood sampling times were used to calculate the median (range) and mean (SD) drug concentrations at each time point. Linear and semi-logarithmic plots of the mean (± standard error) concentration-time data was prepared.

End point type	Secondary

End point timeframe:

Blood samples were taken 1 hour after the patients took netazepide (YF476) 50 mg with breakfast, for assay of the peak concentration of netazepide (YF476). These samples were taken on Visits 3-6, and Visits 9-12.

End point values	netazepide (YF476) 50 mg fed			
Subject group type	Reporting group			
Number of subjects analysed	8[6]			
Units: ng/mL				
arithmetic mean (standard deviation)				
Visit 3	132.38 (± 183.5405)			
Visit 4	222.135 (± 193.1154)			
Visit 5	151.309 (± 214.4784)			
Visit 6	86.946 (± 97.4053)			
Visit 9	134.961 (± 168.6182)			
Visit 10	31.513 (± 29.4088)			
Visit 11	36.561 (± 62.7098)			

Visit 12	83.896 (± 163.9807)			

Notes:

[6] - Except Visits 9-11, where n was 7.

Statistical analyses

No statistical analyses for this end point

Secondary: Trough plasma concentrations of netazepide (YF476)

End point title	Trough plasma concentrations of netazepide (YF476)

End point description:

Nominal blood sampling times were used to calculate the median (range) and mean (SD) drug concentrations at each time point. Linear and semi-logarithmic plots of the mean (± standard error) concentration-time data was prepared.

End point type	Secondary

End point timeframe:

Blood samples were taken before the patients took netazepide (YF476) 50 mg with breakfast, for assay of the trough concentration of netazepide (YF476). These samples were taken on Visits 3-6, and Visits 9-12.

End point values	netazepide (YF476) 50 mg fed			
Subject group type	Reporting group			
Number of subjects analysed	8[7]			
Units: ng/mL				
arithmetic mean (standard deviation)				
Visit 3	4.608 (± 5.025)			
Visit 4	7.018 (± 4.385)			
Visit 5	6.086 (± 6.7024)			
Visit 6	5.883 (± 4.3778)			
Visit 9	3.278 (± 2.7984)			
Visit 10	2.248 (± 0.7157)			
Visit 11	4.696 (± 2.0603)			
Visit 12	2.174 (± 1.0326)			

Notes:

[7] - Except Visits 9, 11 and 12, where n was 5; and Visit 10, where n was 6.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma CgA concentrations

End point title	Plasma CgA concentrations

End point description:

Chromogranin A (CgA) is a biomarker of ECL-cell activity. Blood samples were taken to measure levels of CgA in the plasma.

End point type	Secondary

End point timeframe:

Blood samples were taken, after an overnight fast and before the patients took netazepide (YF476) 50 mg, for assay of concentrations of chromogranin A (CgA) in the plasma. These samples were taken on Visit 1 and Visits 3-12.

End point values	netazepide (YF476) 50 mg fed			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: IU/L				
arithmetic mean (standard deviation)				
Visit 1	63.16 (± 33.18)			
Visit 3	18.95 (± 10.583)			
Visit 4	22.41 (± 19.426)			
Visit 5	18.58 (± 11.683)			
Visit 6	19.6 (± 12.783)			
Visit 7	51.6 (± 24.2)			
Visit 8	45.34 (± 22.426)			
Visit 9	16.24 (± 8.003)			
Visit 10	16.26 (± 7.472)			
Visit 11	18.8 (± 7.779)			
Visit 12	20.88 (± 9.07)			

Attachments (see zip file)	Netazepide-CgA concentrations relationship/F14.2.5

Statistical analyses

No statistical analyses for this end point

Secondary: Serum gastrin concentrations

End point title	Serum gastrin concentrations

End point description:

Serum gastrin is a biomarker for gastric acid production, and mediates gene expression associated with cell division, invasion, angiogenesis and anti-apoptotic activity. Blood samples were taken to measure levels of gastrin in the serum.

End point type	Secondary

End point timeframe:

Blood samples were taken, after an overnight fast and before the patients took netazepide (YF476) 50 mg, for assay of concentrations of gastrin in the serum. These samples were taken on Visit 1 and Visits 3-12.

End point values	netazepide (YF476) 50 mg fed			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: pmol/L				
arithmetic mean (standard deviation)				
Visit 1	554.8 (± 196.48)			
Visit 3	617.6 (± 213.3)			
Visit 4	537.4 (± 224.86)			
Visit 5	574.6 (± 208.99)			
Visit 6	613.2 (± 240.56)			
Visit 7	518.3 (± 140.97)			
Visit 8	462.9 (± 190.54)			
Visit 9	461.4 (± 179.15)			
Visit 10	425.1 (± 122.67)			
Visit 11	413.9 (± 118.93)			
Visit 12	381.8 (± 73.61)			

Attachments (see zip file)	Netazepide-Gastrin concentrations relationship/F14.2.4

Statistical analyses

No statistical analyses for this end point

Secondary: Safety and tolerability: adverse events

End point title	Safety and tolerability: adverse events

End point description:

Overall number of participants with at least 1 adverse event (AE). A breakdown of AEs by system organ class and preferred term is presented in 'Adverse events'.

End point type	Secondary

End point timeframe:

Each subject was monitored throughout the study (from screening until follow-up).

End point values	netazepide (YF476) 50 mg fed			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: participants				
Participants with at least 1 AE	7			

Statistical analyses

No statistical analyses for this end point

Secondary: Safety: values of potential clinical concern

End point title	Safety: values of potential clinical concern

End point description:

Clinical laboratory results, vitals signs and electrocardiogram (ECG) results that were outside acceptable limits and/or that changed from baseline by a pre-determined amount. Abnormal physical examination results.

Reference ranges were not used in this study, as the standard HMR reference ranges are for healthy volunteers. The sponsor agreed that only the investigator's opinion on the clinical significance of an out-of-range laboratory result, for example, was important. The measurements taken at screening were used as the baseline.

In the event, all physical examination and clinical laboratory results were considered to be of no clinical concern. No vital signs were considered to be of potential clinical importance. There was only 1 abnormal ECG finding of potential clinical significance, where the QRS axis of Patient 01 was unknown.

End point type	Secondary

End point timeframe:

From baseline to last visit.

End point values	netazepide (YF476) 50 mg fed			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: participants				
QT interval >450 msec	2			
QTcB >450 msec	3			
QT interval - change from baseline >30 msec	2			
QTcB - change from baseline >30 msec	2			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Each subject was monitored throughout the study (from screening until follow-up).

Adverse event reporting additional description:

The investigator or delegate questioned the subjects about adverse events (AEs) using a non-leading question, such as 'How're you feeling?'. The investigator also recorded AEs reported spontaneously. Other clinically significant changes in the safety assessments could also be recorded as an AE if criteria, described in the protocol, were met.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	netazepide (YF476) 50 mg

Reporting group description: -

Serious adverse events	netazepide (YF476) 50 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 8 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	netazepide (YF476) 50 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 8 (87.50%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Nervous system disorders			

Migraine subjects affected / exposed occurrences (all) Presyncope subjects affected / exposed occurrences (all) Memory impairment subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1		
General disorders and administration site conditions Influenza like illness subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all)	3 / 8 (37.50%) 3 1 / 8 (12.50%) 1		
Eye disorders Eczema eyelids subjects affected / exposed occurrences (all) Dry eye subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1 1 / 8 (12.50%) 1		
Gastrointestinal disorders Irritable bowel syndrome subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Flatulence subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all)	1 / 8 (12.50%) 1 2 / 8 (25.00%) 2 1 / 8 (12.50%) 1 1 / 8 (12.50%) 2		

Diarrhoea subjects affected / exposed occurrences (all) Glossitis subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 2 1 / 8 (12.50%) 1		
Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Acne subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1		
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 1 1 / 8 (12.50%) 1		
Musculoskeletal and connective tissue disorders Musculoskeletal chest pain subjects affected / exposed occurrences (all)	 1 / 8 (12.50%) 1		
Infections and infestations Otitis externa subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Vulvovaginal candidiasis	 1 / 8 (12.50%) 1 3 / 8 (37.50%) 3		

subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	2 / 8 (25.00%)		
occurrences (all)	2		
Respiratory tract infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Urinary tract infection			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		
Gastroenteritis viral			
subjects affected / exposed	1 / 8 (12.50%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2010	The purpose of the amendment was to reduce some of the restrictions on medications given concomitantly with netazepide (YF476). In vitro inhibition studies of netazepide (YF476), with CYP450 enzymes, found no inhibition of CYP2C9 by netazepide (YF476) at the concentrations tested; and that the likelihood of an interaction with CYP2C8 and CYP3A4 was 'possible' and 'remote', respectively. The sponsor therefore removed the restrictions in the protocol on concomitant medications metabolised by CYP2C9 and have softened the restrictions on medications metabolised by CYP3A4 and CYP2C8.
18 January 2012	The purpose of this amendment was to allow patients who had completed the original protocol to receive netazepide (YF476) for up to another 12 months. In another trial, of a gastrin receptor antagonist with very poor bioavailability, a patient's type 1 gastric carcinoids (GCs) regressed substantially after 4 weeks. So 12 weeks' treatment with netazepide (YF476), as described in the original protocol, was deemed long enough to eradicate type 1 GCs. However, preliminary results indicated that although 12 weeks' treatment reduced the number and size of the GCs, it did not eradicate them. For that reason, the protocol was amended to include another 12 months' treatment. It was expected that extended treatment with netazepide (YF476) could eradicate type 1 GCs and minimise the risk of malignancy, as netazepide (YF476) was well tolerated, reduced the number and size of the GCs, reduced circulating CgA to within normal range, and there was an increase in CgA to pre-treatment levels after stopping netazepide (YF476).
16 September 2013	The purpose of the amendment was to bring the protocol in line with an updated version of the Investigator's Brochure (IB; version 14, dated 19 July 2013), and to change the definition of the end of the trial. The sponsor updated the protocol in line with the updated reference safety information in the new version of the IB, so that co-administration of netazepide (YF476) with medicines that are CYP3A4 substrates was allowed. According to the Human Tissue Act, tissue samples that were taken during gastroscopies cannot be stored or analysed after the study has been declared over. To allow time for sample analysis, the sponsor changed the definition of the end of the trial to 'the last visit of the last subject, or completion of bioanalysis, whichever is later'.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported