Clinical trial results:
Randomized, placebo-controlled trial of YF476, a gastrin receptor antagonist, in Barrett's esophagus (10-505; T-016)

Summary

EudraCT number	2014-002418-22
Trial protocol	GB
Global end of trial date	27 December 2017

Results information

Result version number	v1 (current)
This version publication date	03 February 2021
First version publication date	03 February 2021
Summary attachment (see zip file)	10-505 SOTR (10-505 Summary of trial report 23 Nov 2020.pdf)

Trial information

Trial identification

Sponsor protocol code	T-016

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01298999
WHO universal trial number (UTN)	-
Other trial identifiers	HMR code: 10-505

Notes:

Sponsors

Sponsor organisation name	Trio Medicines Ltd
Sponsor organisation address	Cumberland Avenue, London, United Kingdom, NW10 7EW
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	10 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 November 2017
Global end of trial reached?	Yes
Global end of trial date	27 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary:
To determine if administration of YF476 (a CCK2R antagonist) to patients with Barrett's esophagus (BE) decreases tissue Ki67 expression, a marker of cellular proliferation.

Secondary:
To assess the effects of YF476 on biomarkers potentially associated with esophageal adenocarcinoma.
To assess the effects of YF476 on fasting serum gastrin, a marker of gastric acid suppression, and plasma chromogranin A (CgA), a marker of ECL cell hyperplasia.
To determine whether YF476 is safe in patients with BE.

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 was no background therapy used in the trial.

Evidence for comparator:

There were no comparators used in the trial.

Actual start date of recruitment	01 May 2013
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	United States: 12
Country: Number of subjects enrolled	United Kingdom: 12
Worldwide total number of subjects	24
EEA total number of subjects	12

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)	6
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Screening started on 15 May 2013.

Pre-assignment

Screening details:

Confirmation of Barrett's esophagus with no dysplasia (review of endoscopy); review of medication history; medical history, physical examination, ECG and vital signs; laboratory safety tests; and urine pregnancy test.

27 patients were enrolled and 3 failed screening due to elevated lipase, prolonged QTc and being diagnosed with lymphoma.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment

Arm description:

Patients taking 25 mg netazepide (gastrin receptor antagonist) once daily for 12 weeks.

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:

Netazepide 25 mg was taken by mouth once daily for 12 weeks. A single capsule was taken with breakfast except on clinic visit days, when patients fasted overnight and took netazepide after completing study procedures.

Arm title	Placebo

Arm description:

Patients taking matching placebo once daily for 12 weeks

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

Dosage and administration details:

Matching placebo was taken by mouth once daily for 12 weeks. A single capsule was taken with breakfast except on clinic visit days, when patients fasted overnight and took netazepide after completing study procedures.

Number of subjects in period 1	Treatment	Placebo
Started	13	11
Completed	10	10
Not completed	3	1
Recurrent metastatic prostate cancer	-	1
Baseline pathology low grade dysplasia	1	-
Baseline pathology indefinite for dysplasia	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Treatment
Reporting group description:	
Patients taking 25 mg netazepide (gastrin receptor antagonist) once daily for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Patients taking matching placebo once daily for 12 weeks	

Reporting group values	Treatment	Placebo	Total
Number of subjects	13	11	24
Age categorical 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)	4	2	6
From 65-84 years	9	9	18
85 years and over	0	0	0
Age continuous			
For the treatment arm, data has been summarised for 10 patients that completed the trial and excludes 3 patients that were withdrawn after the first study visit, due to reasons unrelated to the treatment.			
Units: years			
arithmetic mean	64.6	68.6	
standard deviation	± 8.1	± 6.6	-
Gender categorical			
F			
Units: Subjects			
Female	2	1	3
Male	11	10	21
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	13	11	24
More than one race	0	0	0
Unknown or not reported	0	0	0
Height			
For the treatment arm, data has been summarised for 10 patients that completed the trial and excludes 3 patients that were withdrawn after the first study visit, due to reasons unrelated to the treatment.			
Units: cm			

arithmetic mean	172.9	171.1	
standard deviation	± 10.8	± 6.5	-
Weight			
For the treatment arm, data has been summarised for 10 patients that completed the trial and excludes 3 patients that were withdrawn after the first study visit, due to reasons unrelated to the treatment.			
Units: kg			
arithmetic mean	83.5	78.5	
standard deviation	± 11.1	± 12.4	-
Body mass index			
For the treatment arm, data has been summarised for 10 patients that completed the trial and excludes 3 patients that were withdrawn after the first study visit, due to reasons unrelated to the treatment.			
Units: kg/m^2			
arithmetic mean	28.2	26.7	
standard deviation	± 5.1	± 3.1	-
Fasting serum gastrin concentration			
For the treatment arm, data has been summarised for 10 patients that completed the trial and excludes 3 patients that were withdrawn after the first study visit, due to reasons unrelated to the treatment.			
Units: pmol/L			
arithmetic mean	66.7	51.9	
standard deviation	± 45.5	± 29.1	-
Fasting plasma CgA concentration			
For the treatment arm, data has been summarised for 10 patients that completed the trial and excludes 3 patients that were withdrawn after the first study visit, due to reasons unrelated to the treatment.			
Units: nmol/L			
arithmetic mean	14.5	9.1	
standard deviation	± 19.4	± 5.0	-
Ki67 expression			
Units: cells/mm^2			
arithmetic mean	1539	1556	
standard deviation	± 514	± 622	-

End points

End points reporting groups

Reporting group title	Treatment
Reporting group description:	
Patients taking 25 mg netazepide (gastrin receptor antagonist) once daily for 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Patients taking matching placebo once daily for 12 weeks	

Primary: Change in Ki67 expression

End point title	Change in Ki67 expression
End point description:	
Results are reported as mean increase in Ki67 positive cells per mm^2 of BE epithelium after 12 weeks netazepide treatment.	
End point type	Primary
End point timeframe:	
Biopsies were taken at baseline and Week 12 to assess Ki67 expression levels.	

End point values	Treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[1]	10[2]		
Units: cells/mm^2				
arithmetic mean (standard deviation)	35.6 (± 620.7)	307.8 (± 640.3)		

Notes:

[1] - 3 patients were withdrawn

[2] - 1 patient was withdrawn

Statistical analyses

Statistical analysis title	Two sample t-tests
Statistical analysis description:	
Two sample t-test to compare placebo and treatment groups. Nominal p-value and 95% confidence intervals for treatment difference were reported.	
Comparison groups	Placebo v Treatment
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)

Confidence interval	
level	95 %
sides	2-sided

Secondary: Fasting serum gastrin concentration

End point title	Fasting serum gastrin concentration

End point description:

After 6 patients (3 per treatment) had their Week 4 and 8 visits, the protocol was amended so that those visits were replaced by a single visit at Week 6 in order to reduce the total number of visits. The number of patients included in the analysis for each study visit is outlined below:
Week 4 - 3 patients per arm
Week 6 - 7 patients in the treatment arm, 8 patients in the placebo arm
Week 8 - 3 patients per arm
Week 12 - 10 patients per arm
Follow up - 10 patients per arm

End point type	Secondary

End point timeframe:

Blood samples were taken periodically for 12 weeks, and at the follow-up visit to measure fasting serum gastrin concentrations.

End point values	Treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[3]	10[4]		
Units: pmol/L				
arithmetic mean (standard deviation)				
Week 4	242.6 (± 142.3)	43.6 (± 9.9)		
Week 6	103.3 (± 89.9)	63.9 (± 32.2)		
Week 8	234.3 (± 156.5)	96.4 (± 54.2)		
Week 12	146.8 (± 112.8)	49.2 (± 20.4)		
Follow up	94.9 (± 78.8)	64.7 (± 37.7)		

Notes:

[3] - The number of patients analysed at each visit differs due to the protocol amendment.

[4] - The number of patients analysed at each visit differs due to the protocol amendment.

Statistical analyses

No statistical analyses for this end point

Secondary: Fasting plasma CgA concentration

End point title	Fasting plasma CgA concentration

End point description:

After 6 patients (3 per treatment) had their Week 4 and 8 visits, the protocol was amended so that those visits were replaced by a single visit at Week 6 in order to reduce the total number of visits. The number of patients included in the analysis for each study visit is outlined below:
Week 4 - 3 patients per arm
Week 6 - 7 patients in the treatment arm, 8 patients in the placebo arm
Week 8 - 3 patients per arm

Week 12 - 10 patients per arm
Follow up - 10 patients per arm

End point type	Secondary

End point timeframe:

Blood samples were taken periodically for 12 weeks, and at the follow-up visit to measure fasting plasma CgA concentrations.

End point values	Treatment	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10[5]	10[6]		
Units: nmol/L				
arithmetic mean (standard deviation)				
Week 4	3.9 (± 1.8)	8.8 (± 3.7)		
Week 6	1.8 (± 0.9)	16.9 (± 9.8)		
Week 8	3.8 (± 1.8)	10.9 (± 6.0)		
Week 12	2.9 (± 2.5)	10.6 (± 7.4)		
Follow up	19.8 (± 26.1)	11.9 (± 7.2)		

Notes:

[5] - The number of patients analysed at each visit differs due to the protocol amendment.

[6] - The number of patients analysed at each visit differs due to the protocol amendment.

Statistical analyses

No statistical analyses for this end point

Secondary: Expression of Biomarkers potentially associated with Esophageal Adenocarcinoma (EAC)

End point title	Expression of Biomarkers potentially associated with Esophageal Adenocarcinoma (EAC)[7]

End point description:

Results are reported as log-fold change in biomarker expression after 12 weeks netazepide treatment. Results for patients in the placebo arm were not provided.

End point type	Secondary

End point timeframe:

Blood samples were taken for assay of biomarkers at baseline and Week 12 to assess the change in expression.

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Results from patients in the placebo arm were not provided, so only data for the treatment are reported.

End point values	Treatment			
Subject group type	Reporting group			
Number of subjects analysed	10[8]			
Units: log-fold change				
number (not applicable)				
CCK2R expression	-1.19			
PTGS2 expression	0.31			
DCLK1 expression	-0.34			

Notes:
[8] - Results for patients in the placebo arm were not provided.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

The investigator or delegate questioned the patients about adverse events (AEs) using non-leading questions, such as 'How are 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	20.1

Reporting groups

Reporting group title	Treatment group

Reporting group description:

Netazepide 25 mg once daily by mouth for 12 weeks.

Reporting group title	Placebo group

Reporting group description:

Matching placebo once daily by mouth for 12 weeks.

Serious adverse events	Treatment group	Placebo group	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Infections and infestations			
Scrotal abscess	Additional description: The patient did not withdraw from the study as the event was concluded to be unrelated to treatment and recovery was seen after 17 days.		
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Treatment group	Placebo group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 13 (76.92%)	7 / 11 (63.64%)	
Cardiac disorders			

Bundle branch block right			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 13 (23.08%)	3 / 11 (27.27%)	
occurrences (all)	3	3	
Presyncope			
subjects affected / exposed	1 / 13 (7.69%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Dizziness			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 13 (15.38%)	1 / 11 (9.09%)	
occurrences (all)	2	1	
Diarrhoea			
subjects affected / exposed	2 / 13 (15.38%)	1 / 11 (9.09%)	
occurrences (all)	3	1	
Abdominal pain			
subjects affected / exposed	1 / 13 (7.69%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	1 / 13 (7.69%)	1 / 11 (9.09%)	
occurrences (all)	1	1	

Rectal haemorrhage			
subjects affected / exposed	1 / 13 (7.69%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Abdominal distension			
subjects affected / exposed	0 / 13 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	0 / 13 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Dyspepsia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 13 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Mouth ulceration			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	0 / 13 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 13 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	3	
Epistaxis			
subjects affected / exposed	0 / 13 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	2	
Oropharyngeal pain			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Rhinitis allergic			
subjects affected / exposed	0 / 13 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			

Dermatitis acneiform			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	0 / 13 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 13 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
Arthralgia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 13 (7.69%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Rash pustular			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	1 / 13 (7.69%)	0 / 11 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported