Hammersmith Medicines Research

Clinical trial report

Trial title	A single centre, pilot trial of YF476 (netazepide) in patients with chronic atrophic gastritis, hypergastrinaemia and type I gastric carcinoids
Version and date of report	Version 1, 03 November 2020
EudraCT number	2007-002916-24
HMR trial code	07-504
Sponsor trial code	T-008
Investigational product	YF476
Trial indication	None
Phase of trial	Phase 2
Place of trial	Royal Liverpool University Hospital Prescot Street Liverpool L7 8XP
Principal investigator	Professor Mark Pritchard PhD FRCP Professor of Gastroenterology Honorary Consultant Gastroenterologist Gastroenterology Unit Royal Liverpool University Hospital Tel: +44 (0)15 1794 5772 Fax: +44 (0)15 1794 6825 Email: mark.pritchard@liverpool.ac.uk
Trial sponsor	Trio Medicines Ltd PO Box 53346 London NW10 7XU
Sponsor signatory	Dr Malcolm Boyce BSc FRCP FFPM FBPhS Tel: +44 (0)20 8961 4130 Fax: +44 (0)20 8961 8665
Date first patient screened	04 Jan 2011
Date of last patient visit	25 Feb 2014

This trial was conducted in accordance with EU Directive 2001/20/EC, applicable national statutory requirements, and ICH GCP, including the archiving of essential documents. The protocol was approved by the

Medicines and Healthcare products Regulatory Agency (MHRA) and an independent recognised research ethics committee (REC) before the trial began, and written informed consent was obtained from each patient.

Synopsis

Sponsor: Trio Medicines Ltd	
Name of finished product: Netazepide capsules	**Name of active ingredient:** Netazepide
Title: A single centre, pilot trial of YF476 (netazepide) in patients with chronic atrophic gastritis, hypergastrinaemia and type 1 gastric carcinoids.	
Investigator(s): Professor Mark Pritchard	
Trial centre(s): Gastroenterology Unit, Royal Liverpool University Hospital, Prescot Street, Liverpool L7 8XP	
Publication(s): Moore *et al*, 2013[1]	
Trial period: 04 Jan 2011–25 Feb 2014	**Phase of Development:** 2

Objectives:

Primary:

To assess if netazepide is an effective medical treatment for type I gastric carcinoids.

Secondary:

To assess the tolerability and safety of netazepide; and
To assess the effect of netazepide on plasma concentration and transcript profiles of biomarkers such as chromogranin A (CgA).

Methods:

This was a single centre, open label, multiple-dose, pilot, phase 2, outpatient trial. 8 patients took active treatment. The study was in 2 parts: Part 1 and Part 2 (extended dosing), with 7 visits in Part 1 and 5 visits in Part 2.

Each patient took the doses as follows:

Part 1: 50 mg netazepide once a day, for 12 weeks (except Patient 08, who took 25 mg once a day, for 6 weeks; then 50 mg netazepide once a day, for 6 more weeks).

Part 2: 50 mg netazepide once a day, for 52 weeks.

The sponsor and the investigators increased or reduced the dose of netazepide at Visit 4, only after reviewing gastric carcinoid status, safety and tolerability.

Patients were screened during Visit 1 (Part 1), before their first dose of trial medication. For each visit, the patients fasted for at least 6 hours (h) before their dose. They left on the same day, at least 1 h after taking a dose of netazepide.

Part 1

At Visit 2, patients underwent gastroscopy, starting treatment the next day. Visits 3, 4, 5 and 6 were to assess tolerability, safety and blood levels of gastrin, CgA and netazepide. Gastroscopies were also done on Visits 4 and 6. Visit 7 was a follow-up visit, with gastroscopy and blood sampling.

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Title: A single centre, pilot trial of YF476 (netazepide) in patients with chronic atrophic gastritis, hypergastrinaemia and type 1 gastric carcinoids.	
Part 2 At Visit 8, patients were informed about the extended dosing period and prescribed netazepide capsules. Baseline gastroscopy and blood sampling were done as required. Visits 9, 10, 11, and 12 were to assess tolerability, safety and blood levels of gastrin, CgA and netazepide. At Visits 10 and 12, gastroscopy was also done. A formal follow-up visit was omitted, as the patients were closely followed by the investigator as part of their standard healthcare.	
Number of patients: Planned: up to 10 Actual: 8	
Diagnosis and main criteria for inclusion: Otherwise healthy men, aged 18 years or over, deemed healthy on the basis of 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; were willing to use suitable contraception and were able to give fully-informed, written consent. Post-menopausal women or pre-menopausal women who had been sterilized by tubal ligation, hysterectomy or bilateral oophorectomy; or used condoms and spermicide, or an intra-uterine device, as contraception.	
Test and reference products, dose, mode of administration and batch numbers: The sponsor, Trio Medicines Ltd, England, supplied netazepide spray-dried dispersion (SDD) powder. Netazepide and HPMC (YF476: HPMC ratio 1:3.5) were dissolved in dichloromethane/isopropanol (7:2 v/v). The solution was spray-dried, and the resulting powder was blended with starch. HMR Pharmacy prepared the netazepide capsules. Netazepide was hand-weighed individually for each capsule according to dose and put into hard, gelatin capsules, with no identifying markings. The batch numbers and expiry dates of netazepide SDD capsules are summarised in the table below.	

Patient	Visit[1]	Netazepide Capsules		
		Release #	Batch # of spray dried capsules	Expiry
01	Screening	NS5350	NS4916	24 Aug 2011
	Visit 8	NT0674	NS7650	29 Apr 2013
	Visit 10	NT1418	NT0159	05 Sep 2014
	Visit 11	NT2114	NT0159/NS8613	05 Sep 2014/12 Apr 2014
02	Screening	NS5350	NS4916	24 Aug 2011
	Visit 8	NT0845[2]	NS6381	02 Feb 2013
	Visit 9	NT0674	NS7650	29 Apr 2013
	Visit 10	NT1418	NT0159	05 Sep 2014
	Visit 11	NS2499	NT1710	04 Jun 2015
03	Screening	NS5350	NS4916	24 Aug 2011
	Visit 8	NT0674	NS7650	29 Apr 2013
	Visit 9	NT0945/6	NT0944/NT0159	29 Apr 2013/27 Nov 2013
	Visit 10	NT1418	NT0159	05 Sep 2014
	Visit 11	NT2113	NS8613/NT0159	12 Apr 2014/05 Sep 2014
04	Screening	NS7603	NS6381	27 Nov 2011
	Visit 4	NS5350	NS4916	24 Aug 2011
	Visit 8	NT0674	NS7650	29 Apr 2013
	Visit 9	NT0946	NT0159	27 Nov 2013
	Visit 10	NT1418	NT0159	05 Sep 2014
	Visit 11	NT2499[4]	NT1710	04 Jun 2015
05	Screening	NS7603	NS6381	27 Nov 2011
	Visit 3	NS5350	NS4916	24 Aug 2011
	Visit 5	NS7737	NS4916	29 Apr 2012
	Visit 8	NT1418	NT0159	05 Sep 2014
	Visit 9	NT2113	NS8613/NT0159	12 Apr 2014/05 Sep 2014
	Visit 10	NT2499	NT1710	04 Jun 2015
	Visit 11	NT2500	NT1710	04 Jun 2015
06	Screening	NS7603	NS6381	27 Nov 2011
	Visit 3	NS5350	NS4916	24 Aug 2011
	Visit 4	NS7737[3]	NS4916	29 Apr 2012
	Visit 8	NT0674	NS7650	29 Apr 2013
	Visit 9	NT0946	NT0159	27 Nov 2013
	Visit 10	NT2113	NS8613/NT0159	12 Apr 2014/05 Sep 2014
	Visit 11	NT2500	NT1710	04 Jun 2015
07	Screening	NS7926	NS7650	29 Apr 2012
	Visit 8	NT0946	NT0159	27 Nov 2013
	Visit 9	NT1418	NT0159	05 Sep 2014
	Visit 10	NT2499	NT1710	04 Jun 2015
08	Screening	NS7926	NS7650	29 Apr 2012
	Visit 8	NT0674	NS7650	29 Apr 2013
	Visit 9	NT1418	NT0159	05 Sep 2014
	Visit 10	NT2113	NS8613/NT0159	12 Apr 2014/05 Sep 2014
	Visit 11	NT2499	NT1710	04 Jun 2015

1. Visit from which the patient took the capsules.
2. Refer to File Note 48.
3. Refer to File Note 46.
4. Refer to File Note 49.

Duration of treatment: In Part 1, patients received a single oral dose of netazepide once a day, for up to 12 weeks. There was a gap of about 12 weeks between the two parts. In the extended treatment (Part 2), patients received a single oral dose of netazepide once a day, for up to 52 weeks.

Criteria for evaluation:

Efficacy: the distribution, number and size of any gastric carcinoids were assessed visually, and were photographed, during gastroscopy. Blood samples for assay of fasting levels of gastrin and CgA were taken. The relationship, if any, between netazepide and gastrin and CgA was assessed.

Safety: physical examination, vital signs, 12-lead ECG, laboratory assessments (routine haematology, biochemistry, and urinalysis) and adverse events (AEs). Evidence of corrected QT interval (QTc) prolongation was sought.

Tolerability: AEs.

Pharmacokinetics: blood samples for assay of netazepide were taken before, and at 1 h after dosing. Pharmacokinetic evaluation was done as an outcome measure of efficacy.

Statistical methods:

This was an exploratory study so no formal calculation of sample size was appropriate, and most of the data were not subject to formal analysis. Where appropriate, data were summarised using descriptive statistics. Serum gastrin and plasma CgA concentrations were compared with baseline using ANOVA, with visit as fixed effect and patient as random effect.

Results:

Efficacy:

The table below shows the total number of type 1 tumours in each patient, before, during, and after netazepide 50 mg daily for 64 weeks (12 weeks up to Visit 6, then at least 12 weeks off treatment before another 52 weeks, starting at Visit 8); taken from source document gastroscopy reports.

Number of type 1 tumours in each patient, before, during and after netazepide 50 mg daily

	Visit						
Patient	**2**	**4**	**6**	**7**	**8**	**10**	**12**
01	8	4	2	3	5	0	0
02	8	8	9	9	12	10	10
03	4	2	2	1	2	0	1
04	9	7	7	6	12	6	10
05	30	20	10	8	12	12	12
06	10	6	6	5	12	10	1
07	12	12	12	14	13	12	12
08	12	10	10	12	n/a	12	15
Mean	**12**	**9**	**7**	**7**	**10**	**8**	**8**

The table below shows the size of the largest tumour (mm) in each patient, before, during and after netazepide 50 mg daily for 64 weeks (12 weeks up to Visit 6, then at least 12 weeks off treatment before another 52 weeks, starting at Visit 8); taken from Listing 16.2.6.1.

Size of the largest tumour (mm) in each patient, before, during and after netazepide 50 mg daily

	Visit						
Patient	**2**	**4**	**6**	**7**	**8**	**10**	**12**
01	6	4	4	2	2	0	0
02	15	10	10	10	12	6	6
03	3	2	2	2	4	0	1
04	5	4	3	2	4	3	2
05	7	5	3	3	4	4	2
06	8	7	5	5	7	3	2
07	10	10	10	10	11	10	6
08	15	10	7	7	n/a	3	6
Mean	**8.6**	**6.5**	**5.5**	**5.1**	**6.3**	**3.6**	**3.1**

At baseline, the mean number of tumours was 12 (range 4–30) and the mean diameter of the largest one was 8.6 mm (range 3–15 mm). After 12 weeks' treatment (Visit 6), most patients had a reduction in the number of tumours and the size of the largest one; all but 1 patient had a decrease in diameter of their largest tumour.

The mean number of tumours and the size of the largest one did not increase in size during the 12 weeks patients were off treatment (between Visits 6 and 7). The mean number of tumours

increased between Visit 7 and Visit 8 (7 tumours vs 10, respectively). But, by Visit 10 the number of tumours almost returned to around the number seen at Visit 7.

Likewise, the size of the largest tumour increased slightly from Visit 7 to Visit 8. But, the size of the largest tumour had halved by Visit 12 (3.1 vs 6.3 mm). During treatment, 1 patient became free of tumours and 2 patients finished with only one tumour.

The table below shows the histology results of the tumour biopsies.

Histology of tumour biopsies

		Visit					
Patient	**Screening**	**4**	**6**	**Follow-up**	**8**	**10**	**12**
01	NET	ECL-M	ECL-M	ECL-M	NET	ECL-M	ECL-M
02	NET	NET	NET	ECL-M	ECL-D	ECL-M	ECL-M
03	ECL-M	ECL-M	ECL-M	ECL-M	ECL-M	ECL-M	ECL-L
04	NET	ECL-M	ECL-M	NET	ECL-M	ECL-M	ECL-M
05	NET	NET	NET	NET	NET	ECL-M	NET
06	NET	NET	ECL-M	NET	NET	NET	NET
07	NET	NET	NET	NET	NET	NET	NET
08	NET	NET	NET	ECL-M	ECL-M[1]	ECL-M	ECL-M

1. Visit 7 and Visit 8 were combined into one.
NET = neuroendocrine tumour; ECL-D = ECL-cell dysplasia;
ECL-M = micronodular ECL-cell hyperplasia; ECL-L = linear ECL-cell hyperplasia.

At baseline, tumour biopsies showed that 7 patients had low grade neuroendocrine tumours (NETs), with one patient that had micronodular ECL-cell hyperplasia (ECL-M). By the end of the study, 4 patients had ECL-M, 1 patient had linear ECL-cell hyperplasia (ECL-L), and 3 patients had low grade NETs. The histology of the flat mucosa was unchanged by netazepide.

The table below shows that there was a reduction in plasma CgA after just 3 weeks' treatment (Visit 3), which was sustained for up to 12 week's treatment (Visit 6). At Visit 7, 12 weeks after stopping treatment, plasma CgA had increased again and recovered, from 19.60 IU/L to 51.60 IU/L. Extended treatment with netazepide (Visits 8–12) brought plasma CgA concentrations back to levels seen in Visit 3 (18.95 IU/L).

Summary of plasma CgA concentrations (IU/L)

Treatment	**Visit**	**n**	**Mean**	**SD**	**Median**	**Min**	**Max**	**Change**
All patients (N=8)	Visit 1 (BL)	8	63.16	33.180	54.95	25.2	128.0	-
Units: IU/L	Visit 3	8	18.95	10.583	14.75	9.3	40.9	−44.21
	Visit 4	8	22.41	19.426	14.70	9.1	68.8	−40.76
	Visit 5	8	18.58	11.683	14.90	8.5	45.4	−44.58
	Visit 6	8	19.60	12.783	14.15	9.1	48.6	−43.56
	Visit 7	8	51.60	24.200	46.15	24.3	98.0	−11.56
	Visit 8 (BL)	8	45.34	22.426	42.75	22.9	91.4	-
	Visit 9	8	16.24	8.003	13.85	8.6	32.0	−29.10
	Visit 10	8	16.26	7.472	14.75	8.2	31.3	−29.08
	Visit 11	8	18.80	7.779	17.05	6.2	31.4	−26.54
	Visit 12	8	20.88	9.070	16.65	10.5	37.8	−24.46

SD: standard deviation. Change: estimate of least squares mean for the difference from baseline (BL; Visits 1 or 8).

The table below shows the effect of netazepide on serum gastrin.

Summary of fasting serum gastrin concentration (pmol/L)

Treatment	Visit	n	Mean	SD	Median	Min	Max	Change
All patients (N=8)	Visit 1 (BL)	8	554.8	196.48	512.5	332	953	-
Units: pmol/L	Visit 3	8	617.6	213.30	639.0	365	890	62.81
	Visit 4	8	537.4	224.86	510.5	211	896	−17.44
	Visit 5	8	574.6	208.99	568.5	335	904	19.81
	Visit 6	8	613.2	240.56	591.0	293	953	58.34
	Visit 7	8	518.3	140.97	457.3	367	742	−36.50
	Visit 8 (BL)	8	462.9	190.54	471.0	193	816	-
	Visit 9	8	461.4	179.15	466.5	168	666	−1.50
	Visit 10	8	425.1	122.67	455.5	179	556	−37.75
	Visit 11	8	413.9	118.93	368.0	307	620	−49.00
	Visit 12	8	381.8	73.61	377.0	257	486	−81.12

SD: standard deviation. Change: estimate of least squares mean for the difference from baseline (BL; Visits 1 or 8).

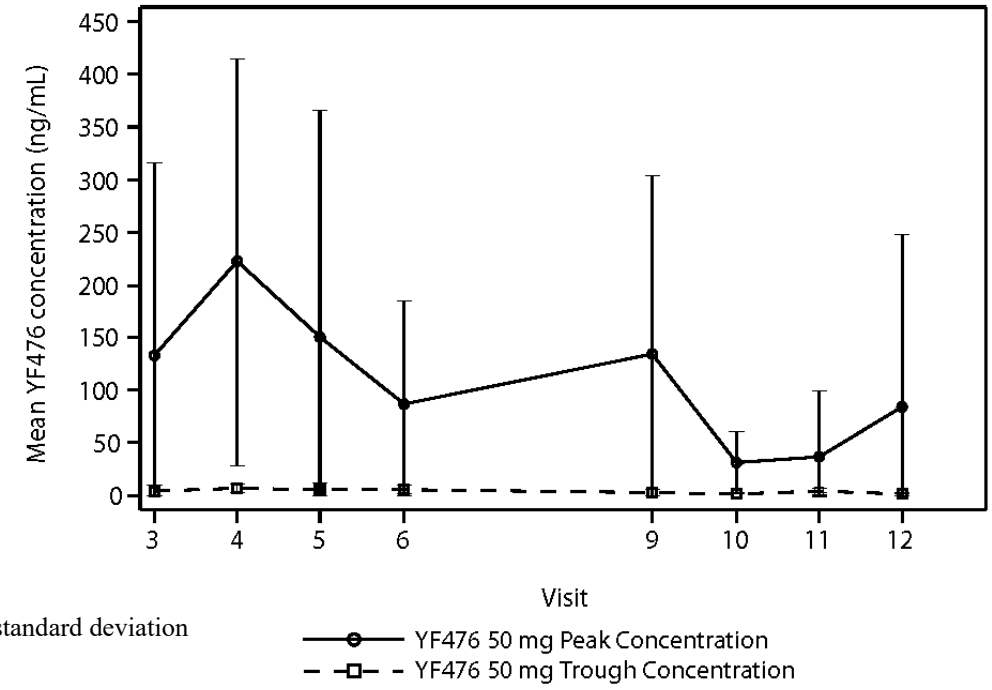
The high serum gastrin at baseline (normal range ≤100 pmol/L) was unaffected by 12 weeks' treatment (Visit 6). But, by Visit 8, the mean serum gastrin concentration had been reduced down to 462.9 pmol/L. This reduction was slight, and the gastrin baseline was still well above the normal range. By Visit 12, the mean serum gastrin concentration was 381.8 pmol/L.

Pharmacokinetics (efficacy outcome measure):

Netazepide (YF476) plasma concentrations were measured to confirm patient compliance and provide additional data such as the relationship between plasma netazepide (YF476) concentration and plasma CgA concentration, or serum gastrin concentration.

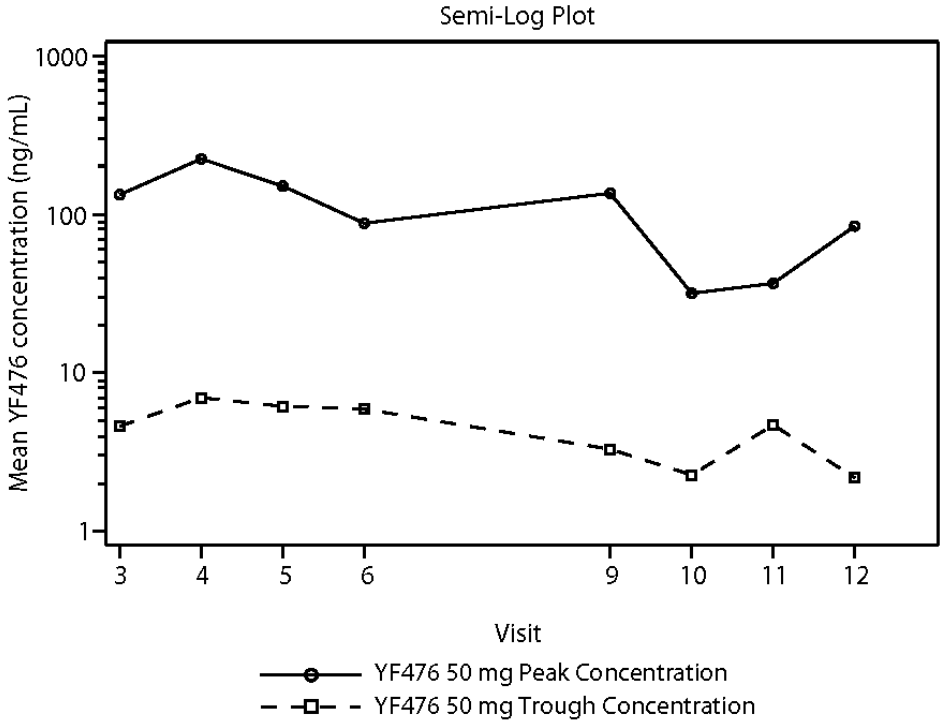
The figures below show the mean plasma concentrations of netazepide, on both a linear and semi-logarithmic (semi-log) scale.

Mean (+SD) netazepide plasma concentration-time plots (linear) in patients after single daily oral doses of netazepide



SD: standard deviation

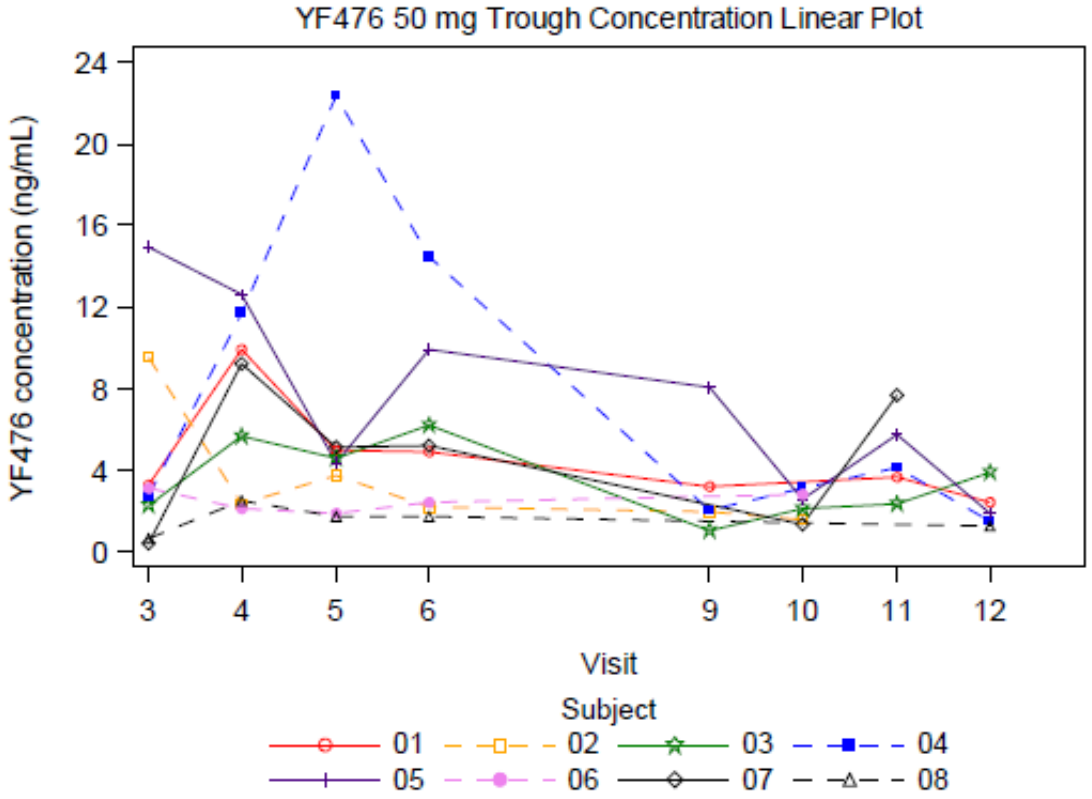
Mean netazepide plasma concentration-time plots (semi-log) in patients after single daily oral doses of netazepide



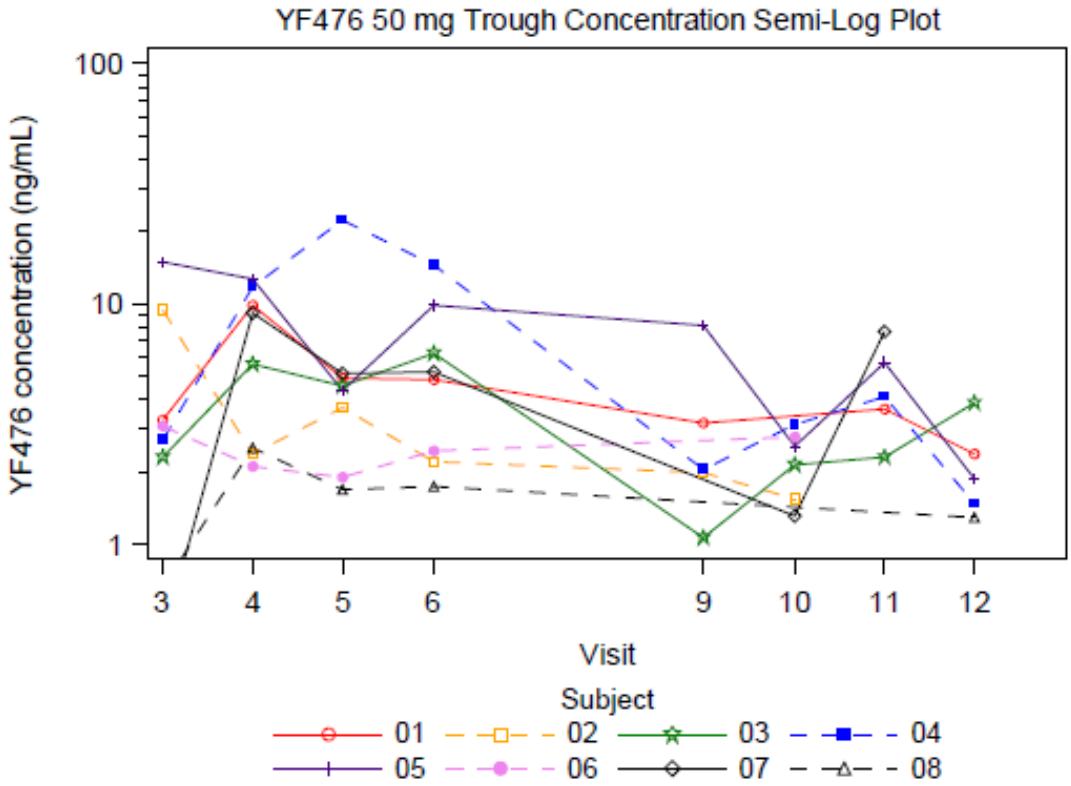
After repeated doses for the initial 12 weeks (up to Visit 6), netazepide reached steady state, with the plasma concentration variability reducing over visits. After repeated doses for the extended home dosing weeks (Visits 9–12), the plasma concentration levels were more variable than those in the initial 12 weeks, but this could be explained by a lower compliance rate; for example, Patient 07 missed 18 doses over this time. The trough concentrations remained consistent over visits. It appears that there was a steady level of exposure in patients over time.

The figures below show the trough plasma concentrations of netazepide, in individual patients, on both a linear and semi-logarithmic (semi-log) scale.

Netazepide plasma concentration-time plots (linear) in individual patients after single daily oral doses of netazepide

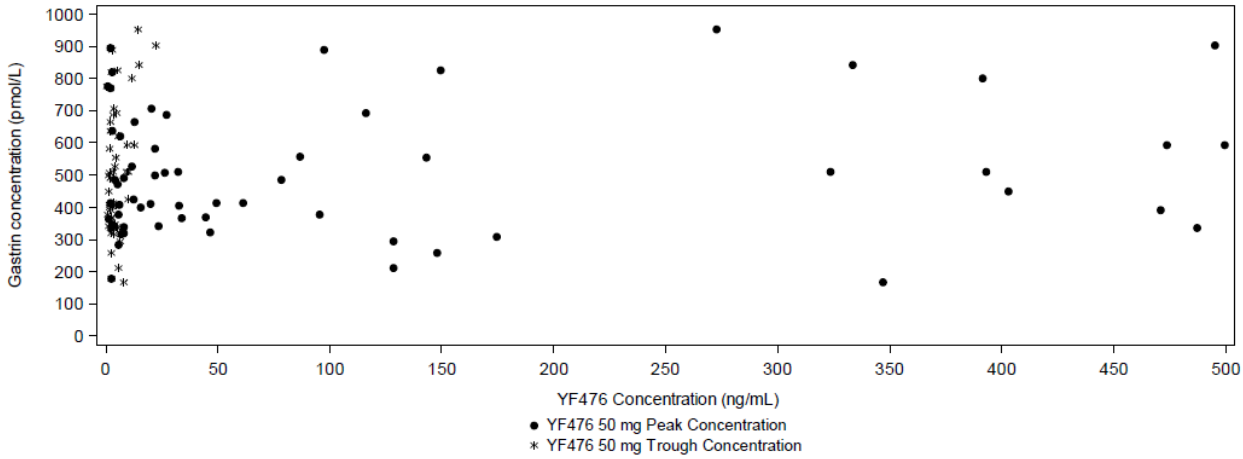


Netazepide plasma concentration-time plots (semi-log) in individual patients after single daily oral doses of netazepide



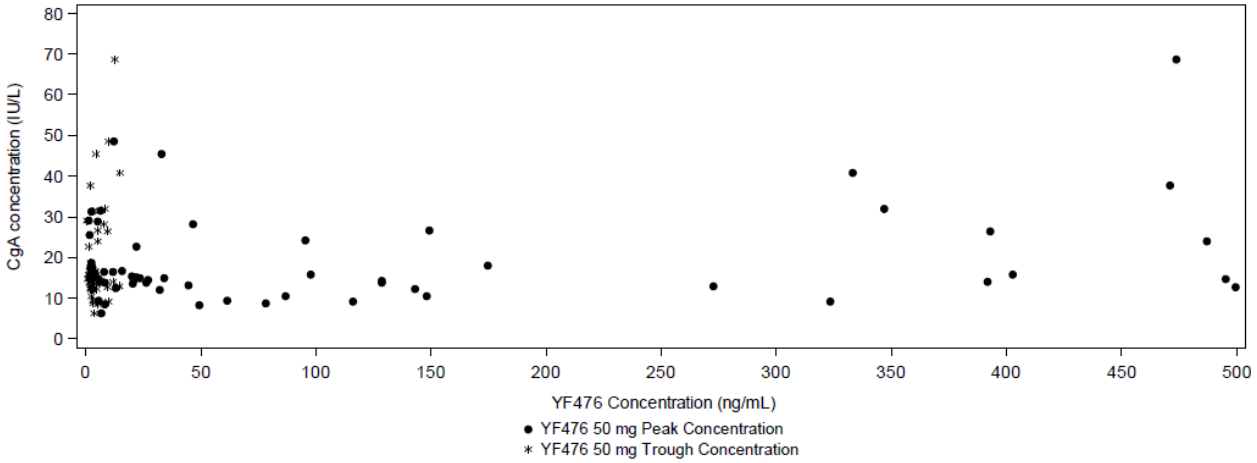
The figures below show the relationship between netazepide (YF476) dose and serum gastrin or plasma CgA concentration.

Scatter plot showing the relationship between netazepide plasma concentration and serum gastrin concentration



From this scatter plot, it appears that there was not a correlation between netazepide plasma concentration and serum gastrin levels, in these patients.

Scatter plot showing the relationship between netazepide plasma concentration and plasma CgA concentration



There could be a weak correlation between netazepide (YF476) plasma concentration and plasma CgA concentration, but we cannot confirm a correlation from this scatter plot alone.

Safety and tolerability:

The table below shows the total number of treatment-emergent adverse events (TEAEs), and the number of TEAEs that were deemed to be possibly related to netazepide.

The number of AEs appears high, at 36, but the patients were followed for 52 weeks. This means that there were only 4.5 AEs per patient over the whole year, which isn't many.

Treatment-emergent adverse events

	YF476 (50 mg) N=8
Total number of patients with TEAEs (number of TEAEs)	7 (36)
Number of patients with YF476-related TEAEs (number of TEAEs)	0

There were no fatal or other serious AEs.

There were no clinical laboratory variables of potential clinical importance. The results of some of the physical examinations were abnormal, but were of no clinical significance.

Any measurements of heart rate, systolic blood pressure (BP) and diastolic BP that were abnormal, were considered by the investigator to be not clinically significant.

There were no clinically significant abnormal ECG findings.

Conclusions:

- Netazepide is safe and well tolerated.
- Netazepide is an orally active gastrin receptor antagonist.
- Netazepide is a potential medical and targeted treatment for type 1 g-NETs, and an alternative to regular gastroscopy or surgery.
- Netazepide would need to be taken as a continuous, chronic treatment because tumours regrow once treatment is stopped.
- Netazepide reduced the number and size of tumours, suggesting type 1 g-NETs is gastrin-driven.
- Netazepide reduced the concentration of CgA in plasma, suggesting that netazepide reduces ECL-cell activity in CAG patients.
- Netazepide does not increase gastrin concentrations in the serum of patients.

Date of the report: 03 November 2020