Hammersmith Medicines Research

Clinical trial report

Study title	Does adding YF476 to amoxicillin and clarithromycin aid eradication of *H. pylori* from healthy carriers?
Brief description	Double-blind, randomised, comparative, parallel-group, in-patient trial in asymptomatic carriers of *Helicobacter pylori* (*H. pylori)* to assess the efficacy, safety and tolerability of triple therapy with YF476 100 mg, amoxicillin and clarithromycin. Study terminated early due to a poor formulation. 2 subjects were dosed.
Version and date of report	Version 1, 17 March 2016
EudraCT number	2007-002137-37
HMR study code	07-501
Sponsor study code	T-004
Investigational product	YF476 (netazepide), amoxicillin and clarithromycin
Trial indication	*H. pylori* carrier
Phase of study	Phase 2
Place of study	Hammersmith Medicines Research (HMR) Central Middlesex Hospital Acton Lane London NW10 7NS England **HMR's current address:** Cumberland Avenue Park Royal London NW10 7EW
Principal investigator	Malcolm Boyce BSc FRCP FFPM Hammersmith Medicines Research tel: 020 8961 4130 fax: 020 8961 8665

Trial sponsor	Trio Medicines Ltd PO Box 53346 London NW10 7XU
Sponsor signatory	Malcolm Boyce BSc FRCP FFPM Trio Medicines Ltd tel: 020 8961 4130 fax: 020 8961 8665
Date first subject screened	16 August 2007
Date of last subject visit	23 October 2007

This trial was conducted in accordance with EU Directive 2001/20/EC, applicable national statutory requirements, and ICH GCP (International Conference on Harmonisation Good Clinical Practice), including the archiving of essential documents. The protocol was approved by the Medicines and Healthcare products Regulatory Agency and an independent recognised research ethics committee before the study began, and written informed consent was obtained from each subject.

1 Signatures

We, the undersigned, confirm that this abbreviated report is an accurate and comprehensive record of important aspects of the study:

Principal investigator

Dr Malcolm Boyce
Hammersmith Medicines Research Signature Date

Statistician

Toni Mitchell
Hammersmith Medicines Research Signature Date

Sponsor

Dr Malcolm Boyce
Trio Medicines Ltd Signature Date

I, the undersigned, confirm that audits have been done on this study. The results of those audits revealed no significant deviations from the International Conference on Harmonisation Guideline for Good Clinical Practice.

Afia Miah
Quality Manager Signature Date
Hammersmith Medicines Research

2 Synopsis

Sponsor: Trio Medicines Ltd	
Name of finished product: YF476 (netazepide), amoxicillin capsules and clarithromycin tablets	**Name of active ingredient:** YF476 (netazepide), amoxicillin and clarithromycin
Title: Does adding YF476 to amoxicillin and clarithromycin aid eradication of *H. pylori* from healthy carriers?	
Investigator: Dr Malcolm Boyce	
Study centre: Hammersmith Medicines Research, Cumberland Avenue, Park Royal, London NW10 7EW	
Publication(s): None at the time of this report.	
Study period: (16 Aug 2007)–(23 Oct 2007)	**Phase of Development:** 2

Objectives:

Primary: to assess if adding YF476 to amoxicillin and clarithromycin therapy increases the eradication rate of *H. pylori* in healthy carriers.

Secondary: 1) to assess the tolerability and safety of triple therapy with YF476, amoxicillin and clarithromycin.

2) to obtain the pharmacokinetic parameters of YF476, clarithromycin and amoxicillin after dual and triple therapy, and seek evidence of pharmacokinetic interaction.

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Methods:

This was a double-blind, randomised, comparative, parallel-group, in-patient trial in asymptomatic *H. pylori*-positive healthy men or women. The protocol required 30 subjects to be randomised to treatment by mouth, twice-daily, for 7½ days with:

- YF476 100 mg, amoxicillin 1000 mg and clarithromycin 500 mg; **or**
- YF476 placebo, amoxicillin 1000 mg and clarithromycin 500 mg.

On Day 8, subjects took one dose only (in the morning).

The protocol specified that 20 subjects should receive the treatment containing active YF476, and 10 subjects should receive the treatment containing placebo YF476. Our aim was to recruit an equal number of men and women in each treatment group.

There were 5 visits (4 out-patient and 1 in-patient stay of 9 consecutive nights).

At **Visit 1**, subjects were screened for *H. pylori*.

At **Visit 2** – up to 2 weeks after Visit 1 – *H. pylori*-positive subjects had the rest of the screening.

At **Visit 3** – up to 2 weeks after Visit 2 – eligible subjects stayed on the ward for 9 consecutive nights. Subjects were admitted to the ward on the evening before the start of treatment. On Days 1–7, subjects took their allocated treatment twice daily. On Day 8, subjects took only the morning dose. Morning doses were about 1 hour before breakfast, and evening doses about 1 hour before the evening meal. Frequent blood samples were collected 0–24 hours (h) after dosing on Day 8, for measurement of concentrations of YF476, amoxicillin and clarithromycin.

Cohorts of subjects were studied at weekly intervals. 2 male subjects (1 subject taking treatment containing active YF476 and 1 subject taking treatment containing placebo YF476) were dosed first. Thereafter, cohorts of up to 6 subjects should have been studied. Subjects were discharged on the morning of Day 9, if all was well.

At **Visit 4** – about 7 days after the last dose of treatment – subjects had a follow-up visit.

At **Visit 5** – 6 weeks after the last dose – subjects had a second *H. pylori* test.

Subjects who passed screening took about 11 weeks to complete the trial.

Number of subjects: Planned: 30
Actual: 2 (2 men)

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Diagnosis and main criteria for inclusion:

Inclusion criteria
Asymptomatic *H. pylori*-positive healthy men or women, judged healthy on the basis of a medical history, medical examination, electrocardiogram (ECG; especially QTc (corrected QT) interval <450 msec) and laboratory tests of blood and urine, and able to give fully-informed, written consent. Pre-menopausal women who are sexually active must have an intrauterine device, or have had a hysterectomy or bilateral oophorectomy, or their partner must use a condom and spermicide. Men must use a condom and spermicide as contraception.

Exclusion criteria
Positive tests for hepatitis B & C, human immunodeficiency virus (HIV) 1 & 2; severe adverse reaction to any drug; sensitivity to trial medication; drug or alcohol abuse; smoking of more than 5 cigarettes per week; over-the-counter medication within previous 7 days (with the exception of acetaminophen); treatment with a proton pump inhibitor (PPI), H_2-receptor antagonist or antibiotics in the last 3 months, other prescribed medication in last 28 days; participation in other clinical trials of unlicensed medicines within the previous 3 months; clinically relevant abnormal findings at the screening assessment; clinically relevant abnormal medical history or concurrent medical condition; possibility that the subject will not cooperate; pre-menopausal females who are pregnant, lactating or using a hormonal contraceptive.

Test and reference products, dose, mode of administration and batch numbers:

- YF476: two 50 mg capsule (100 mg)
- Amoxicillin: two 500 mg capsules (1000 mg)
- Clarithromycin: one 500 mg tablet (500 mg)
- YF476 placebo: two capsules

All doses were taken orally twice daily.

Batch numbers:

	Batch number	Expiry date
YF476 capsules 50 mg	N7651	28 March 2008
Amoxicillin capsules	268367	September 2011
Clarithromycin tablets	49770VA	January 2010
Placebo to match YF476 capsules 50 mg	N8701	14 June 2008

Duration of treatment: 7½ days

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Criteria for evaluation: ***Efficacy:*** *H. pylori* status (^{13}C urea breath test) ***Safety:*** 24-h (hour) ECG monitoring; QT interval; medical examination, vital signs; and safety tests of blood and urine. ***Tolerability:*** adverse events. ***Pharmacokinetics:*** C_{max}, t_{max}, AUC_{0-24} (area under the curve between 0-24 hours), $AUC_{0-\infty}$ (the total area under the curve), $t_{½}$ of YF476 after triple therapy. C_{max}, t_{max}, AUC_{0-24}, $AUC_{0-\infty}$, $t_{½}$ of clarithromycin and amoxicillin after triple and dual therapy. Not done due to trial being terminated early.	
Statistical methods: Not done due to trial being terminated early.	
Efficacy: H. pylori *status* *H. pylori* was eradicated (^{13}C urea breath test was negative) in the subject on placebo but not in the subject on active treatment. No conclusion of efficacy can be drawn from this result. ***Safety:*** *12-lead ECG and cardiac monitoring* There were no important changes in ECG, including QTc interval and PR interval. *Medical examination* All medical examinations at admission and discharge were normal. *Vital signs* There were no important changes in any of the subjects. *Safety tests of blood and urine* All laboratory tests were within acceptable limits. ***Tolerability:*** YF476 was well tolerated by the 1 subject that took it. *Adverse events* There were no serious adverse events. All other adverse events were mild or moderate and are listed in Table 1.	

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Conclusions: No conclusions can be drawn since only 2 subjects took part and 1 of those was on placebo therapy.	
Date of the report: 17 March 2016	