Clinical trial report

Confidential

Trial title	A randomised, double-blind, placebo-controlled, single and repeated dose escalation study to assess the safety, tolerability, pharmacokinetics and food effect of a new formulation of AUT00206 in healthy men and women
Version and date of report	Version 1, 04 October 2022
EudraCT number	2021-003211-26
HMR trial code	21-009
Sponsor trial code	AUT041206
Investigational product	AUT00206
Trial indication	None
Phase of trial	Phase 1
Principal investigator	[redacted] HMR Cumberland Avenue, Park Royal London NW10 7EW, UK tel: [redacted] email: [redacted]
Trial sponsor	Autifony Therapeutics Limited c/o Stevenage Bioscience Catalyst Incubator Gunnels Wood Road, Stevenage Herts SG1 2FX UK
Sponsor signatory	Daniel Umbricht MD tel: [redacted] email: [redacted]
Date first subject screened	16 August 2021
Date of last subject visit	08 April 2022

This trial was conducted in accordance with applicable UK statutory requirements and ICH GCP, 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 trial began, and written informed consent was obtained from each subject. This report has been prepared in accordance with ICH E3 and ICH M4E.

1 Signatures

We, the undersigned, confirm that this report is an accurate and comprehensive record of those parts of the trial for which we are responsible:

Principal investigator

[redacted]

HMR

[redacted]

Statistician

[redacted]

HMR

[redacted]

Sponsor

[redacted]

Autifony Therapeutics Limited

[redacted]

I, the undersigned, confirm that an audit has been done on this trial report. The results of that audit revealed no significant deviations from the International Council for Harmonisation Guideline for Good Clinical Practice.

[redacted]

Head of Quality Assurance and Monitoring
HMR

[redacted]

2 Synopsis

Sponsor: Autifony Therapeutics Limited	
Name of finished product: AUT00206	**Name of active ingredient:** AUT00206
Title: A randomised, double-blind, placebo-controlled, single and repeated dose escalation study to assess the safety, tolerability, pharmacokinetics and food effect of a new formulation of AUT00206 in healthy men and women	
Investigator(s): [redacted]	
Trial centre(s): HMR, Cumberland Avenue, Park Royal, London NW10 7EW	
Publication(s): None at the time of this report.	
Trial period: 16 August 2021–08 April 2022	**Phase of Development:** 1
Date of the report: 04 October 2022	

Objectives

Primary:

Part A1

- To assess the pharmacokinetic (PK) profile of AUT00206 after single oral doses of AUT00206 in healthy men
- To determine the effect of food on the bioavailability of single oral doses of AUT00206 in healthy men

Part A2 (optional)

- To assess the PK profile of AUT00206 after single oral doses of AUT00206 in healthy women

Part B (optional)

- To assess the PK profile of AUT00206 after repeated oral doses of AUT00206 in healthy men

Secondary:

- *Part A1:* To assess the safety and tolerability of single oral doses of AUT00206 in healthy men
- *Part A2 (optional):* To assess the safety and tolerability of single oral doses of AUT00206 in healthy women
- *Part B (optional):* To assess the safety and tolerability of repeated oral doses of AUT00206 in healthy men

Methods

This was a randomised, double-blind, placebo-controlled, single ascending and multiple ascending dose trial to assess the safety, tolerability, and PK of AUT00206 in healthy volunteers. The trial was conducted in 2 parts (Parts A and B), as follows.

Part A was divided into 2 sub-parts.

- Part A1 was a crossover comparison of single rising oral doses in healthy men.
- Part A2 was a crossover comparison of single rising oral doses in healthy women.

Part B assessed repeated doses in healthy men.

In the study, doses were only escalated if the safety and tolerability of the previous dose were acceptable, and no dose escalation stopping criteria were met (including ensuring AUT00206 levels were predicted to remain below the relevant protocol-defined toxicokinetic limit).

Part A

There was a washout of at least 10 days between doses in Part A.

Part A1

In Part A1, 2 groups of 8 healthy men each were enrolled (Groups 1 and 2). In Group 1 each subject had 4 study sessions (Sessions 1–4), and in Group 2, subjects had 2 study sessions. In each session, subjects received a single dose of AUT00206 or placebo in the morning, by mouth. Each subject received up to 1 dose of placebo and up to 3 doses of AUT00206 during the trial.

Subjects were randomised to 1 of 4 treatment sequences (Table S1) such that, in each session, 2 subjects received placebo and 6 received AUT00206 (1:3 ratio).

Table S1 Part A1 treatment sequences

Treatment sequence	Session 1	Session 2	Session 3	Session 4
1 (n=2)	placebo	dose 2	dose 3	dose 4
2 (n=2)	dose 1	placebo	dose 3	dose 4
3 (n=2)	dose 1	dose 2	placebo	dose 4
4 (n=2)	dose 1	dose 2	dose 3	placebo

Subjects dosed on the same day were dosed at intervals of at least 10 min.

As planned, the starting dose for Group 1 Session 1 was 200 mg AUT00206. All subsequent doses were selected by the Safety Review Group (SRG) based on the safety, tolerability and PK results of previous doses.

AUT00206 had previously been tested in humans as a capsule formulation. Therefore, staggered dosing – in which 2 sentinel subjects were dosed first and the remaining subjects were dosed at least 23 h later – were only used, if at a proposed dose level, exposure was predicted to exceed that previously observed in humans. In Part A1, sentinels were used in Group 1 (Sessions 2, 3 and 4) and Group 2 (Sessions 1 and 2).

Subjects in Group 1 received AUT00206 in the fasted state in Sessions 1 and 2. To assess the effect of food on the PK of AUT00206, doses in some of the subsequent sessions were given in the fed state – either after a high-fat or a standard breakfast – as detailed in Table S2. Doses selected for the fed sessions were predicted to remain below the protocol-defined exposure limit, allowing for a potential increase in bioavailability owing to a food effect.

The doses received by subjects in Part A1 are in Table S2.

Table S2: Part A1 doses of AUT00206

Group	Session 1	Session 2	Session 3	Session 4
1	200 mg	400 mg	1000 mg	400 mg*
2	800 mg*	800 mg†	–‡	–‡

* given in the fed state after a standard breakfast; † given in the fed state after a high-fat breakfast. All other doses were given in the fasted state. ‡ Because the sponsor expected that higher dose levels would exceed the protocol-defined exposure limits, subjects in Group 2 received no further doses.

Part A2

Part A2 did not start until the SRG had reviewed safety, tolerability and PK data (up to 24 h after dosing) from at least 1 dose level in Part A1.

One group of 8 healthy women were enrolled. Each subject had up to 2 study sessions in which they received a single dose of AUT00206 or placebo in the morning, by mouth.

Subjects were randomised to one of 3 treatment sequences (Table S3) such that, in each session, 2 subjects received placebo and 6 received AUT00206 (1:3 ratio).

Table S3: Summary of treatment sequences (Part A2)

Treatment sequence	Session 1	Session 2
1 (n=2)	placebo	dose 2
2 (n=2)	dose 1	placebo
3 (n=4)	dose 1	dose 2

Subjects dosed on the same day were dosed at intervals of at least 10 min.

All doses, dosing regimen, and whether the doses were taken fed or fasted, were determined by the SRG based on the safety, tolerability and PK results of previous doses in Part A1 and A2. As required by the protocol, the first dose in women (Part A2, Session 1) was no higher than 50% of the highest dose previously tested in men (Part A1) that caused no safety concerns.

The doses received by subjects in Part A2 are in Table S4.

Table S4: Part A2 doses of AUT00206

Group	Session 1	Session 2
1	400 mg	800 mg*

* given in the fed state after a high-fat breakfast. All other doses were given in the fasted state.

Part B

Part B did not start until the SRG had reviewed safety, tolerability and PK data (up to 24 h after dosing) from at least 2 dose levels in Part A1.

Enrolment of up to 4 groups of 8 healthy men each (Groups B1–B4) was planned but only 2 groups were enrolled. Each subject had 1 study session, in which they received AUT00206 or placebo (by mouth) once daily for 7 days. In each group, 6 subjects received AUT00206 and 2 received placebo (3:1 ratio).

The dose, dosing regimen, duration of dosing, and whether the dose was taken fed or fasted, was determined by the SRG based on review of the available safety, tolerability and PK results from Part A and previous groups in Part B.

To account for possible accumulation, the first daily dose selected for Part B was no higher than 50% of the highest single dose tested in Part A that caused no safety concerns.

The doses received by subjects in Part B are shown in Table S5.

Table S5: Part B doses of AUT00206

Group	Dose
B1*	7 days' repeated 400 mg QD
B2†	7 days' repeated 600 mg QD

*[redacted], subjects were dosed in the fasted state on Days 1–3. Subsequent doses were given in the fed state after a standard breakfast. † Doses were given in the fed state after a standard breakfast. QD = once daily.

Subject visits

Subjects were screened during the 28 days before their first dose of trial medication. In each study session, subjects were resident on the ward from the day before dosing (Day –1) until completion of procedures at 48 h after their (final) dose (Part A1 and A2: Day 3; Part B: Day 9). They attended 4 short outpatient visits, as follows:

- Part A: Days 4, 5, 7 and 9
- Part B: Days 10, 11, 13 and 15

Subjects also attended a follow-up visit at about 12–16 days after their (final) dose of trial medication (Part A: Days 13–17; Part B: Days 19–23).

The end of the trial was defined as the last visit by the last subject.

Number of subjects

Planned: ≤ 56 (≤ 16 in Part A1, ≤ 8 in Part A2, and ≤ 32 in Part B)

Enrolled: 41 (17 in Part A1, 8 in Part A2 and 16 in Part B)

Completed: 40 (16 in Part A1, 8 in Part A2 and 16 in Part B)

Diagnosis and main criteria for inclusion

Non-smoking men (Part A1 and B only) or women (Part A2 only), aged 18–45 (Parts A1, A2, and B [Groups B1 and B2]) or ≥ 18 years (Part B [Groups B3 and B4]) and with a body mass

index (BMI) of 18.0–31.0 kg/m^2, who were deemed healthy on the basis of a medical history, physical examination, vital signs, ECG and clinical laboratory evaluations; agreed not to donate blood or blood products during the study and for 3 months after dosing; and gave fully informed written consent.

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

Film-coated tablets containing 200 mg AUT00206, and matching placebo tablets containing excipients only, were manufactured and provided to the HMR Pharmacy by Aptuit (Verona, Italy) for use in the trial. The tablets were packaged in opaque white, high density polyethylene bottles with child-resistant closures that were induction sealed.

Actual doses administered are in Table S2 (Part A1), Table S4 (Part A2), and Table S5 (Part B). All treatments were administered orally, in the fasted or fed state, with about 240 mL of water.

Batch numbers of AUT00206 and placebo are in Table S6.

[redacted]

Duration of treatment

In Part A1 and A2, each subject received up to 4 single doses of AUT00206 or placebo. In Part B, each subject received a single daily dose of AUT00206 or placebo for 7 days.

Criteria for evaluation and endpoints

Pharmacokinetics: blood samples for assay of AUT00206 were taken before, and at frequent time points up to 192 h after, dosing and at follow up. The following PK parameters were derived in Parts A1 and A2: C_{max}, t_{max}, AUC_{24}, AUC_{last}, AUC_{inf}, $t_{½}$, λ_Z, CL/F, V_Z/F, MRT_{last} and MRT_{inf}. The following PK parameters were derived in Part B: C_{max}, t_{max}, AUC_{tau}, AUC_{12}, AUC_{last}, AUC_{inf}, $t_{½}$, λ_Z, CL_{SS}/F, V_Z/F, MRT_{tau}, $RAC(C_{max})$, $R_{AC}(AUC_{12})$, $R_{AC}(AUC_{tau})$, and C_{trough}.

Safety: vital signs (blood pressure, heart rate, tympanic temperature, and respiratory rate), 12-lead electrocardiogram (ECG), physical examination, laboratory safety tests (haematology, clinical chemistry, thyroid function, and urinalysis), Columbia-Suicide Severity Rating Scale (C-SSRS) and adverse events (AEs).

Tolerability: AEs

Statistical methods

This was a phase 1 trial evaluating pharmacokinetics and safety of a new formulation, so no formal calculation of sample size was appropriate.

Safety and tolerability data: Safety and tolerability data were not subjected to formal analysis. All data were summarised using descriptive statistics.

Pharmacokinetic data: PK parameters were summarized using descriptive statistics.

Food effect

To assess the effect of food on the bioavailability of single oral doses of AUT00206 in Part A1, C_{max}, AUC_{inf} and AUC_{last} were logarithmically transformed and subjected to analysis of variance (ANOVA), with treatment as a fixed effect and subject as a random effect. The estimated least squares means and residual variation from the model were used to construct the 90% CIs of the ratio (fed:fasted) of geometric means of the PK parameters. The geometric mean ratios comparing fed versus fasted conditions and their corresponding 90% confidence interval (CI) were presented.

Food effect was concluded if the 90% CI of the ratio (fed:fasted) was not included within the range 80–125%.

Results

[redacted]

Pharmacokinetics

PK parameters of AUT00206 are summarised in Table S7 (Part A, male subjects), Table S8 (Part A, female subjects), and Table S9 (Part B).

Part A

AUT00206 was rapidly absorbed in Part A. In male subjects (Table S7), median t_{max} was similar (2–3 h) after single doses of up to 1,000 mg given in either the fasted or fed state (following a standard breakfast), but slightly longer (4 h) after 800 mg given following a high-fat breakfast; individual values broadly ranged about 1–4 h across dose levels, but a single subject had t_{max} of 6 h after 800 mg AUT00206 in both fed states. After AUT00206 given in the fasted state, C_{max} and AUC increased with dose, though increases were only dose-proportional for AUC over the 200 to 400 mg (fasted) dose range. 400 mg fed doses resulted in C_{max} and AUC up to 1.6-fold higher than that seen after the same fasted dose (the effect of food is discussed further below). However, the increase in plasma concentration between 800 mg fed doses after a high-fat rather than standard breakfast was minimal.

In female subjects, t_{max} and C_{max} after 400 mg (fasted) and 800 mg (fed, high-fat breakfast) were generally similar to those in male subjects given equivalent doses (Table S8). AUC parameters were also similar to those recorded in their male counterparts, albeit slightly higher (1.3-fold) after the 800 mg dose.

Generally, elimination was more rapid after doses given in the fed state: across both sexes, arithmetic mean $t_{½}$ was 11.5–12.5 h after fasted (%CVb 17.6–34.3) and 9.0–9.7 h after fed doses (%CVb 24.2–41.6), except for a slightly longer $t_{½}$ recorded after 400 mg given in the fed state (standard breakfast) in male subjects (13.8 h; range 7.97–24.4 h; %CVb 41.6). MRT parameters showed similar trends, with some minimal differences between sexes.

ANOVA confirmed that prior feeding with a standard breakfast increased the bioavailability of 400 mg AUT00206 in male subjects: geometric LS mean ratios (fed:fasted) were 1.46, 1.25, and 1.26 for C_{max}, AUC_{inf}, and AUC_{last}, respectively, with all > 90% confidence intervals outside the range 0.8–1.25.

Altogether, these results indicate that, when given as single doses, the PK profile of AUT00206 did not notably differ between the sexes. However, an effect of food was seen across the dosing groups, albeit statistically confirmed only after 400 mg AUT00206.

Part B

In Part B, 400 mg and 600 mg of AUT00206 were rapidly absorbed after single and repeated doses: Days 1 and 7 t_{max} were similar and ranged 2–6 h and 1–6 h, respectively (Table S9).

Parameters of plasma concentration increased between dose levels: on Days 1 and 7, geometric mean C_{max} was 2,489 and 4,861 ng/mL, AUC_{12} was 19,971 and 38,368 h·ng/mL, and AUC_{24} was 29,979 and 54,083 h·ng/mL after 400 mg once daily (QD); C_{max} was 5,068 and 5,668 ng/mL, AUC_{12} was 35,170 and 45,913 h·ng/mL, and AUC_{24} was 49,171 and 66,729 h·ng/mL after 600 mg QD, respectively. [redacted]

C_{trough} over Days 2–7 suggest that plasma concentrations of AUT00206 reached steady state around Day 3–4 in both 400 mg QD and 600 mg QD dose groups. [redacted]

Accumulation in C_{max} and AUC after 7 days' AUT00206 QD was higher (about 1.8 to 2.0-fold) after 400 mg doses than after 600 mg AUT00206 QD (about 1.1 to 1.4-fold), [redacted] After 600 mg QD, derived arithmetic mean accumulation ratios for C_{max}, AUC_{12}, and AUC_{24} were 1.13–1.37.

(Continued on page 12)

Table S7: Summary of AUT00206 plasma pharmacokinetic parameters after single 200–1,000 mg doses in the fasted and fed state (Part A1; male subjects only)

AUT00206 parameter		Part A1 (male subjects)					
		200 mg [fasted] (N=6)	400 mg [fasted] (N=6)	400 mg [std fed] (N=6)	800 mg [std fed] (N=6)	800 mg [high fed] (N=6)	1,000 mg [fasted] (N=6)
C_{max} (ng/mL)	Geo mean[a]	1,367	2,376	3,591	5,201	6,548	3,839
	Geo %CVb	31.5	21.5	14.2	32.5	34.6	17.2
	Range	868–2,230	1,720–3,070	2,950–4,440	3,540–7,840	3,980–9,960	2,850–4,530
t_{max} (h)	Median	2.00	2.00	3.00	2.00	4.00	2.00
	Range	1.00–4.00	1.00–2.02	2.00–4.13	1.03–6.00	2.00–6.00	2.00–4.00
AUC_{24} (h·ng/mL)	Geo mean[a]	12,295	24,504	33,149	55,234	62,086	45,162
	Geo %CVb	25.9	24.4	19.5	26.9	26.1	31.0
	Range	8,555–16,499	17,728–32,346	24,131–40,352	39,180–78,896	45,482–84,755	30,011–65,116
AUC_{last} (h·ng/mL)	Geo mean[a]	15,577	32,095	43,287	65,258	73,989	63,668
	Geo %CVb	30.1	25.4	21.6	22.2	29.3	48.4
	Range	10,122–21,740	22,928–42,579	31,992–55,466	52,714–92,355	55,114–104,924	33,558–116,286
AUC_{inf} (h·ng/mL)	Geo mean[a]	16,191	33,448	44,047	65,879	74,733	65,268
	Geo %CVb	29.5	24.3	22.1	22.0	29.1	47.2
	Range	10,446–22,638	24,810–43,759	32,601–57,589	53,251–92,860	56,013–105,679	35,782–118,500
$t_{½}$ (h)	Mean[b]	11.8	12.5	13.8	9.03	9.69	11.5
	SD (%CVb)	2.77 (23.4)	3.80 (30.4)	5.72 (41.6)	2.23 (24.7)	2.34 (24.2)	2.03 (17.6)
	Range	9.05–16.8	8.62–19.5	7.97–24.4	6.62–11.5	7.19–13.5	8.97–14.9

%CVb: between-subject coefficient of variation; AUC: area under the plasma concentration–time curve; AUC_{24}: AUC from time 0 to 24 h after dosing; AUC_{inf}: AUC extrapolated to infinity; AUC_{last}: AUC up to the last measurable concentration; C_{max}: maximum (peak) plasma concentration; N: total number of subjects; SD: standard deviation;. std fed: standard breakfast; t_{max}: time of C_{max}; $t_{½}$: terminal elimination half-life.
[a] geometric mean; [b] arithmetic mean

Table S8: Summary of AUT00206 plasma pharmacokinetic parameters after single 400 and 800 mg doses in the fasted and fed state (Part A2; female subjects only)

AUT00206 parameter		Part A2 (female subjects)	
		400 mg [fasted] (N=6)	800 mg [high fed] (N=6)
C_{max} (ng/mL)	Geo mean[a]	2,249	7,000
	Geo %CVb	31.5	43.5
	Range	1,250–2,940	3,680–10,400
t_{max} (h)	Median	2.00	2.01
	Range	1.00–4.00	2.00–12.0
AUC_{24} (h·ng/mL)	Geo mean[a]	24,243	79,683
	Geo %CVb	28.6	38.7
	Range	15,354–32,990	55,955–136,264
AUC_{last} (h·ng/mL)	Geo mean[a]	35,600	96,498
	Geo %CVb	44.2	41.1
	Range	23,360–68,640	64,918–183,630
AUC_{inf} (h·ng/mL)	Geo mean[a]	36,786	97,501
	Geo %CVb	42.6	40.6
	Range	23,862–69,319	65,753–184,094
$t_{½}$ (h)	Mean[b]	12.3	9.44
	SD (%CVb)	4.21 (34.3)	2.97 (31.5)
	Range	8.43–19.8	7.28–14.9

%CVb: between-subject coefficient of variation; AUC: area under the plasma concentration–time curve; AUC_{24}: AUC from time 0 to 24 h after dosing; AUC_{inf}: AUC extrapolated to infinity; AUC_{last}: AUC up to the last measurable concentration; C_{max}: maximum (peak) plasma concentration; N: total number of subjects; SD: standard deviation;.t_{max}: time of C_{max}; $t_{½}$: terminal elimination half-life.
[a] geometric mean; [b] arithmetic mean

Table S9: Summary of AUT00206 plasma pharmacokinetic parameters after 7 days' repeated 400 or 600 mg doses in (Part B; male subjects)

AUT00206 parameter		400 mg AUT00206 QD (N=6)		600 mg AUT00206 QD (N=6)	
		Day 1*	Day 7	Day 1	Day 7
C_{max} (ng/mL)	Geo mean[a]	2,489	4,861	5,068	5,668
	Geo %CVb	26.8	26.4	15.1	22.9
	Range	1,570–3,540	3,410–7,110	4,090–6,050	4,140–7,420
t_{max} (h)	Median	4.00	3.00	3.05	5.00
	Range	2.00–4.00	1.00–4.00	2.00–6.00	1.00–6.05
AUC_{12} (h·ng/mL)	Geo mean[a]	19,971	38,368	35,170	45,913
	Geo %CVb	28.0	25.3	19.9	24.5
	Range	11,650–23,969	25,120–49,137	26,577–46,876	31,896–62,057
AUC_{24} (h·ng/mL)	Geo mean[a]	29,979	54,083	49,171	66,729
	Geo %CVb	30.1	28.6	24.4	29.2
	Range	16,610–36,748	35,405–69,515	37,008–72,277	43,618–97,652

AUT00206 parameter		400 mg AUT00206 QD (N=6)		600 mg AUT00206 QD (N=6)	
		Day 1*	Day 7	Day 1	Day 7
AUC_{last} (h·ng/mL)	Geo mean[a]	–	64,279	–	83,676
	Geo %CVb	–	32.5	–	39.9
	Range	–	43,576–89,211	–	47,613–142,051
AUC_{inf} (h·ng/mL)	Geo mean[a]	–	64,832	–	84,664
	Geo %CVb	–	32.2	–	39.9
	Range	–	44,007–89,724	–	47,933–143,745
$t_{½}$ (h)	Mean[b]	–	9.45	–	11.0
	SD (%CVb)	–	3.06 (32.4)	–	3.14 (28.6)
	Range	–	5.11–13.5	–	6.35–14.9

%CVb: between-subject coefficient of variation; λ_z: terminal rate constant; AUC: area under the plasma concentration–time curve; AUC_{12}: AUC from time 0 to 12 h after dosing; AUC_{24}: AUC from time 0 to 24 h after dosing; AUC_{inf}: AUC extrapolated to infinity; AUC_{last}: AUC up to the last measurable concentration; C_{max}: maximum (peak) plasma concentration; N: total number of subjects; QD: once daily; SD: standard deviation; t_{max}: time of C_{max}; $t_{½}$: terminal elimination half-life.
* [redacted], 400 mg AUT00206 QD subjects were dosed in the fasted state on Days 1–3.
[a] geometric mean; [b] arithmetic mean

Part B (continued)

After 7 days' AUT00206 QD, arithmetic mean $t_{½}$ was slightly longer in the 600 mg QD group (11.0 h) than in the 400 mg QD group (9.45 h), with broadly similar ranges in individual subjects (5.11–14.9 h overall; Table S9). In the lower dose group, $t_{½}$ was shorter than those recorded in Part A after single 400 mg doses in the fasted (12.5 h) and fed state (13.8 h), and closer to that recorded after 800 mg fed-state doses (9.03 h [standard breakfast]; 9.69 h [high-fat breakfast]). MRT_{tau} was similar across dose levels, ranging 7.6–10.3 h overall.

Tablet formulation of AUT00206 (all parts)

The film-coated tablet formulation used in this study was developed with the intention of reducing the food effect and increasing the absorption of AUT00206 when compared with the capsule formulation used in previous clinical trials.

After 200 and 400 mg doses given in the fasted state, geometric mean C_{max} after tablet doses in the present study (1,367 and 2,376 ng/mL, respectively; Part A) were about 4 to 5-fold higher than after the same doses given as capsules in a previous study (371.2 and 476.9 ng/mL, respectively; study AUT011206). t_{max} was also shorter at those doses in the present study (ranges 1–4 h and 1–2 h, respectively) than in study AUT011206 (ranges 2–24 h and 1–48 h, respectively). Hence, based on these results, the rate and extent of absorption of AUT00206 was greater with the tablet formulation than the capsule.

Statistical analyses confirmed an effect of food (standard breakfast) on AUT00206 bioavailability after a single dose of 400 mg tablet formulation (ratio of LS means 1.25–1.46). However, that effect was notably lower than seen after the capsule formulation in study AUT011206, in which, for example, C_{max}, AUC_{10}, and AUC_{24} were 3.5 to 5 times higher after prior feeding. Hence, based on these results, the tablet formulation demonstrated a reduced food effect than the capsule formulation.

Safety and tolerability

Overall, AUT00206 was safe and well-tolerated at all doses investigated during the study, and when taken in both the fed and fasted state. There were no deaths, non-fatal SAEs, or other significant AEs during the study. All treatment emergent adverse events (TEAEs) were mild or moderate in severity. 1 subject in Part A was withdrawn owing to a moderate COVID-19 infection that was considered by the investigator as unlikely to be related to the study medicine. Otherwise, there were no TEAEs leading to withdrawal during the study.

Table S10: Summary of treatment-emergent adverse events

	Part A (N=25)	Part B (N=16)	All Subjects (N=41)
Subjects with:	**n (%) [number of TEAEs]**		
Any TEAE	11 (44.0) [25]	3 (18.8) [3]	14 (34.1) [28]
Any serious TEAE	0	0	0
Any drug-related TEAE	6 (24.0) [12]	0	6 (14.6) [12]
Mild as highest TEAE severity	6 (24.0)	0	6 (14.6)
Moderate as highest TEAE severity	5 (20.0)	3 (18.8)	8 (19.5)
Severe as highest TEAE severity	0	0	0
Life-threatening as highest TEAE severity	0	0	0
TEAEs leading to withdrawal	1 (4.0)	0	1 (2.4)

N: total number of subjects; n: number of subjects with a TEAE; TEAE: treatment-emergent adverse event. Subjects with > 1 TEAE in any treatment session are counted only once per system organ class and preferred term.

Part A

Across all dose levels, 44.0% of subjects had at least 1 TEAE, and 24.0% of subjects had at least 1 TEAE considered by the investigator to be possibly related to treatment.

The most frequently reported system organ class (SOC) of TEAE was nervous system disorders, recorded in 28.0% of subjects across all treatment sessions (including placebo). Headache was the most common TEAE, reported by 20.0% of subjects overall; each instance was considered by the investigator to be possibly drug-related. The occurrence of headache, as well as the other drug-related nervous system disorders reported in Part A, can be considered consistent with the mode of action of AUT00206 and the findings from previous clinical studies with the compound. Other drug-related TEAEs were all reported after 800 mg AUT00206 given in the fed state (high fat breakfast); notably, this group had the highest mean plasma concentration of AUT00206 (6,047 ng/mL in male subjects, and 6,833 ng/mL in female subjects). These TEAEs included single instances of fatigue, dizziness, and somnolence (1 subject who received placebo also reported somnolence).

There was little evidence of an effect of AUT00206 dose on TEAE incidence in male subjects: no possibly drug-related TEAEs were recorded after 200 mg, 400 mg, and 1,000 mg given in the fasted state, nor 400 mg given in the fed state after a standard breakfast. However, possibly drug-related TEAEs were more frequently reported in female subjects – in 50% after 400 mg in the fasted state and 66.7% after 800 mg in the fed state (high-fat breakfast) – consistent with a possible exposure-, sex-, and/or food-related trend. Generally, drug-related TEAEs were more common after fed doses in both populations – recorded in at

least 1 male or female subject after 800 mg following either a standard or high-fat breakfast. However, because the overall incidence of possibly drug-related TEAEs was low, such trends should be interpreted with caution.

1 male subject had clinically-significant raised body temperature, recorded as a TEAE of moderate pyrexia, but that was considered by the investigator as unlikely to be related to treatment. Otherwise, there were no clinically-significant effects on vital signs in Part A. There were no positive C-SSRS results in Part A.

Part B

In Part B, male subjects received 7 days' 400 (Group B1) or 600 mg AUT00206 QD (Group B2). All subjects were dosed in the fed state after a standard breakfast, except those in Group B1, who [redacted] received doses on Days 1–3 in the fasted state [redacted]

There were few TEAEs in Part B: 18.8% of subjects reported only 3 TEAEs across dose levels (single instances of non-cardiac chest pain and arthralgia in subjects after 600 mg QD, and suicidal ideation in 1 subject after placebo QD). No TEAE was considered by the investigator to be possibly related to treatment.

The AE of 'suicidal ideation' was recorded after 1 subject (placebo treatment) returned a positive C-SSRS result at their follow-up visit. He did not have any suicidal thoughts before entering the study, or in the period during and immediately after dosing; the investigator reported that the thoughts were triggered by significant pressures on the subject's personal and working life following his inpatient visit, as well as possible association with heavy alcohol intake. The subject was attended at home by a mental health services team for treatment. He responded 'no' to all relevant questions on a C-SSRS given 19 days after onset of the AE. The investigator and sponsor consider the AE closed with an outcome of 'recovered/resolved'.

There were no clinically significant effects on vital signs in Part B.

All study parts

There were no clinically significant physical examination findings, or changes in body weight, laboratory variables or ECGs, during either study part. Overall, single doses of 200–1,000 mg and repeated 400 or 600 mg AUT00206 QD given in the fed and fasted state were safe and well-tolerated in healthy men and women.

Conclusions

Pharmacokinetics

- AUT00206 was rapidly absorbed after single doses of 200–1,000 mg and 7 days' 400 or 600 mg QD in healthy volunteers: t_{max} was 1–6 h in most subjects. After single doses, the PK profile of AUT00206 was broadly similar in women to that seen in men.

- C_{max} and AUC increased with AUT00206 dose, though often less than dose-proportionally. Between-subject variation in those parameters was low to moderate across all dose levels.
- After single doses, AUT00206 $t_{½}$ was generally shorter after fed doses (about 9 h) than after fasted doses (about 12 h). Overall, $t_{½}$ after repeated doses was in a broadly similar range. Individual λ regression lines showed $t_{½}$ estimates were reliable.
- ANOVA confirmed that prior feeding with a standard breakfast resulted in increased AUT00206 bioavailability after 400 mg doses in healthy men. Other parameters did not clearly demonstrate a further increase in plasma concentration after dosing with a high-fat breakfast.
- After 7 days' 400 or 600 mg AUT00206 QD, C_{trough} showed that steady state was achieved on Days 3 and 4, respectively. [redacted]
- Overall, the tablet formulation of AUT00206 resulted in a reduced food effect and an increased rate and extent of absorption of AUT00206 when compared with the capsule formulation used in previous clinical studies.

Safety and tolerability

- Single doses of 200–1,000 mg and repeat doses of 400 or 600 mg AUT00206 QD, given in either the fed or fasted state, were safe and well-tolerated in healthy volunteers. There was some evidence to suggest a sex-, food-, and/or exposure-related effect on safety and tolerability. TEAEs were reported more frequently in female subjects, particularly in those receiving a higher dose of AUT00206 and those dosed in the fed state.
- There were no deaths, non-fatal SAEs, or other significant AEs, and no treatment-related AEs leading to subject withdrawal from treatment. All TEAEs were mild or moderate in severity.
- There were no clinically significant physical examination findings, or changes in body weight, vital signs, laboratory variables or safety ECGs, during either study part. A single instance of suicidal ideation that occurred after placebo dosing was considered by the investigator to be unrelated to treatment, and was deemed 'recovered/resolved' by the end of the study.