ISRCTN40495811 https://doi.org/10.1186/ISRCTN40495811

A three-part study to investigate ADD008 in comparison to EpiPen®

Submission date
12/04/2024

Recruitment status
No longer recruiting

Registration date
12/04/2024

Overall study status
Deferred

Last Edited
11/03/2026

Condition category
Other

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
The purpose of this study was to investigate the study drug ADD008 (active ingredient adrenaline, herein referred to as epinephrine as this is the applied term for the synthetic (man-made) form of adrenaline), in comparison with EpiPen®. This study was split into four parts and the overall objectives of the study were to determine the safety, tolerability (degree to which side effects of a drug can be tolerated) and concentration in the blood of epinephrine when evaluated in different conditions i.e., single and repeat doses, different dose strengths and in different forms i.e., in the form of a sublingual tablet (which dissolves under the tongue – test drug ADD008) in comparison with EpiPen® (a marketed form of injectable epinephrine used in the treatment of severe allergic reactions) and another marketed form of injectable epinephrine similar to EpiPen® (at a higher dose). The purpose of the overall study was to determine as to which dose strength of ADD008 demonstrated the most comparable concentrations in the blood to the standard dose of the current recommended standard treatment for allergic reactions (EpiPen®).

Who can participate?
A total of 24 participants were enrolled in this study with 18 fully completing. Participants were healthy adult males or females aged between 18 and 60.

What does the study involve?
The purpose of Part 1a & Part 1b was to evaluate the study objectives when ADD008 was administered as a single dose at increasing dose strengths, in comparison with a single dose of EpiPen®. Part 1 consisted of 24 participants total (18 fully completing) with participants receiving ADD008 and EpiPen® across 6 treatment periods. For the first treatment period, all participants received a 0.3 milligram (mg) dose of EpiPen® and for the remaining 5 treatment periods, all participants received increasing doses of ADD008 ranging from 2 mg up to 30 mg. The main difference between the two aspects of Part 1 was that in Part 1a, participants were required to hold the ADD008 tablet under the tongue for a period of 3 minutes whereas in Part 1b, participants were required to hold the ADD008 tablet under the tongue for a period of 20 minutes. Part 1 of the study consisted of a screening visit (between 28 and 2 days prior to the first dose), 6 treatment periods (consisting of one overnight stay per treatment period with doses between the first and second treatment period separated by 24 hours and doses between

each subsequent treatment period (2-6) separated by 5 days) and a post-study follow-up visit 2-5 days after the last dose in treatment period 6.

Blood samples were taken at set timepoints throughout each part of the study in order to measure the levels of epinephrine in the blood. The results between each treatment period and each study part have been compared to determine if there are any significant differences in the safety of epinephrine, the concentration of epinephrine in the blood and how this concentration changed over time or when epinephrine was administered in different conditions i.e., single and repeat doses, different dose strengths and in different forms.

What are the possible benefits and risks of participating?
Taking part in this study was not expected to provide participants with any direct medical benefit. However, the information we get from this study may help improve the treatment of severe allergic reactions.

Possible risks included the following:

Blood Sampling
During the course of the study, the volume of blood to be taken did not exceed 420 mL. This is slightly less than is given during a standard blood donation (approximately 470 mL). The volume to be taken was spread over a period of time and participants were monitored for any potential side effects following blood sampling. This included monitoring for any symptoms associated with low blood iron levels such as tiredness, fatigue etc. If these effects were noted and were determined to be related to the blood sampling procedures for the study, then participants were considered for withdrawal from the study. The procedure for blood collection either by direct venepuncture or indwelling cannula may cause mild pain and bruising at the collection site. Placement of an indwelling catheter was proposed in order to minimise these effects for rapid PK sampling. Very rarely, a blockage of a vein or a small nerve injury can occur, resulting in numbness and pain. If this occurs, it will resolve with time.

Blood pressure and pulse rate
The participant's blood pressure and pulse were measured using an inflatable cuff which will be placed on the arm. They may have experienced mild discomfort in the arm whilst the cuff is inflated.

ECG
Small sticky pads were placed on the participants' upper bodies before the ECG and an ECG machine measured the electrical activity of the participant's heart. Before the pads were applied, the skin was cleaned. Trained staff may have needed to shave/clip small patches of the participant's hair in these areas. Like Elastoplast® these sticky pads were uncomfortable to remove.

COVID-19 Risks
Participants were also made aware of the risks of exposure to COVID-19. When participants attended the clinical unit at each visit, they may have been asked to complete a self-declaration form and temperature check to confirm that they were not showing any early signs of COVID-19 infection and that they had not had any contact with individuals who were currently self-isolating or tested positive (dependent on risk mitigation measures employed at the clinical unit at the time of clinical conduct).

Participants may also have been required to have a negative COVID-19 test prior to admission to the clinical unit for any overnight stays as defined within the study protocol. This procedure may

have caused some mild discomfort in the nose or throat when the swab was being taken but this resolved after the procedure has been completed.

Additionally, at the clinical unit, participants may have been asked to wear a facemask during procedures where clinical staff cannot maintain a 2 m distance. It is noted that if participants had a medical exemption from wearing a face mask, they would not have been required to do so. In any circumstance, to prevent risk of transmission between staff and participants, all staff were wearing appropriate personal protective equipment i.e., face masks, face shields etc during the course of the study.

Harm to the unborn child
The treatment might harm the unborn child; therefore, volunteers who were pregnant, breastfeeding or who intended to become pregnant 2 weeks following the last dose were not eligible to take part. For male participants and female participants (of childbearing potential), they were required to use an effective method of contraception from the point of the screening visit until at least 2 weeks following the last dose. In addition, for female participants (of childbearing potential) a negative pregnancy result was required prior the start of the study.

Throughout the study the health of the participants was regularly monitored and appropriate treatment for any medical condition was provided if required. All doctors employed by Simbec-Orion are trained and certified in Advanced Life Support Procedures in order to deal with a medical emergency. Nurses and other clinical staff are also trained in emergency procedures. Simbec-Orion also has an agreement with Prince Charles Hospital for referral of participants if required following a medical emergency.

Where is the study run from?
The study was conducted at Simbec-Orion Clinical Pharmacology Unit, an MHRA Phase 1 accredited CRO based in South Wales.

When is the study starting and how long is it expected to run for?
The study commenced in May 2024 and completed in January 2025.

Who is funding the study?
This study is funded and sponsored by THERAVIA, based and headquartered in France.

Who is the main contact?
Laura Thomas-Bourgneuf, THERAVIA

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Additional identifiers

Integrated Research Application System (IRAS)
1008056

Protocol serial number
ADR-UK-23-1

Study information

Scientific Title
A Phase 1, three-part, open label, single centre study to investigate the safety, tolerability, and pharmacokinetics of ADD008 in comparison with EpiPen®

Acronym
ADR-UK-23-1

Study objectives
The primary objectives of this study were:

Part 1a and 1b:

1. To determine the recommended dose of ADD008 by comparison of the pharmacokinetic (PK) profiles between ADD008 and EpiPen® 0.3 mg.

Part 2:

1. To demonstrate a similar PK profile between the recommended dose of ADD008 and EpiPen® 0.3 mg:

- With one product administration (Part 2a).
- With 2 product administrations (Part 2b).

The secondary objectives of this study were:

Part 1a and 1b:

1. To assess the secondary PK parameters of ADD008 and EpiPen®.

2. To assess the safety, including local irritation, and tolerability of ADD008.

3. To assess the pharmacodynamics (PD) of ADD008.

Part 2:

1. To assess the secondary PK parameters of ADD008 and EpiPen®:
- With one product administration (Part 2a).
- With 2 product administrations (Part 2b).

2. Part 2a: To assess the PD, safety including local irritation, and tolerability of ADD008 and EpiPen® 0.3 mg when administered as a single dose.

3. Part 2b: To assess the PD, safety including local irritation, and tolerability of both ADD008 and EpiPen® 0.3 mg when administered as repeat/multiple doses.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 16/01/2024, Wales Research Ethics Committee 2 (Health and Care Research Wales, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, United Kingdom; +44 (0)2922 941119; Wales.REC2@wales.nhs.uk), ref: 23.WA.0204

Study design
Three-part open-label study in up to 100 healthy participants

Primary study design
Interventional

Study type(s)
Safety, Other

Health condition(s) or problem(s) studied
Healthy volunteers

Interventions
This was a Phase 1, open-label study to characterise the PK of adrenaline from ADD008 (test IMP) and EpiPen® (reference IMP) (Part 1 [1a and 1b) and to determine the recommended dose of ADD008 for comparison with EpiPen® (reference IMP) (Part 2) following single dose (Part 2a)

and repeat dose (Part 2b) administration in healthy male and female participants in a fasted state. An additional treatment period in Part 2a aimed to contextualise the PK profile of ADD008 in comparison to Anapen® (reference IMP).

Part 1 (1a and 1b): Part 1 was an open-label, crossover, 2-part (Part 1a and Part 1b), PK, safety and PD study of 5 sub-lingual doses of ADD008 vs EpiPen® in 20 participants (10 per part).

Each part within Part 1 comprised of a screening visit conducted within 28 days prior to the first dose of IMP, followed by 6 treatment periods and a post-study follow-up.

Treatment Periods 1 to 6 (Day -1 to Day 1): Eligible participants in Part 1a and Part 1b received a single dose of IMP over 6 treatment periods as follows:

Treatment Period 1:
Reference IMP: A single dose of 0.3 mg adrenaline from EpiPen® auto injector delivered IM via the anterolateral aspect of the thigh (through clothing, if necessary).

Treatment Periods 2-6:
Test IMP: A single dose (ascending order over sequential treatment periods) of:

- 2 mg (2 x 1 mg) adrenaline from ADD008 placed sublingually.

- 5 mg (1 x 5 mg) adrenaline from ADD008 placed sublingually.

- 10 mg (1 x 10 mg) adrenaline from ADD008 placed sublingually.

- 20 mg (Part 1a [1 x 20 mg], Part 1b [2 x 10 mg]) adrenaline from ADD008 placed sublingually.

- 30 mg (1 x 20 mg & 1 x 10 mg) adrenaline from ADD008 placed sublingually.

For Part 1a, participants were required to hold the ADD008 sublingual tablet under the tongue for a period of 3 mins and for Part 1b, participants were required to hold the ADD008 sublingual tablet under the tongue for a period of 20 mins. ADD008 was placed under the tongue until dissolution and was not to be swallowed. There was a minimum of 24 h between the reference IMP dose and first dose of ADD008. There were at least 5 days between ADD008 dose levels. In each ADD008 treatment period, 3 participants were dosed at least 48 hours before the remaining 7 participants.

Post-Study: Post study assessments were conducted 2 to 5 days after administration of the last dose of IMP (i.e., 30 mg/treatment period 6).

Part 2 was planned to be a randomized, 2-part (Part 2a and Part 2b), PK, safety and PD study in 80 participants (up to 40 per part). Part 2a was designed to investigate the recommended dose of sublingual ADD008 vs 0.3 mg EpiPen® IM (2-period crossover) and, in participants weighing >60 kg, the effects of 0.5 mg adrenaline IM (Anapen®) for further PK contextualization (additional treatment period 3). Part 2b was designed to investigate the effects of repeat administration (randomized IMP administered twice at 10 min intervals on each dosing day) of the recommended dose of sublingual ADD008 and 0.3 mg EpiPen® IM (2-period crossover). There was a 24 h washout planned between each dosing day.

Note: Following completion of the interim analysis, it was determined that the PK data generated for ADD008 in Part 1 was insufficient to support adequate dose selection for Part 2 and therefore, Part 2 was not conducted.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
Test: ADD008 sublingual tablet (2, 5, 10, 20 & 30 mg) Reference: EpiPen® (0.3 mg) Reference: Anapen® (0.5 mg) – Part 2a only

Primary outcome(s)
The primary endpoints for Part 1a and Part 1b of this study were pharmacokinetic parameters derived from analysis of plasma samples for concentrations of epinephrine from ADD008, EpiPen® & Anapen and were defined as follows:
1. Maximum plasma concentration (Cmax)
2. First maximum plasma concentration (Cmax1)
3. Time to Cmax (Tmax)
4. Time to Cmax1 (Tmax1)
5. Endogenous adrenaline levels at baseline, prior to adrenaline (unadjusted C0)
6. Time delay between drug administration and the last time prior to first observed concentration above baseline (Tlag)
7. Area under the concentration-time curve (AUC) from time of dosing to 10 min post-dose (AUC0-10)
8. AUC from time of dosing to 20 min post-dose (AUC0-20)
9. AUC from time of dosing to 30 min post-dose (AUC0-30)
10. AUC from time of dosing to time of last measurable concentration (AUC0-t)

Timepoints for Assessment in Part 1a and Part 1b were as follows:
Day 1: -60, -30, immediately pre-dose and 2, 4, 6, 8, 10, 12, 15, 20, 30 min, 1h, 2h & 4h post-dose (applies across all 6 treatment periods).

Key secondary outcome(s))
The secondary endpoints for Part 1a and Part 1b of this study were PK endpoints and safety endpoints and were defined as follows:
PK Endpoints:
1. Elimination rate constant (λz)
2. Terminal elimination half-life (t1/2)
3. AUC extrapolated to infinity (AUC0-inf)
4. AUC%extrapolated (residual area)
Safety Endpoints:
1. Adverse Events (AEs)
2. Vital Signs (systolic/diastolic pressure, heart rate, oral temperature)
3. 12-lead ECG (heart rate, PR interval, QRS width, QT interval and QT interval corrected using Fridericia's (QTcF interval) formula
4. Laboratory safety (biochemistry, haematology, and urinalysis)
5. Oral Cavity assessments

5.1. Oral Cavity (4-point scoring scale)
5.2. Irritation (8-point scoring scale)
5.3. Blanching (Yes or No)

Timepoints for Assessment in Part 1a and Part 1b were as follows:
PK:
Day 1: -60, -30, immediately pre-dose and 2, 4, 6, 8, 10, 12, 15, 20, 30 min, 1h, 2h & 4h post-dose (applies across all 6 treatment periods).
Adverse Events:
AEs will be recorded from the point of informed consent up to final post-study follow up visit.
Vital Signs (All Parts):
Screening, Day -1, Day 1 of each Treatment Period at pre-dose and 10, 15, 45 min, 1, 2, 4 h post-dose & post-study follow up visit.
12 Lead ECG (All Parts):
Screening, Day -1 of each Treatment Period & post-study follow up visit.
Laboratory Safety Testing (All Parts):
Screening, Day -1 of each Treatment Period & post-study follow up visit.
Oral Cavity Assessments (All Parts):
Day 1 of each Treatment Period where ADD008 is administered at pre-dose and 3 min, 10 min, 30 min & 1 h post-dose.

Completion date
10/01/2025

Eligibility

Key inclusion criteria
1. Healthy male and female participant, between 18 and 60 years of age, inclusive.
2. a) Female participant of childbearing potential willing to use an effective method of contraception, if applicable (unless of non-childbearing potential or where abstaining from sexual intercourse was in line with the preferred and usual lifestyle of the participant) from screening until 2 weeks after the last dose of IMP.
b) Female participant of non-childbearing potential. For the purposes of this study, this was defined as the participant being postmenopausal with no menses for at least 12 consecutive months without an alternative medical cause, or at least 4 months post-surgical sterilisation (including bilateral salpingectomy or bilateral oophorectomy with or without hysterectomy).
3. Female participant with a negative pregnancy test at screening.
4. Female participant of menopausal status confirmed by demonstrating at screening that the serum level of follicle stimulating hormone (FSH) fell within the respective pathology reference range. A high FSH level in the postmenopausal range may have been used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement was insufficient.
5. Male participant (and partner of childbearing potential) willing to use an effective method of contraception, if applicable (unless anatomically sterile or where abstaining from sexual intercourse was in line with the preferred and usual lifestyle of the participant) from screening until 2 weeks after last dose of IMP.
6. Participant with a body mass index (BMI) of 18-32 kg/m^2. BMI = body weight (kg) / [height (m)]^2.
7. No clinically significant history of previous allergy / sensitivity to adrenaline or any of the excipients contained within the IMP(s).

8. No clinically significant abnormal test results for serum biochemistry, haematology and/or urine analyses within 35 days before the first dose administration of the IMP.
9. No clinically significant medical history of cardiovascular disease/identified cardiovascular risks or clinically significant medical history of any other condition/disease, as determined by medical history evaluation by the Investigator within 35 days before the first dose administration of the IMP (i.e., during screening).
10. Participant with a negative urinary drugs of abuse screen (including alcohol) test results, determined within 35 days before the first dose administration of the IMP (N.B.: A positive test result may be repeated at the Investigator's discretion).
11. Participant with negative human immunodeficiency virus, hepatitis B surface antigen and hepatitis C virus antibody test results at screening.
12. No clinically significant abnormalities in 12-lead electrocardiogram (ECG) determined within 35 days before first dose of IMP including a PR interval ≤ 220 ms, QRS width ≤ 120 ms and QT interval corrected using Fredericia's formula (QTcF) ≤ 450 ms.
13. No clinically significant abnormalities in vital signs (blood pressure/heart rate, oral temperature) determined within 35 days before first dose of IMP.
14. Participant was available to complete the study (including all follow-up visits).
15. Participant satisfied an Investigator about his/her fitness to participate in the study i.e., participant was able to understand the informed consent form and associated study restrictions, and willing to participate on this basis, inclusive of completeness of all required visits.
16. Participant provided written informed consent to participate in the study.

Participant type(s)
Healthy volunteer

Healthy volunteers allowed
Yes

Age group
Adult

Lower age limit
18 years

Upper age limit
60 years

Sex
All

Total final enrolment
24

Key exclusion criteria
1. Participants who had a clinically significant maxillofacial pathology (including of the oral mucosa and/or dentition) or were still in convalescence following recent maxillofacial surgery as deemed by the Investigator.
2. Presence of any tongue piercings or history of any tongue piercings in the last 90 days prior to Day -1.
3. Use of prescription or non-prescription drugs, within 35 days or 5 half-lives (whichever is longer) prior to the first dose of IMP.

4. Use of dietary and herbal supplements within 14 days prior to the first dose of IMP.
5. Evidence of ongoing or clinical history of renal, hepatic, central nervous system, respiratory, cardiovascular, or metabolic comorbidities.
6. A clinically significant history of drug or alcohol abuse (defined as the consumption of more than 14 units for male and female participants of alcohol a week) within the past two years.
7. Inability to communicate well with the Investigators (i.e., language problem, poor mental development, or impaired cerebral function).
8. Participation in a new chemical entity clinical study within the previous 3 months or five half-lives whichever was the longest, or a marketed drug clinical study within the 30 days or five half-lives whichever was the longest, before the first dose of IMP.(Washout period between studies was defined as the period of time elapsed between the last dose of the previous study and the first dose of the next study).
9. Donation of 450 mL or more blood within the 3 months before the first dose of IMP.
10. Users of nicotine products i.e., current smokers or ex-smokers who had smoked within 6 months prior to first dose administration with the study medication or users of cigarette replacements (i.e., e-cigarettes, nicotine patches or gums).
11. Female participants who were pregnant, breastfeeding or lactating.
12. Participants with veins unsuitable for venepuncture and cannulation.
13. Participants who had received either any live vaccine(s) within 1 month prior to screening or inactivated vaccine(s) 1-2 weeks prior to screening or planned to receive such vaccines during the study.

Date of first enrolment
02/05/2024

Date of final enrolment
18/12/2024

Locations

Countries of recruitment
United Kingdom

Wales

Study participating centre
Simbec Research Limited
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Sponsor information

Organisation
Theravia

Funder(s)

Funder type
Industry

Funder Name
Theravia

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results	version 1.0	10/03/2026	11/03/2026	No	No