A single ascending dose trial to investigate the safety, tolerability, pharmacokinetics, pharmacodynamics, and food effect of orally administered AS-0871 in healthy subjects

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The primary objective is to investigate the safety and tolerability of AS-0871 following single-dose oral administration in healthy subjects.The secondary objectives are:To investigate the PK of AS-0871 (in plasma) following single-dose oral…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON49497

Source
ToetsingOnline

Brief title
190388-CS0338

Condition

- Other condition
- Autoimmune disorders

Synonym
Chronic spontaneous urticaria, Rheumatoid arthritis

Health condition

Inflammatory disorders

Research involving
Human

Sponsors and support

Primary sponsor: Carna Biosciences, Inc.
Source(s) of monetary or material Support: Carna Biosciences;Inc.

Intervention

Keyword: AS-0871, orally administered, Safety, Tolerability

Outcome measures

Primary outcome

safety and tolerability assessments as per protocol.

Secondary outcome

1. PK of AS-0871 in plasma following 7 single dose oral administrations under

fasted conditions;

One single dose level will be tested under fed conditions to assess the food

effect of AS-0871.

2. B-cell and basophil responses to anti-IgD and anti-IgE stimulation of

AS-0871 in blood following single dose oral administrations

3. Potential QT effects of AS-0871 following single dose oral administations by

exposure-response analysis

Study description

Background summary

AS-0871 is a low molecular weight compound belonging to a class of drugs called *kinase inhibitor*, currently under development for the treatment of inflammatory and autoimmune disorders (e.g., rheumatoid arthritis, chronic spontaneous urticaria). AS-0871 is a non-covalent/reversible and highly

selective Bruton*s tyrosine kinase (BTK) inhibitor with an anticipated lower safety risk in human as compared to covalent/irreversible BTK inhibitors; 2 covalent/irreversible BTK inhibitors, ibrutinib and acalabrutinib, are already on the market. In an in vitro model of B cell activation (CD69 expression induced by anti-human immunoglobulin D [IgD] in naïve B cells) and basophil activation (CD63 expression, histamine release, and interleukin [IL]-4 secretion induced by combination of anti-human immunoglobulin E (IgE) and IL-13 treatment) in whole blood obtained from healthy subjects, AS-0871 showed a concentration-dependent inhibition of B cell and basophil activation with relative 50% and 90% inhibitory concentration (IC50/IC90) values of 103/677 nM for CD69 expression, 163/804 nM for CD63 expression, 267/1606 nM for histamine release, and 83/504 nM for IL-4 secretion, respectively. In addition, AS-0871 showed preventive as well as therapeutic efficacy in a mouse model of collagen-induced arthritis.

Study objective

The primary objective is to investigate the safety and tolerability of AS-0871 following single-dose oral administration in healthy subjects.

The secondary objectives are:
To investigate the PK of AS-0871 (in plasma) following single-dose oral administration in healthy subjects.
To investigate the PD of AS-0871 (in blood) following single-dose oral administration in healthy subjects.
To investigate the effect of food on the PK of AS-0871 (in plasma) following single-dose oral administration in healthy subjects.
To investigate potential QT effects of AS-0871 following single-dose oral administration in healthy subjects, using serial electrocardiograms (ECGs) extracted from continuous recordings (Holter) combined with AS-0871 plasma concentration-QT interval corrected for heart rate (QTc) analysis.

The exploratory objectives are:
To collect blood and urine samples for (future) screening of metabolites of AS-0871 following single-dose oral administration in healthy subjects.
To investigate the PK of AS-0871 in urine following single-dose oral administration in healthy subjects.

Study design

This is an FIH, double-blind, placebo-controlled, randomized, single-centre trial in 2 alternating cohorts of healthy adult male and female subjects.

Intervention

AS-0871

Placebo

Study burden and risks

The risk to health at these dose levels is limited but you may experience one of the in the ICF mentioned side-effects or other symptoms not previously reported. Your health will be closely monitored during the study to minimize these risks. If you experience any side effects, the research physician will treat these where necessary. If new information becomes available about the safety of the study drug, you will be informed as soon as possible. For more information refer to the IB.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Must have signed an ICF prior to screening, indicating that he/she understands the purpose of, and procedures required for, the trial, and indicating that he/she is willing to participate in the trial.
2. Healthy males or females of non-childbearing potential, between 18 and 64 years of age, inclusive, at screening.
3. Body Mass Index (BMI) between 18.0 and 30.0 kg/m2, inclusive, at screening.
4. Good physical and mental health as established by medical history, physical examination, ECG, and vital signs (including temporal body temperature) recording, and results of biochemistry, haematology, and urinalysis tests during screening as judged by the investigator.
5. Non-smoker/non-user of nicotine-containing products for at least 3 months prior to screening, to be confirmed by a urine cotinine dipstick test at screening and on Day -1 of the first treatment period of each cohort.
6. Availability and willingness to complete the trial and follow the instructions of the investigator or trial-site personnel.
7. Willing and able to adhere to the prohibitions and restrictions specified in the protocol.
8. Easy venous accessibility.
9. During the trial (from the day of first trial medication onwards) and for a minimum of 1 spermatogenesis cycle (defined as approximately 90 days) after the last trial medication intake, a male subject must agree:
to wear a condom when engaging in any activity that allows for passage of ejaculate to another person (male subject should also be advised of the benefit for a female partner to use a highly effective method of contraception as condom may break or leak);
not to donate sperm for the purpose of reproduction.
Contraceptive use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical trials.
10. At screening, a female subject must be not of childbearing potential defined as:
postmenopausal A postmenopausal state is defined as no menses for > 12 months without an alternative medical explanation. A high follicle stimulating hormone (FSH) level (> 40 IU/L or mIU/mL) in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy. In the absence of > 12 months of amenorrhea, 2 FSH measurements have to be available, measured at least 3 months apart,
or
permanently sterile Permanent sterilization methods include hysterectomy, bilateral salpingectomy, bilateral tubal occlusion/ligation procedures, and bilateral oophorectomy.
11. Female subject, except if postmenopausal, must have a negative highly sensitive serum (*-human chorionic gonadotropin [*-hCG]) pregnancy test at screening and female subject must have a negative urine pregnancy test on Day -1 of the first treatment period of each cohort.

12. Female subject must agree not to donate eggs (ova, oocytes) for the purposes of assisted reproduction during the trial and for at least 90 days after the last trial medication intake in the last treatment period.
13. Able to communicate well with the investigator, in the local language, and to understand and comply with the requirements of the trial.

Exclusion criteria

1. History of or current clinically significant medical illness including (but not limited to) gastrointestinal, cardiovascular, neurologic, psychiatric, metabolic, endocrinologic, genitourinary, renal, hepatic, respiratory, inflammatory, neoplastic, haematologic, or infectious disease, or any other illness that the investigator considers should exclude the subject or that could interfere with the interpretation of the trial results.
2. Clinically relevant abnormal values for haematology, biochemistry, or urinalysis at screening or on Day -1 of the first treatment period, as judged by the investigator.
3. Values of hepatic aminotransferase (ALT and/or AST) > 1.5 × the upper limit of normal range (ULN) at screening or on Day -1 of the first treatment period.
4. Values of GGT and/or ALP > 1.25 x ULN at screening or on Day -1 of the first treatment period.
5. Values of total cholesterol > ULN and LDL cholesterol > 1.25 x ULN at screening or on Day -1 of the first treatment period.
6. Values of total bilirubin > ULN at screening or on Day -1 of the first treatment period.
7. Values of urea >1.5 × ULN at screening or on Day -1 of the first treatment period.
8. A QTcF > 450 ms for male subjects and > 470 ms for female subjects.
9. Clinically significant abnormal complete physical examination at screening or on Day -1 of the first treatment period, or clinically significant abnormal symptom-driven physical examination at predose on Day 1 of the first treatment period (if applicable), or clinically significant abnormal values for vital signs (including temporal body temperature) or 12-lead ECG at screening or at predose on Day 1 of the first treatment period, as judged by the investigator.
10. Clinically significant presence or history of allergy or intolerance (including lactose) as judged by the investigator.
11. Previously demonstrated clinically significant allergy or hypersensitivity to any of the components of the trial medication (see IB8).
12. Positive serology for hepatitis A virus (HAV) immunoglobulin M (IgM), hepatitis B virus surface antigen (HBsAg), anti-hepatitis C virus antibodies (anti-HCV-AB), or anti human immunodeficiency virus antibodies 1 + 2 (anti-HIV-AB 1 + 2) at screening.
13. History of alcohol or drug abuse within the last 2 years before screening or positive test result(s) for alcohol and/or drugs of abuse at screening or on Day *1 of the first treatment period of each cohort.

Note: A positive alcohol and/or drug test may be repeated once (as soon as possible and within the screening period) to exclude a technical error. Subjects with a negative alcohol and/or drug test at retest may be included.
14. Regular alcohol consumption > 14 units per week (1 unit = a 200-mL glass of average-strength beer, 25 mL of 40% spirit. A 125-mL glass of wine is 1.5 unit).
15. A history of cancer excluding carcinoma in situ or intra-mucosal cancer.
16. Surgery of gastro-intestinal tract that might interfere with absorption (subjects who have had cholecystectomy may be included). Subject has currently significant and active diarrhoea, nausea, or constipation that in the investigator*s opinion could influence drug absorption or bioavailability.
17. Intake of any disallowed therapies (see Section 5.10, Prior and Concomitant Medication) before the first trial medication intake.
18. Donation of blood or blood products or substantial loss of blood (more than 500 mL) within 3 months before the first trial medication intake or the intention to donate blood or blood products during the trial.
19. Participation in a clinical trial of an investigational product or an experimental medical device within 60 days or within a period less than 5 times the drug*s half-live, whichever is longer, prior to the first trial medication intake.
20. Major surgery, fracture, or prolonged immobilization (more than 2 weeks) within 3 months preceding screening, or surgery has been planned during the time the subject is expected to participate in the trial.
21. Female subject who is breastfeeding at screening.
22. Trial site employee or immediate family members of a trial site or sponsor employee.
23. Has previously been enrolled in this trial.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-02-2020
Enrollment:	16
Type:	Actual

Ethics review

Approved WMO Date:	07-01-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	03-02-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-03-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-07-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-11-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2019-004348-31-NL
CCMO	NL72381.056.19

Study results

Results posted: 01-11-2021

First publication
09-07-2021