A Phase 2a, Randomised, Double-Blind, Placebo Controlled Study to Assess Efficacy and Safety of Atuliflapon Given Orally Once Daily for Twelve Weeks in Adults with Moderate-to-Severe Uncontrolled Asthma

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This study has been transitioned to CTIS with ID 2023-509243-27-00 check the CTIS register for the current data. Primary:- To evaluate the clinical efficacy of Atuliflapon 250 mg QD as compared to placebo in uLTE4-high adult participants with...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Lower respiratory tract disorders (excl obstruction and infection)
Study type	Interventional

Summary

ID

NL-OMON53653

Source
ToetsingOnline

Brief title
FLASH

Condition

- Lower respiratory tract disorders (excl obstruction and infection)

Synonym
Asthma

Research involving

Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Asthma, Atuliflapon, Double-Blind, Placebo-Controlled

Outcome measures

Primary outcome

Primary endpoint:

- time to first CompEx Asthma event

Secondary outcome

Secundary endpoint:

- Endpoint and population-level summary measure are the same as for the primary objectives

Further endpoints: change from baseline in:

- pre-BD FEV1: Baseline, Week 4, and Week 12

- SGRQ: Baseline, Week 4, and Week 12

- ACQ-6: Baseline, Week 4, Week 8, Week 12, and average over the 12-week treatment period

- average morning and average evening PEF: Baseline, Week 4, Week 8, Week 12, and average over the 12-week treatment period

- daily asthma symptom score (total, daytime, and night-time): Baseline, Week 4, Week 8, Week 12, and average over the 12-week treatment period

- time to first severe asthma exacerbation

- event status (CompEx Asthma event yes/no)

PK endpoints:

- AZD5718 plasma concentrations and PK parameters

- AZD5718 plasma concentrations: pre-dose samples at Baseline, Week 4, and Week 12

Safety endpoints:

- safety and tolerability evaluations using AEs, vital sign measures, clinical laboratory assessments, ECG, and C-SSRS

Study description

Background summary

Atuliflapon (previously identified as AZD5718), is an oral selective 5-lipoxygenase activating protein (FLAP) inhibitor being developed for the treatment of asthma. Inhibition of FLAP activity will attenuate production of pro inflammatory and vasoactive leukotrienes by leukocytes. Atuliflapon is hypothesised to improve asthma disease status in participants with elevated activity of the leukotriene pathway by reducing symptoms and frequency of asthma exacerbations, as a result of a reduction in inflammation and improvements in physiological measures of lung function, thereby improving the quality of life of asthma patients.

Study objective

This study has been transitioned to CTIS with ID 2023-509243-27-00 check the CTIS register for the current data.

Primary:
- To evaluate the clinical efficacy of Atuliflapon 250 mg QD as compared to placebo in uLTE4-high adult participants with moderate to severe uncontrolled

asthma

Secondary:
- To determine an optimal uLTE4 threshold for clinical efficacy of AZD5718 250 mg QD as compared to placebo in adult participants with moderate-to- severe uncontrolled asthma
- To evaluate the clinical efficacy of Atuliflapon 250 mg QD as compared to placebo in adult participants with moderate to severe uncontrolled asthma
- To evaluate the clinical efficacy of AZD5718 250 mg QD as compared to placebo in adult participants with moderate-to-severe uncontrolled

To further evaluate the:
- Clinical efficacy of Atuliflapon as compared to placebo in uLTE4-high adult participants with moderate to severe uncontrolled asthma
- Clinical efficacy of Atuliflapon 250 mg QD as compared to placebo in adult participants with moderate to severe uncontrolled asthma

To evaluate the PK of AZD5718 in:
- Participants in a Lead-in PK cohort, after 1 day and 14 days dosing (AZD5718 250 mg QD)
- All participants (pre-dose samples) after 4 weeks and 12 weeks dosing (Part 1)

Safety:
To assess the safety and tolerability of AZD5718 in adult participants with moderate-to-severe uncontrolled asthma

Study design

This is a randomised, placebo-controlled, double-blind study to assess the efficacy and safety of Atuliflapon orally administered once daily (QD) over a 12-week treatment period to adult participants with asthma. The enrolled patients are on low dose ICS-LABA or medium to high dose ICS with or without LABA background treatment and were uncontrolled based on their exacerbation history plus asthma symptom control level. For the purpose of this study, we describe the population as participants with moderate to severe uncontrolled asthma.
The study will be initiated by a Lead-in PK Cohort to confirm PK of 250 mg Atuliflapon in participants with asthma after 14 days of treatment. Participants for Part 1 will only enter the run-in period after the PK in participants with asthma has been confirmed by the Lead-in PK Cohort. Approximately 666 participants will be randomised globally, including 18 participants in the Lead-in PK Cohort and 648 participants in Part 1 of the study.
In the Lead-in PK Cohort, approximately 18 participants will be randomised 2:1 to 14 days treatment with 250 mg Atuliflapon QD or placebo. This cohort will not continue treatment after 14 days (± 1 day) and will not be included in

efficacy analysis. Recruitment for this cohort has been completed as of CSP Amendment 3.
Randomisation in Part 1 will be stratified by geographical region (Central and Eastern Europe, Western Europe, Asia, North America, and Rest of the World) and by uLTE4 level at Screening (Visit 1).
A predefined threshold level for uLTE4-high was set to 150 pg/mg creatinine, approximately corresponding to the 75th percentile of the distribution of uLTE4 levels in patients with moderate to severe asthma (data on file, the observational NOVELTY study). Based on creatinine normalised uLTE4 levels from the first 100 participants fulfilling the inclusion criteria at Part 1 Pre-screening (data were collected until Pre-screening was removed as of CSP Amendment 3), the predefined threshold for uLTE4-high will be confirmed and the thresholds for stratification levels will then be adjusted accordingly to the 50th and 75th percentile of the creatinine normalised uLTE4 distribution of the 100 participants.
In Part 1 of the study, approximately 648 participants will be stratified as uLTE4-high or uLTE4-low at Screening (Visit 1) and randomised 1:1 to Atuliflapon 250 mg QD or placebo. Urine LTE4-high will include participants with uLTE4 according to the adjusted predefined thresholds below:
• uLTE4 >= 75th percentile (approximately 25% of the total number of participants in Part 1).
• uLTE4 >= 50th percentile to < 75th percentile (approximately 25% of the total number of participants in Part 1).

Urine LTE4-low will include participants with uLTE4 < 50th percentile (approximately 50% of the total number of participants in Part 1).
An event-driven interim analysis (IA) will be performed once 30 participants with at least 1 CompEx event are observed in the uLTE4-high group. This corresponds to approximately 40% of the uLTE4-high participants in Part 1 having completed 12-weeks treatment (assuming the CompEx Asthma event frequency over 12 weeks within placebo is 0.3). However, the IA may be triggered at any time if the frequency of blinded events is lower than expected.
A PD sub-study will be conducted in a subset of participants. The PD sub study aims to recruit approximately 10 participants on Atuliflapon 250 mg and approximately 10 participants on placebo overall (ie, across the uLTE4 stratifications). As part of this sub study, additional PD samples will be collected.

Intervention

Eligible participants with moderate-to-severe uncontrolled asthma will be randomised to 1 of 2 separate treatment groups.

In the Lead-in PK cohort and Part 1 of the study, participants will be randomised to AZD5718 250 mg QD or placebo.

The duration of study will vary depending on what part participants are randomised to:
*Lead-in PK Cohort: The overall study period is approximately 7 weeks; a screening period of up to 28 days, a 2-week treatment period and a 1-week follow-up.
*Part 1: The overall study period is approximately 19 weeks; a 2-week screening period (not including Visit 0), a 4-week run-in period, a
12-week treatment period, and a 1-week follow-up.

Study burden and risks

For this study, the subjects will come to the center approximately 7 times (1 visit will take place by telephone or video calling)

The study load includes:
- Blood draw
- Urine test for pregnancy for women
- EKG
- Physical examination
- Various interviews and questionnaires
- COVID-19 PCR test
- Keep digital diary
- Spirometry test

The subject may experience physical or psychological discomfort from the above tests, procedures and questionnaires.
The subject may experience side effects from the study medication.

Contacts

Public
Astra Zeneca

Kvarnbergagatan 12
Södertälje 151 36
SE
Scientific
Astra Zeneca

Kvarnbergagatan 12
Södertälje 151 36
SE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Part 1 and Part 2 protocol 5.1.2.

General Inclusion Criteria for Part 1 and Part 2
10. Capable of giving signed informed consent
11. Provision of signed and dated written Optional Genetic Research Information informed
consent prior to collection of samples for optional genetic research that supports Genomic
Initiative.
12. Participant is willing and able to follow study procedures and restrictions.
13. Participant must be 18 to 80 years of age inclusive, at the time of signing the ICF.
14. Body weight 50 - 120 kg and body mass index (BMI) 18 -35 kg/m2.
15. Documented physician-diagnosed asthma >= 12 months prior to Visit 1.
16. Able to perform acceptable lung function testing for FEV1 according to ATS/ERS 2019
acceptability criteria.
17. Documented evidence of asthma as demonstrated by either:
* Post-BD reversibility of FEV1 >= 12% and >= 200 within 5 years prior to Visit 1, or at Visit 1, or
* PEF average daily variability > 10% over a 2-week period within 5 years prior to Visit 1, or
* Variability of FEV1 > 12% and 200 mL between any two clinical visits within 5 years prior to Visit 1, or
* Positive methacholine challenge test within the 5 years prior to Visit 1. A positive result is defined as a PC20 <= 8 mg/mL.
18. Morning pre-BD FEV1 between >= 40% and <= 80% predicted at Visit 1.
19. Documented history of >= 1 severe asthma exacerbation within 3 years prior to Visit 1.

20. Treated with low dose ICS-LABA or medium-high dose ICS (as per GINA 2021 ICS equivalence table - Appendix C) alone or in combination with LABA at a stable dose for
at least 3 months prior to Visit 1. (The ICS can be contained within an ICS-LABA fixed
dose combination product).
* Treatment with additional asthma controller therapies (eg, LAMA) at a stable dose
>= 3 months prior to Visit 1 is allowed. (Treatment with LTRAs or 5-LO inhibitors is not allowed.
21. An ACQ-6 score >= 1.5 at Visit 1 and at Visit 3.
22. Able and willing to comply with the requirements of the protocol including ability to
read, write, be fluent in the translated language of all participant facing questionnaires
used at site, and use electronic devices, eg, eCOA device and spirometry.
28. At least 80% compliance with usual asthma background medication during run-in period
(from Visit 2 to Visit 3) based on the daily asthma ePROs.
29. Minimum 80% compliance with daily eCOA assessments.
24. For female participants, a negative serum pregnancy test.
25. Contraceptive use by female participants should be consistent with local regulations
regarding the methods of contraception for those participating in clinical studies. There
are no restrictions on male participants or their female partners.

Exclusion criteria

Protocol 5.2.1. 1. A severe asthma exacerbation within 8 weeks of randomisation. 2. A positive nucleic acid test (eg RT-PCR) at Visit 1 or at Visit 3 for SARS-CoV-2, the virus responsible for COVID-19. 3. Participants with a significant COVID-19 illness within 6 months of enrolment: * Participants with a diagnosis of COVID-19 pneumonia based on radiological assessment. * Participants with a diagnosis of COVID-19 requiring hospitalisation and/or oxygen supplementation therapy. 4. Clinically important pulmonary disease other than asthma eg, active lung infection, COPD, bronchiectasis, pulmonary fibrosis, cystic fibrosis, hypoventilation syndrome associated with obesity, lung cancer, history or planned lung lobectomy, alpha-1 anti-trypsin deficiency, primary ciliary dyskinesia, Churg-Strauss syndrome, allergic bronchopulmonary aspergillosis and hyper-eosinophilic syndrome. 6. Any disorder, including, but not limited to, cardiovascular, gastrointestinal, hepatic, renal, neurological, musculoskeletal, infectious, endocrine, metabolic, haematological, psychiatric, or major physical impairment that is not stable in the opinion of the investigator and could: * Affect the

safety of the participant throughout the study. * Influence the findings of the study or the interpretation. * Impede the participant's ability to complete the entire duration of study. 7. Any clinically significant cardiac disease: * Acute coronary syndrome (acute myocardial infarction, unstable angina), coronary intervention with percutaneous coronary intervention/coronary artery bypass surgery or stroke within 6 months. * Heart failure NYHA II-IV. * Untreated high degree atrioventricular-block (>= 3:1 conduction rate/Grade III block)/ significant sinus node dysfunction/pause or therapy requiring tachyarrhythmia. * History or family history of long QT-syndrome. * History of QT prolongation associated with other medications that required discontinuation of that medication. * Hypertrophic cardiomyopathy or clinically significant valvular heart disease. * Stroke within 3 months of Visit 1. 8. History of severe renal disease (CKD stage 4 or 5) or history of creatinine clearance < 30 mL/min × m2 calculated using Cockcroft-Gault equation. 9. Severe hepatic impairment (Child-Pugh class C). 10. Previous hepatotoxicity related to zileuton or LTRAs (eg montelukast) 11. Participants with a recent history of, or who have a positive test for, infective hepatitis or unexplained jaundice, or participants who have been treated for hepatitis B, hepatitis C, or HIV. For the hepatitis B testing (HbsAg, anti-HBs, and anti-HBc), any of the following would exclude the participant from the study: * Participants positive for HbsAg. * Participants positive for anti-HBc. 12. Evidence of active or untreated latent TB: * Positive IGRA, or repeated indeterminate IGRAs, no evidence of active TB and untreated for LTBI, unable to be treated for, or declines treatment of LTBI. * Participants newly diagnosed with LTBI at Visit 1 could be considered for rescreening if they complete a full course of treatment for LTBI in accordance with recommended treatment guidelines prior to rescreening. In this situation, repeat IGRA test is not required after completion of treatment for LTBI. * Participants with an indeterminate IGRA should undergo a repeat test and if still indeterminate may be enrolled only after being treated for LTBI. 13. Any other clinically relevant abnormal findings on physical examination or laboratory testing including haematology, coagulation, serum chemistry, urinalysis, or ECG between Visit 1 and Visit 3 (randomisation), that in the opinion of the investigator or medical monitor might compromise the safety of the participant in the study or interfere with evaluation of the study intervention. Abnormal findings include, but are not limited to: * ALT or AST >= 2 × ULN. * TBL >= 1.5 × ULN (unless due to Gilbert*s disease). * Evidence of chronic liver disease. * Abnormal vital signs, after 5 minutes of supine or sitting rest (confirmed by one controlled measurement), defined as any of the following: o SBP < 80 mmHg or >= 150 mmHg. o DBP < 50 mmHg or >= 95 mmHg. o Pulse < 45 or > 100 beats per minute. * Signs of pulmonary oedema or volume overload. * Any clinically significant rhythm, conduction, or morphology abnormalities in the ECG including but not limited to QTcF > 450 ms. 34. Smokers with smoking history of <10 pack-years or users of vaping or e-cigarettes, must have stopped at least 6 months prior to Visit 1 Please refer to the protocol for the full list of exclusion criteria.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	14-12-2023
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Atuliflapon
Generic name:	Atuliflapon

Ethics review

Approved WMO Date:	23-05-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	21-09-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	28-02-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-03-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-06-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-10-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-10-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	17-01-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-02-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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
EU-CTR	CTIS2023-509243-27-00
EudraCT	EUCTR2021-003338-35-NL
CCMO	NL80393.028.22