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A study to evaluate the efficacy and safety of atumelnant in adults with ACTH-dependent Cushing's syndrome

Submission date
30/05/2026

Recruitment status
Not yet recruiting

Registration date
03/11/2026

Overall study status
Ongoing

Last Edited
03/11/2026

Condition category
Nutritional, Metabolic, Endocrine

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Crinetics is developing a new medicine called atumelnant for the treatment of ACTH-dependent Cushing's syndrome (ADCS, also called Cushing's syndrome) in adults. In Cushing's syndrome, the body makes too much of a hormone called adrenocorticotropic hormone (ACTH), which leads to having too much cortisol in the body.
The goal of treatment for patients with Cushing's syndrome is normalization of cortisol levels, measured as urinary free cortisol (UFC) over a 24-hour period. The goals of this study are to determine the following:
1. How well atumelnant can lower cortisol levels.
2. The appropriate dose of atumelnant for the treatment of Cushing's syndrome (Part A only).
3. How safe atumelnant is at different doses and with long-term use, and how well the body accepts (tolerates) it.
4. How atumelnant moves through the body (how it gets in, spreads around, gets used, and then leaves), also known as pharmacokinetics (PK).
5. What effects atumelnant has on the body and how it works, also known as pharmacodynamics (PD).

Who can participate?
Patients aged 18 to 74 years with Cushing's syndrome.

What does the study involve?
This study will consist of three parts: Part A, Part B, and Part C. Participants from Part A or Part B, as well as those who completed screening for Part B after enrollment for Part B was completed, may be eligible for Part C.
Part A and Part B will last for up to 7 months each. Part C lasts for up to 2 years. For participants who decide to continue into Part C (extension study), the entire length of the study (Part A or B, plus Part C) is about 2 years and 7 months.
In Part A (Arm 1), all participants will receive atumelnant.

In Part A (Arms 2, 3, and 4) and Part B, participants randomly receive either atumelnant or placebo. The use of placebo helps Crinetics determine how well atumelnant works to help control ACTH levels in the body. In Part C, all participants receive atumelnant.

What are the possible benefits and risks of participating?
The following side effects were reported by people in other studies with atumelnant:
1. Not enough cortisol in the body. Signs and symptoms may include nausea, vomiting, diarrhoea, stomach-ache, tiredness, loss of appetite, lightheadedness, muscle and joint pain, higher levels of potassium in the blood, low blood pressure, and low blood sugar
2. Itchy rash
3. Headache
4. COVID-19 infection
5. Respiratory infection like a cold
6. Anxiety
7. Skin redness
8. Inflammation of skin
9. Darkening of skin
10. Feeling of heart pounding or racing
11. Higher liver blood test results than normal
12. Increase creatinine in blood
13. Gastrointestinal (GI) bleed. A GI bleed means bleeding that occurs within the digestive tract, from mouth to anus, and can appear as blood in vomit, stool, or both.

For placebo:
Placebo looks like a study drug, but it has no active ingredients that are known to cause side effects.

There are other side effects that have been reported. Participants should always let the study doctor and site staff know if they notice any change.

Atumelnant works by lowering cortisol, a hormone that your body produces in excess when you are diagnosed with Cushing's syndrome. Atumelnant works by lowering the amount of cortisol your body makes. It does not only remove the extra cortisol that causes your symptoms; it also lowers the normal amount of cortisol your body needs every day to function. Because of this, you will take a glucocorticoid (steroid) medicine to replace the cortisol your body is no longer making. Together, atumelnant and the steroid medicine keep your cortisol at a healthy level. On days when you are sick, your body needs more cortisol than usual, so your doctor may tell you to take a higher dose of the glucocorticoid until you feel better.

Stopping your current treatment for Cushing's may cause your Cushing's syndrome symptoms to temporarily worsen.

There may be risks if participants become pregnant. No one knows if the study drug may affect an unborn or a nursing baby.

Mitigation Strategy: Your study doctor will check on you regularly to watch for any side effects. If you have symptoms, you may receive treatment to help you feel better, and if needed, the study drug may be paused for a time. Your safety will be reviewed on an ongoing basis throughout the study.

As is true for any experimental drug, there may be unknown and potentially serious or life-threatening side effects or risks that could occur with atumelnant. Observed side effects to date

will be explained to participants during the informed consent discussion. Participants will be told about any new findings that develop during the study, which may affect their decision to stay on the study.

Participants will be followed throughout the study for any side effects. They will be provided with a phone number so that they can contact study staff if they have any concerns.

Study visits: The number of visits required is over and above normal clinical practice and participants will need to make an additional time commitment. However, bearing in mind that this study is assessing the use of a potential new medicine and it's potential side effects, regular monitoring and assessment is imperative.

The DXA scan will be used to measure body composition and bone density. The amount of radiation exposure from a DXA scan is low and comparable to background radiation. It is much less than the amount of radiation from a chest x-ray.

Contraception:
Participants will be counselled by the doctor on highly effective birth control methods during the participation in the study until at least 2 weeks after the last dose of study drug. In the event of a pregnancy during the study, the participants will be withdrawn and the pregnancy will be followed through the delivery and after birth. Men are not allowed to donate sperm during the participation in the study until at least 2 weeks after the last dose of study drug

Confidentiality:
Ethical concerns relating to personal data are addressed by ensuring security of personal data acquired for the study and by following good clinical practice and the requirements of UK data protection law and data protection regulations of the countries to which study data may be transferred for analysis. No named participant data will leave the hospital site.

It is not known whether you will get any benefit from taking part in this study. If atumelnant works for you, your Cushing's syndrome may get better, and this may help you. If you are assigned to placebo, you will not receive atumelnant at first. If your Cushing's syndrome does not improve or gets worse while you are in the study, your study doctor may give you rescue treatment to help control your symptoms and you may later be able to receive atumelnant in this study. There is no guarantee that atumelnant treatment in this study will help you. What is learned from this study may help other people with Cushing's syndrome in the future and will help the study Sponsor and doctors learn more about atumelnant.

Where is the study run from?
Crinetics Pharmaceuticals, Inc. (USA)

When is the study starting and how long is it expected to run for?
November 2026 to April 2032

Who is funding the study?
Crinetics Pharmaceuticals, Inc. (USA)

Who is the main contact?
Crinetics Pharmaceuticals Clinical Trial Team, clinicaltrials@crinetics.com

Contact information

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Principal investigator, Public

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Clinical Trials Information System (CTIS)
2025-522648-42-01

Integrated Research Application System (IRAS)
1013109

Sponsor's Protocol Code Number
CRN04894-331

Study information

Scientific Title
A multicenter, Phase II/III, dose range finding study to evaluate the efficacy and safety of atumelnant in adults with ACTH-dependent Cushing’s syndrome (ADCS) including an open-label extension for long-term assessment (EQUILIBRIUM-ADCS)

Acronym
EQUILIBRIUM-ADCS

Study objectives

1. To evaluate the effect of atumelnant on mUFC at Week 12.
2. To evaluate the (long-term) side effects of atumelnant.
3. Evaluating the effect of atumelnant on specific PD biomarkers
4. Evaluating the effect of atumelnant on quality of life (QOL).

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 28/07/2026, East Midlands - Derby Research Ethics Committee (2 Redman Place, London, DC20 1JQ, United Kingdom; +44 (0)207 104 8154; derby.rec@hra.nhs.uk), ref: 26/EM/0125

Primary study design
Interventional

Allocation
Randomized controlled trial

Masking
Blinded (masking used)

Control
Placebo

Assignment
Parallel

Purpose
Safety

Study type(s)

Health condition(s) or problem(s) studied
ACTH-dependent Cushing’s syndrome (ADCS)

Interventions
Participants will undergo a screening and washout phase of about 12 weeks (about three site visits) before entering the treatment phase.

In Part A (Arm 1), participants will receive atumelnant 20 mg by mouth and steroids if needed. During treatment, there will be up to 14 site visits on Days 1 to 14 and up to 6 during Weeks 3 to 12. Participants may be required to stay close to the study site for up to the first 14 days. This will be followed by a 4-week follow-up phase with up to four visits.

In Part A (Arms 2, 3 and 4), participants will be assigned via an online tool (IRT) to receive atumelnant 40 mg, atumelnant 80 mg, or placebo by mouth in a 1:1:1 ratio (for every 1 participant who receives atumelnant 40 mg, one participant will receive atumelnant 80 mg and one participant will receive placebo). Treatment allocation will be determined by chance. The

participant, their caregiver(s), and the investigators will be blinded to treatment assignment. During treatment, there will up to five visits on Days 1 to 14 and up to 4 on Weeks 4 to 12. This will be followed by a 4-week follow-up phase with up to four visits.

In Part B, participants will be assigned via an online tool (IRT) to receive atumelnant or placebo by mouth in a 2:1 ratio (for every two participants who receive atumelnant, one participant will receive placebo). Treatment allocation will be determined by chance. The participant, their caregiver(s), and the investigators will be blinded to treatment assignment. During treatment, there will be up to five visits on days 1 to 14 and up to 4 during Weeks 4 to 12. This will be followed by a 4-week follow-up phase with up to four visits.

In Part C, participants will receive atumelnant up to 120 mg by mouth. During treatment, there will be up to five visits during Days 1 to 14 and up to 12 site visits during Weeks 4 to 96. This will be followed by a 4-week follow-up phase with up to four visits.

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Atumelnant

Primary outcome(s)
1. Mean urinary free cortisol (mUFC) less than or equal to upper limit of normal (ULN) measured using 24-hour urine collections at 12 weeks (Part A and Part B)

2. Treatment-emergent adverse events (TAEs) and adverse events of special interest (AESI) measured using participant-reported symptoms via interview and direct questioning by site staff and investigator as events occur, at 12 weeks or at discontinuation (Part A and Part B) and at 102 weeks post intervention commencement (Part C)

3. Vital signs (blood pressure, respiratory rate, body temperature) measured using medical equipment (e.g. validated digital blood pressure monitors, thermometers, and standard respiratory rate assessment techniques as events occur, at 12 weeks or at discontinuation (Part A and Part B) and at 102 weeks post intervention commencement (Part C)

4. Laboratory assessment (including safety laboratory assessments) measured using laboratory methods by certified and accredited local or central laboratories as event occurs, at 12 weeks or at discontinuation (Part A and Part B) and at 102 weeks post intervention commencement (Part C)

Key secondary outcome(s)
1. Effect of atumelnant on specific pharmacodynamic (PD) biomarkers measured using the change from baseline in mean urinary free cortisol (mUFC) and late-night salivary cortisol at 12 weeks (Part A and Part B) at 102 weeks post intervention commencement (Part C)

2. Quality of life (for Part B and C) measured using the baseline QoL value compared to the QoL value at 12 weeks (Part B) and at 102 weeks post intervention commencement (Part C)

Completion date
30/04/2032

Eligibility

Key inclusion criteria
1. Participants must have confirmed ADCS (pituitary, ectopic, or unknown source of ADCS after appropriate investigation) as evidenced by mean urinary free cortisol (mUFC) >1.3 x upper limit of normal (ULN), confirmed by the central laboratory and available before Day 1 using adequate UFC samples as defined in the protocol.
2. Male or female, between 18 up to and including 74 years of age at the time of signing the informed consent form (ICF).
3. Morning plasma ACTH greater than 10 pg/mL during screening confirmed by the central laboratory and available prior to randomization on Day 1.
4. Part C (includes Part A and B inclusion criteria and the following): Part A Arms 2, 3, and 4: Complete the 12-week Treatment Period on study drug or standard of care medication and, in the Investigator's opinion, would benefit from participation in the OLE.
5. Part C (includes Part A and B inclusion criteria and the following): Late Screeners: When enrollment into Part B is closed, participants who were undergoing screening for Part B and who meet all Part B inclusion criteria may enroll directly into Part C.

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
74 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Use of ketoconazole, levoketoconazole, or metyrapone within 2 weeks; osilodrostat, mifepristone, or cabergoline within 4 weeks; or pasireotide LAR within 8 weeks prior to screening.
2. History of major surgery within 1 month prior to screening.
3. Pituitary surgery within 1 month of screening.
4. Participants who received pituitary radiation within the last 3 years.
5. Participants who have previously taken atumelnant.
6. Participants who will not benefit from chronic treatment with study drug or have a life

expectancy of less than 6 months.
7. Clinically significant concomitant disease considered by the Investigator likely to affect safe participation in the study.

Date of first enrolment
16/11/2026

Date of final enrolment
30/01/2030

Locations

Countries of recruitment
United Kingdom

England

Argentina

Australia

Brazil

Canada

France

Germany

Italy

Netherlands

Peru

Poland

Spain

Sweden

Study participating centre
Salford Royal Hospital
Stott Lane
Salford
England
M6 8HD

Study participating centre
Imperial College London
Exhibition Road, South Kensington
London
England
SW7 2BU

Study participating centre
Sheffield Childrens Hospital
Western Bank
Sheffield
England
S10 2TH

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
England
B15 2GW

Sponsor information

Organisation
Crinetics Pharmaceuticals (United States)

ROR
https://ror.org/02ha0t079

Funder(s)

Funder type

Funder Name
Crinetics Pharmaceuticals, Inc.

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date