



Clinical trial results:

A randomised, double-blind, placebo controlled, parallel study to assess the benefits of acridinium bromide in the relief of COPD symptoms including cough when administered to patients with COPD

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2014-004715-37 |
| Trial protocol | DE GB HU IT ES |
| Global end of trial date | 17 November 2015 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 12 November 2016 |
| First version publication date | 12 November 2016 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | M-34273-46 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02375724 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Alternative sponsor identifier: D6560C00001 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | AstraZeneca |
| Sponsor organisation address | 2 Kingdom St, London, United Kingdom, W2 6BD |
| Public contact | Study Director, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com |
| Scientific contact | Study Director, AstraZeneca, ClinicalTrialTransparency@astrazeneca.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 17 November 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 November 2015 |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 November 2015 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of acclidinium bromide 400 µg administered twice a day on COPD symptoms including cough and on cough-related quality of life measures in patients with moderate COPD compared to placebo

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation/Good Clinical Practice and applicable regulatory requirements and the AstraZeneca policy on Bioethics

Before enrolment into the study, all patients were comprehensively informed by the investigator (or the personnel identified as designated staff) orally and by means of the patient information sheet about the characteristics of the investigational medicinal products to be administered, the nature of the clinical investigation, the risks and the discomfort that could reasonably be expected as a result of their participation and about their right to withdraw at any time from the study, without prejudice and without any need to specify the reasons

Patients documented their willingness to participate in the study by giving their written consent by signing the Informed Consent Form before the start of any study procedure

Salbutamol pMDI (100 µg/puff) was allowed as relief medication

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 23 March 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Germany: 115 |
| Country: Number of subjects enrolled | Hungary: 88 |
| Country: Number of subjects enrolled | Italy: 3 |
| Country: Number of subjects enrolled | Spain: 27 |
| Country: Number of subjects enrolled | United Kingdom: 36 |
| Worldwide total number of subjects | 269 |
| EEA total number of subjects | 269 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 163 |
| From 65 to 84 years | 105 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

Patients were randomized in 30 study sites in 5 countries Germany (10 sites), Hungary (6), Italy (2), Spain (9) and the United Kingdom (3)

First patient was enrolled in March 2015 and last patient last visit was in November 2015

Pre-assignment

Screening details:

300 patients were screened; 269 were assessed as eligible and were randomized into the study

Thirty-one patients failed screening, with the main reason for screening failure being non-fulfilment of the inclusion or exclusion criteria (24 patients)

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Investigator, Subject |

Arms

| | |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Acidinium 400 µg |

Arm description:

Acidinium bromide 400 µg BID administered by Genuair® multidose dry powder inhaler

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Acidinium |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

1 puff of 400 µg in the morning (09:00±1 hour) and in the evening (21:00±1 hour)

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Placebo BID administered by Genuair® multidose dry powder inhaler

| | |
|--|-------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Inhalation powder |
| Routes of administration | Inhalation use |

Dosage and administration details:

1 puff of 400 µg in the morning (09:00±1 hour) and in the evening (21:00±1 hour)

| Number of subjects in period 1 | Acridinium 400 µg | Placebo |
|---------------------------------------|-------------------|---------|
| Started | 135 | 134 |
| Completed | 129 | 128 |
| Not completed | 6 | 6 |
| Consent withdrawn by subject | 1 | 1 |
| Adverse event, non-fatal | 2 | 4 |
| Lost to follow-up | 1 | - |
| Lack of efficacy | 1 | 1 |
| Protocol deviation | 1 | - |

Baseline characteristics

Reporting groups

| | |
|--|------------------|
| Reporting group title | Acidinium 400 µg |
| Reporting group description: Acidinium bromide 400 µg BID administered by Genuair® multidose dry powder inhaler | |
| Reporting group title | Placebo |
| Reporting group description: Placebo BID administered by Genuair® multidose dry powder inhaler | |

| Reporting group values | Acidinium 400 µg | Placebo | Total |
|--|------------------|---------|-------|
| Number of subjects | 135 | 134 | 269 |
| Age categorical Units: Subjects | | | |
| Adults (18-65 years) | 89 | 81 | 170 |
| From 66-84 years | 45 | 53 | 98 |
| 85 years and over | 1 | 0 | 1 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 62 | 62 | |
| standard deviation | ± 8.4 | ± 9.1 | - |
| Gender, Male/Female Units: Participants | | | |
| Female | 57 | 50 | 107 |
| Male | 78 | 84 | 162 |

End points

End points reporting groups

| | |
|--|--------------------|
| Reporting group title | Acclidinium 400 µg |
| Reporting group description: Acclidinium bromide 400 µg BID administered by Genuair® multidose dry powder inhaler | |
| Reporting group title | Placebo |
| Reporting group description: Placebo BID administered by Genuair® multidose dry powder inhaler | |

Primary: Change from baseline in overall Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms (E-RS) total score

| | |
|---|---|
| End point title | Change from baseline in overall Exacerbations of Chronic Pulmonary Disease Tool-Respiratory Symptoms (E-RS) total score |
| End point description: The EXACT-Respiratory Symptoms (E-RS) questionnaire was completed every evening The E-RS scale is an instrument comprising a subset of EXACT items to test the effect of treatment on the severity of respiratory symptoms in stable COPD Eleven of the 14-items of the EXACT questionnaire provides information about COPD symptoms: The E-RS Total Score is an aggregate of three domains: chest symptoms (derived sum of 3 items), cough and sputum (derived sum of 3 items) and RS-breathlessness (derived sum of 4 items) Individual scores are rated from 0 to 4 | |
| End point type | Primary |
| End point timeframe: Week 8 | |

| End point values | Acclidinium 400 µg | Placebo | | |
|-------------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 133 | | |
| Units: Score | | | | |
| least squares mean (standard error) | -1.75 (± 0.342) | -0.73 (± 0.342) | | |

Statistical analyses

| | |
|----------------------------|------------------------------|
| Statistical analysis title | Acclidinium v Placebo |
| Comparison groups | Acclidinium 400 µg v Placebo |

| | |
|---|-------------------------------|
| Number of subjects included in analysis | 264 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0306 |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | -1.02 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.94 |
| upper limit | -0.1 |

Secondary: Change from baseline in overall E-RS cough and sputum domain score

| | |
|------------------------|--|
| End point title | Change from baseline in overall E-RS cough and sputum domain score |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Week 8 | |

| End point values | Acclidinium 400 µg | Placebo | | |
|-------------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 131 | 133 | | |
| Units: Score | | | | |
| least squares mean (standard error) | -0.54 (± 0.09) | -0.33 (± 0.09) | | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Acclidinium v Placebo |
| Comparison groups | Acclidinium 400 µg v Placebo |
| Number of subjects included in analysis | 264 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0793 |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | -0.22 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.46 |
| upper limit | 0.03 |

Secondary: Change from baseline in the Leicester Cough Questionnaire (LCQ) total score

| | |
|---|---|
| End point title | Change from baseline in the Leicester Cough Questionnaire (LCQ) total score |
| End point description: | |
| The LCQ is a self-administered questionnaire that assesses cough related quality of life | |
| The LCQ comprises 19 items and 3 domains (physical, psychological and social) | |
| The total score ranges from 3 to 21 and each domain scores range from 1 to 7; a higher score indicates a better quality of life | |
| End point type | Secondary |
| End point timeframe: | |
| Week 8 | |

| End point values | Acclidinium 400 µg | Placebo | | |
|-------------------------------------|--------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 126 | 128 | | |
| Units: Score | | | | |
| least squares mean (standard error) | 1.18 (± 0.214) | 1.24 (± 0.214) | | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Acclidinium v Placebo |
| Comparison groups | Acclidinium 400 µg v Placebo |
| Number of subjects included in analysis | 254 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.844 |
| Method | Mixed models analysis |
| Parameter estimate | Least squares mean difference |
| Point estimate | -0.06 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.64 |
| upper limit | 0.52 |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Day 70±3

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Placebo BID administered by Genuair® multidose dry powder inhaler

| | |
|-----------------------|--------------------|
| Reporting group title | Acclidinium 400 µg |
|-----------------------|--------------------|

Reporting group description:

Acclidinium bromide 400 µg BID administered by Genuair® multidose dry powder inhaler

| Serious adverse events | Placebo | Acclidinium 400 µg | |
|---|-----------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 134 (1.49%) | 2 / 135 (1.48%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Cartilage injury | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | 1 / 135 (0.74%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 134 (0.00%) | 1 / 135 (0.74%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 135 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 134 (0.75%) | 0 / 135 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Placebo | Acridinium 400 µg | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 20 / 134 (14.93%) | 11 / 135 (8.15%) | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 13 / 134 (9.70%) | 7 / 135 (5.19%) | |
| occurrences (all) | 25 | 9 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 9 / 134 (6.72%) | 4 / 135 (2.96%) | |
| occurrences (all) | 10 | 4 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 05 December 2014 | Correction included, as the Investigator Brochure was not provided along with the protocol and was available on request; Modification of the clarification note of inclusion criteria 1, as a serum pregnancy test was not performed in the study, but a urine pregnancy test was performed; Correction on the number of digits for site identification, as the first 5 digits representing the investigator identifier was replaced by the first 4 digits representing the site identifier |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported