



Clinical trial results:

Dose Escalation Part:

MULTIDOSE SAFETY AND TOLERABILITY STUDY OF DOSE ESCALATION OF LIPOSOMAL AMIKACIN FOR INHALATION (ARIKACE™) IN CYSTIC FIBROSIS PATIENTS WITH CHRONIC INFECTIONS DUE TO PSEUDOMONAS AERUGINOSA

Extension Part:

MULTIDOSE SAFETY AND TOLERABILITY STUDY OF DOSE ESCALATION OF LIPOSOMAL AMIKACIN FOR INHALATION (ARIKACE™) IN CYSTIC FIBROSIS PATIENTS WITH CHRONIC INFECTIONS DUE TO PSEUDOMONAS AERUGINOSA

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2006-006980-22 |
| Trial protocol | HU SK BE PL |
| Global end of trial date | 02 November 2010 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 04 August 2020 |
| First version publication date | 04 August 2020 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | TR02-105 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00777296 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Insmmed Incorporated |
| Sponsor organisation address | 700 US Highway 202/206, Bridgewater, United States, 08807-1704 |
| Public contact | Tom Vanthienen, Insmmed Incorporated, +41 795432860, tom.vanthienen@insmed.com |
| Scientific contact | Tom Vanthienen, Insmmed Incorporated, +41 795432860, tom.vanthienen@insmed.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No | No |

| | |
|--|----|
| 1901/2006 apply to this trial? | |
| 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 | 11 July 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 27 February 2008 |
| Global end of trial reached? | Yes |
| Global end of trial date | 02 November 2010 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Dose Escalation Part:

To evaluate the safety and tolerability of 28 days of daily dosing of two dose cohorts of nebulized Arikace™, liposomal amikacin for inhalation.

Extension Part:

To evaluate the longer-term safety, tolerability and efficacy of 560 mg once daily (QD) dose of Arikace™ administered for 6 cycles over 18 months. Each cycle comprised 28 days on treatment followed by 56 days off treatment.

Protection of trial subjects:

This study was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents, the International Council for Harmonisation (ICH) Guidelines, and is consistent with the ethical principles of the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 22 February 2007 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--|
| Country: Number of subjects enrolled | Poland: 18 |
| Country: Number of subjects enrolled | Slovakia: 12 |
| Country: Number of subjects enrolled | Belgium: 4 |
| Country: Number of subjects enrolled | Hungary: 23 |
| Country: Number of subjects enrolled | Macedonia, the former Yugoslav Republic of: 25 |
| Country: Number of subjects enrolled | Serbia: 18 |
| Country: Number of subjects enrolled | Ukraine: 24 |
| Worldwide total number of subjects | 124 |
| EEA total number of subjects | 57 |

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) | 27 |
| Adolescents (12-17 years) | 46 |
| Adults (18-64 years) | 51 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited at 15 study centres for the Dose Escalation Part of the study, and at 11 study centres for the Extension Part.

Pre-assignment

Screening details:

The 2 cohorts involved in the Dose Escalation Part of the study were randomised to receive Arikace™ or a placebo at a 2:1 ratio. All subjects who progressed into the Extension Part of the study received Arikace™.

Period 1

| | |
|------------------------------|---------------------------|
| Period 1 title | TR02-105 (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|---|
| Arm title | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ |
|------------------|---|

Arm description:

Subjects in this cohort received 280 mg of Arikace™.

| | |
|--|-----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Arikace™ |
| Investigational medicinal product code | |
| Other name | Liposomal amikacin for inhalation |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Subjects received a once daily dose of Arikace™ 280 mg for 28 days in Cohort 1. Subjects received a once daily dose of Arikace™ 560 mg for 28 days in Cohort 2. Arikace™ was administered via a PARI eFlow nebulizer over approximately 20 minutes.

| | |
|------------------|---|
| Arm title | Dose Escalation Part - Cohort 1 - Placebo |
|------------------|---|

Arm description:

Subjects in this arm of Cohort 1 received matching placebo.

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

Dosage and administration details:

Subjects received a once daily dose of the placebo for 28 days in Cohort 1. Subjects received a once daily dose of the placebo for 28 days in Cohort 2. The placebo was administered via a PARI eFlow nebulizer over approximately 20 minutes.

| | |
|------------------|---|
| Arm title | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ |
|------------------|---|

Arm description:

Subjects in this cohort received 560 mg of Arikace™.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|-----------------------------------|
| Investigational medicinal product name | Arikace™ |
| Investigational medicinal product code | |
| Other name | Liposomal amikacin for inhalation |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

Subjects received a once daily dose of Arikace™ 280 mg for 28 days in Cohort 1. Subjects received a once daily dose of Arikace™ 560 mg for 28 days in Cohort 2. Arikace™ was administered via a PARI eFlow nebulizer over approximately 20 minutes.

| | |
|------------------|---|
| Arm title | Dose Escalation Part - Cohort 2 - Placebo |
|------------------|---|

Arm description:

Subjects in this arm of Cohort 2 received matching placebo.

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

Dosage and administration details:

Subjects received a once daily dose of the placebo for 28 days in Cohort 1. Subjects received a once daily dose of the placebo for 28 days in Cohort 2. The placebo was administered via a PARI eFlow nebulizer over approximately 20 minutes.

| | |
|------------------|----------------|
| Arm title | Extension Part |
|------------------|----------------|

Arm description:

Subjects in the Extension Part received 560 mg of Arikace™.

| | |
|--|-------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Arikace™ |
| Investigational medicinal product code | |
| Other name | Liposomal amikacin inhalation |
| Pharmaceutical forms | Inhalation solution |
| Routes of administration | Inhalation use |

Dosage and administration details:

All subjects received a dose of 560 mg of Arikace™ once daily for 28 days. Arikace™ was administered via a PARI eFlow nebulizer over approximately 10 minutes.

| Number of subjects in period 1 ^[1] | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ | Dose Escalation Part - Cohort 1 - Placebo | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ |
|---|---|---|---|
| | Started | 21 | 11 |
| Completed | 20 | 10 | 21 |
| Not completed | 1 | 1 | 2 |
| Consent withdrawn by subject | 1 | - | - |
| Adverse event, non-fatal | - | 1 | - |
| Pregnancy | - | - | - |
| Completed study but not 24 of 28 days | - | - | - |
| Case Report Form (CRF) not completed | - | - | 2 |
| Lack of efficacy | - | - | - |

| Number of subjects in period 1[1] | Dose Escalation Part - Cohort 2 - Placebo | Extension Part |
|---------------------------------------|--|----------------|
| | Started | 11 |
| Completed | 10 | 41 |
| Not completed | 1 | 8 |
| Consent withdrawn by subject | - | 3 |
| Adverse event, non-fatal | 1 | 1 |
| Pregnancy | - | 1 |
| Completed study but not 24 of 28 days | - | 2 |
| Case Report Form (CRF) not completed | - | - |
| Lack of efficacy | - | 1 |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Eligible subjects in the Dose Escalation Part of the study moved onto the Extension Part of the study.

Baseline characteristics

Reporting groups

| | |
|---|---|
| Reporting group title | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ |
| Reporting group description: Subjects in this cohort received 280 mg of Arikace™. | |
| Reporting group title | Dose Escalation Part - Cohort 1 - Placebo |
| Reporting group description: Subjects in this arm of Cohort 1 received matching placebo. | |
| Reporting group title | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ |
| Reporting group description: Subjects in this cohort received 560 mg of Arikace™. | |
| Reporting group title | Dose Escalation Part - Cohort 2 - Placebo |
| Reporting group description: Subjects in this arm of Cohort 2 received matching placebo. | |
| Reporting group title | Extension Part |
| Reporting group description: Subjects in the Extension Part received 560 mg of Arikace™. | |

| Reporting group values | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ | Dose Escalation Part - Cohort 1 - Placebo | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ |
|---|---|---|---|
| Number of subjects | 21 | 11 | 23 |
| Age categorical Units: Subjects | | | |
| In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over | | | |
| Age continuous Units: years | | | |
| arithmetic mean | 16.0 | 16.9 | 16.6 |
| standard deviation | ± 5.3 | ± 7.9 | ± 6.1 |
| Gender categorical Units: Subjects | | | |
| Female | 16 | 8 | 11 |
| Male | 5 | 3 | 12 |

| Reporting group values | Dose Escalation Part - Cohort 2 - Placebo | Extension Part | Total |
|------------------------------------|---|----------------|-------|
| Number of subjects | 11 | 49 | 115 |
| Age categorical Units: Subjects | | | |
| In utero | | | 0 |

| | | | |
|---|-------|--------|----|
| Preterm newborn infants (gestational age < 37 wks) | | | 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) | | | 0 |
| From 65-84 years | | | 0 |
| 85 years and over | | | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 17.2 | 17.4 | |
| standard deviation | ± 5.8 | ± 6.22 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 4 | 29 | 68 |
| Male | 7 | 20 | 47 |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ |
| Reporting group description: | |
| Subjects in this cohort received 280 mg of Arikace™. | |
| Reporting group title | Dose Escalation Part - Cohort 1 - Placebo |
| Reporting group description: | |
| Subjects in this arm of Cohort 1 received matching placebo. | |
| Reporting group title | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ |
| Reporting group description: | |
| Subjects in this cohort received 560 mg of Arikace™. | |
| Reporting group title | Dose Escalation Part - Cohort 2 - Placebo |
| Reporting group description: | |
| Subjects in this arm of Cohort 2 received matching placebo. | |
| Reporting group title | Extension Part |
| Reporting group description: | |
| Subjects in the Extension Part received 560 mg of Arikace™. | |
| Subject analysis set title | Pooled Placebo |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Placebo is a pooled value from cohort 280 mg and cohort 560 mg. | |
| Subject analysis set title | Arikace™ |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: | |
| Subjects who received either the 280 mg or the 560 mg doses of the Arikace™. | |

Primary: Dose Escalation Part: Clinically Significant Laboratory Abnormalities

| | |
|---|---|
| End point title | Dose Escalation Part: Clinically Significant Laboratory Abnormalities ^{[1][2]} |
| End point description: | |
| Changes in chemistry and hematology lab tests (clinically significant value of Common Terminology Criteria for Adverse Events [CTCAE] grade \geq 3). | |
| The analysis population is the modified intent-to-treat (mITT) population, defined as all randomised subjects who received at least one dose of study drug. | |
| End point type | Primary |
| End point timeframe: | |
| 28 Days | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Statistical analysis was not planned for this endpoint.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

| End point values | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ | Dose Escalation Part - Cohort 1 - Placebo | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ | Dose Escalation Part - Cohort 2 - Placebo |
|-----------------------------|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 11 | 21 | 11 |
| Units: Subjects | | | | |
| Neutrophils absolute | 1 | 0 | 8 | 7 |
| Leucocytes | 1 | 0 | 3 | 3 |
| Glucose | 0 | 0 | 2 | 0 |
| Lymphocytes absolute | 1 | 0 | 2 | 0 |
| Calcium | 0 | 0 | 1 | 0 |
| Creatinine clearance | 0 | 0 | 1 | 0 |
| Potassium | 3 | 1 | 1 | 0 |

Statistical analyses

No statistical analyses for this end point

Primary: Extension Part: Adverse Event Profile of 560 mg Once Daily Dose of Arikace™ Administered for Six Cycles Over Eighteen Months

| | |
|-----------------|--|
| End point title | Extension Part: Adverse Event Profile of 560 mg Once Daily Dose of Arikace™ Administered for Six Cycles Over Eighteen Months ^{[3][4]} |
|-----------------|--|

End point description:

Number of subjects with indicated adverse events in subject receiving 560 mg once daily dose of Arikace™ administered for 6 cycles over 18 months.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

18 Months

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis was planned for this endpoint.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

| End point values | Extension Part | | | |
|--|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: Subjects | | | | |
| Any Adverse Event | 48 | | | |
| Treatment-related adverse events | 15 | | | |
| Grade 1: Mild | 28 | | | |
| Grade 2: Moderate | 15 | | | |
| Grade 3: Severe | 4 | | | |
| Grade 4: Life-threatening or disabling | 1 | | | |
| Grade 5: Death | 0 | | | |
| Serious Adverse Events | 15 | | | |

| | | | | |
|--|---|--|--|--|
| Treatment-related serious adverse events | 0 | | | |
| Deaths | 0 | | | |
| Permanent discontinuations due to adverse events | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Pharmacokinetics (PK) of Arikace™ in Serum

| | |
|-----------------|---|
| End point title | Dose Escalation Part: Pharmacokinetics (PK) of Arikace™ in Serum ^[5] |
|-----------------|---|

End point description:

Measure PK parameters (AUC0-infinity) of Arikace™ in serum.

The PK population consisted of subjects who received amikacin, had at least one serum PK assessment and were not replaced.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1, Day 14 and Day 28

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

| End point values | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ | | |
|--------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 21 | | |
| Units: mg.hr/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 | 5.73 (± 3.40) | 7.92 (± 3.55) | | |
| Day 14 | 7.61 (± 4.04) | 12.5 (± 10.9) | | |
| Day 28 | 8.03 (± 6.12) | 14.6 (± 11.7) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Pharmacokinetic (PK) of Arikace™ in Serum (Cmax)

| | |
|-----------------|---|
| End point title | Dose Escalation Part: Pharmacokinetic (PK) of Arikace™ in Serum (Cmax) ^[6] |
|-----------------|---|

End point description:

Measure PK parameter (Cmax) of Arikace™ in serum.

The PK population consisted of subjects who received Arikace™, had at least one serum PK assessment and were not replaced.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1, Day 14 and Day 28

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

| End point values | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 21 | | |
| Units: mg/L | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 | 0.95 (± 0.58) | 1.08 (± 0.51) | | |
| Day 14 | 1.28 (± 1.02) | 1.84 (± 1.35) | | |
| Day 28 | 1.42 (± 1.45) | 2.27 (± 1.58) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Pharmacokinetics (PK) of Arikace™ in Sputum (AUC)

| | |
|-----------------|--|
| End point title | Dose Escalation Part: Pharmacokinetics (PK) of Arikace™ in Sputum (AUC) ^[7] |
|-----------------|--|

End point description:

Measure PK parameter (AUC₀₋₂₄) of Arikace™ in sputum.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

28 days

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

| End point values | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 21 | | |
| Units: mcg*hr/g | | | | |
| arithmetic mean (standard deviation) | 13120 (± 21386) | 22445 (± 18652) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Pharmacokinetics (PK) of Arikace™ in Urine

| | |
|-----------------|---|
| End point title | Dose Escalation Part: Pharmacokinetics (PK) of Arikace™ in Urine ^[8] |
|-----------------|---|

End point description:

Measure PK parameter (Ae0-24 ((mg)) of Arikace™.

The PK population consisted of subjects who received amikacin, had at least one serum PK assessment and were not replaced.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1, Day 14 and Day 28

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

| End point values | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ | | |
|--------------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 21 | | |
| Units: mg | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 | 17.7 (± 12.3) | 27.0 (± 25.2) | | |
| Day 14 | 27.3 (± 16.5) | 39.8 (± 42.7) | | |
| Day 28 | 25.2 (± 19.5) | 43.7 (± 48.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Sputum Amikacin Levels of Arikace™

| | |
|-----------------|---|
| End point title | Dose Escalation Part: Sputum Amikacin Levels of Arikace™ ^[9] |
|-----------------|---|

End point description:

Measure PK parameter (sputum amikacin concentration) of Arikace™ in sputum.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1, Day 14 and Day 28

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

| End point values | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 21 | 21 | | |
| Units: mcg/g | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1 | 1197 (± 1.56) | 2395 (± 0.866) | | |
| Day 14 | 1174 (± 1.01) | 3496 (± 0.973) | | |
| Day 28 | 1911 (± 1.28) | 2635 (± 1.23) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Pulmonary Function: FEV1 %-Predicted

| | |
|-----------------|---|
| End point title | Dose Escalation Part: Pulmonary Function: FEV1 %- |
|-----------------|---|

End point description:

Relative change (%) from baseline to end of treatment (Day 28) and Day 56 in pulmonary function.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Day 28 and Day 56

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

| End point values | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ | Pooled Placebo | |
|--|--|--|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 21 | 21 | 22 | |
| Units: Relative Percent (%) change in FEV1 | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 66.4 (± 20.0) | 62.9 (± 18.2) | 68.0 (± 22.4) | |
| Day 28 | 9.6 (± 13.7) | 11.0 (± 16.4) | 0.5 (± 10.5) | |
| Day 56 | 1.8 (± 8.8) | 13.8 (± 26.2) | -3.8 (± 13.5) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Pulmonary Function: FEV1

End point title | Dose Escalation Part: Pulmonary Function: FEV1^[11]

End point description:

Mean percent change (%) from baseline to end of treatment (Day 28) and Day 56 in pulmonary function.

The analysis population is the modified intent-to-treat (mITT) population, defined as all randomised subjects who received at least one dose of study drug.

End point type | Secondary

End point timeframe:

Baseline, Day 28 and Day 56

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

| End point values | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ | Pooled Placebo | |
|--|---|---|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 21 | 21 | 22 | |
| Units: Mean Percent (%) Change in FEV1 | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 2.022 (± 0.788) | 1.937 (± 0.936) | 1.968 (± 0.654) | |
| Day 28 | 10.1 (± 12.8) | 13.2 (± 16.2) | 2.2 (± 11.9) | |
| Day 56 | 2.0 (± 8.6) | 13.2 (± 24.3) | -4.4 (± 13.0) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Change From Baseline in Log10CFU Per Gram (Density) of Pseudomonas Aeruginosa in Sputum

End point title | Dose Escalation Part: Change From Baseline in Log10CFU Per Gram (Density) of Pseudomonas Aeruginosa in Sputum^[12]

End point description:

End of treatment (Day 28) from baseline in density of P. aeruginosa (log10 CFU/g) in sputum.

The analysis population is the modified intent-to-treat (mITT) population, defined as all randomised subjects who received at least one dose of study drug.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 7, Day 14, Day 21, Day 28 and Day 35 | |

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

| End point values | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ | Pooled Placebo | |
|---------------------------------------|--|--|----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 21 | 21 | 22 | |
| Units: log ₁₀ CFU per gram | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 7 | 0.080 (± 1.882) | -1.101 (± 2.170) | 0.052 (± 1.303) | |
| Day 14 | -1.366 (± 2.013) | -1.570 (± 2.161) | -0.574 (± 1.006) | |
| Day 21 | -1.044 (± 2.155) | -2.283 (± 2.775) | -0.440 (± 1.280) | |
| Day 28 | -0.622 (± 1.881) | -1.515 (± 1.699) | -0.677 (± 1.043) | |
| Day 35 | -0.380 (± 1.425) | -1.313 (± 2.852) | -0.445 (± 1.201) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Duration of Systemic Antipseudomonal Rescue Therapy

| | |
|-----------------|---|
| End point title | Dose Escalation Part: Duration of Systemic Antipseudomonal Rescue Therapy ^[13] |
|-----------------|---|

End point description:

Duration of systemic antipseudomonal rescue therapy during the study in both the Arikace™ and placebo groups.

The analysis population is the modified intent-to-treat (mITT) population, defined as all randomised subjects who received at least one dose of study drug.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Through study duration, approximately 56 days | |

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

| End point values | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ | Dose Escalation Part - Cohort 1 - Placebo | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ | Dose Escalation Part - Cohort 2 - Placebo |
|--------------------------------------|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 11 ^[14] | 21 ^[15] | 11 |
| Units: Days | | | | |
| arithmetic mean (standard deviation) | 14.00 (± 0.00) | 27.00 (± 99999) | 19.00 (± 99999) | 21.00 (± 11.31) |

Notes:

[14] - 99999 is used where standard deviation doesn't apply as only 1 subject required rescue therapy.

[15] - 99999 is used where standard deviation doesn't apply as only 1 subject required rescue therapy.

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: Number of Subjects Requiring Antipseudomonal Rescue Therapy

| | |
|-----------------|---|
| End point title | Dose Escalation Part: Number of Subjects Requiring Antipseudomonal Rescue Therapy |
|-----------------|---|

End point description:

Number of subjects requiring systemic antipseudomonal rescue therapy during the study in both the Arikace™ and placebo groups.

The analysis population is the modified intent-to-treat (mITT) population, defined as all randomised subjects who received at least one dose of study drug.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Through study duration, approximately 56 days

| End point values | Pooled Placebo | Arikace™ | | |
|-----------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 22 | 42 | | |
| Units: Subjects | 3 | 4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Dose Escalation Part: CFQ-R Respiratory Scale (Absolute Change From Baseline)

| | |
|-----------------|---|
| End point title | Dose Escalation Part: CFQ-R Respiratory Scale (Absolute Change From Baseline) ^[16] |
|-----------------|---|

End point description:

Quality of Life was measured by the absolute change from baseline in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory scale. Disease specific instrument designed to measure impact on overall health, daily life, perceived well-being and symptoms in subjects with a diagnosis of cystic fibrosis. Scores range from 0 to 100, with higher scores indicating better health. Scores for each Health Related Quality of Life (HRQoL) domain; after recoding, each item is summed to generate a domain score and

standardized.

The analysis population is the modified intent-to-treat (mITT) population, defined as all randomised subjects who received at least one dose of study drug.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline/Day 1, Day 15, Day 28 and Day 42 | |

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

| End point values | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ | Dose Escalation Part - Cohort 1 - Placebo | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ | Dose Escalation Part - Cohort 2 - Placebo |
|--------------------------------------|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 11 | 21 | 11 |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 1/Baseline | 72.619 (± 11.630) | 71.212 (± 14.921) | 67.989 (± 12.748) | 61.364 (± 21.425) |
| Day 15 | 2.632 (± 10.078) | -0.505 (± 12.349) | 3.704 (± 16.133) | -2.778 (± 16.054) |
| Day 28 | 4.306 (± 12.760) | -3.283 (± 14.154) | 5.688 (± 11.669) | 1.667 (± 13.302) |
| Day 42 | 1.080 (± 12.169) | -4.012 (± 19.598) | 3.042 (± 18.213) | 0.556 (± 12.200) |

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Part: FEV1 % Predicted

| | |
|-----------------|--|
| End point title | Extension Part: FEV1 % Predicted ^[17] |
|-----------------|--|

End point description:

A summary of relative change from the Extension Part of the study baseline time points in FEV1 % predicted is presented for the overall safety population and by treatment received.

Safety population.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline, Days 1, 14, 28, 56, 70, 85, 98, 112, 140, 154, 169, 182, 196, 224, 238, 253, 266, 280, 308, 322, 337, 350, 364, 392, 406, 421, 434, 448, 476, 490 and 504 | |

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

| End point values | Extension Part | | | |
|--------------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 ^[18] | | | |
| Units: Percent (%) predicted | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 59.73 (± 20.047) | | | |
| Day 1 | 3.13 (± 8.553) | | | |
| Day 14 | 7.62 (± 15.246) | | | |
| Day 28 | 6.83 (± 14.593) | | | |
| Day 56 | 3.02 (± 11.174) | | | |
| Day 70 | 2.96 (± 13.580) | | | |
| Day 85 | 4.04 (± 15.450) | | | |
| Day 98 | 9.97 (± 16.594) | | | |
| Day 112 | 8.19 (± 20.116) | | | |
| Day 140 | 4.86 (± 19.337) | | | |
| Day 154 | 6.76 (± 20.633) | | | |
| Day 169 | 3.90 (± 19.141) | | | |
| Day 182 | 10.22 (± 18.349) | | | |
| Day 196 | 7.56 (± 20.607) | | | |
| Day 224 | 2.57 (± 19.165) | | | |
| Day 238 | 5.46 (± 17.872) | | | |
| Day 253 | 3.37 (± 17.755) | | | |
| Day 266 | 9.07 (± 19.747) | | | |
| Day 280 | 8.54 (± 19.179) | | | |
| Day 308 | 5.77 (± 19.633) | | | |
| Day 322 | 5.25 (± 20.946) | | | |
| Day 337 | 5.18 (± 21.740) | | | |
| Day 350 | 10.49 (± 21.615) | | | |
| Day 364 | 3.82 (± 18.895) | | | |
| Day 392 | 3.07 (± 18.380) | | | |
| Day 406 | 2.74 (± 18.301) | | | |
| Day 421 | 1.63 (± 19.094) | | | |
| Day 434 | 7.11 (± 20.022) | | | |

| | | | | |
|---------|----------------------|--|--|--|
| Day 448 | 5.66 (\pm 20.422) | | | |
| Day 476 | 0.83 (\pm 21.741) | | | |
| Day 490 | 1.61 (\pm 19.922) | | | |
| Day 504 | 0.06 (\pm 22.196) | | | |

Notes:

[18] - Number of subjects analysed ranged from 49 to 42.

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Part: Absolute Change in Sputum Density

| | |
|-----------------|---|
| End point title | Extension Part: Absolute Change in Sputum Density ^[19] |
|-----------------|---|

End point description:

A summary of change from the Extension Part baseline to all post-baseline time points during the treatment periods and at the end of the off treatment periods in P aeruginosa sputum density (log₁₀ CFU/mL) is presented for the overall safety population and by treatment received.

Per Protocol population defined as all subjects who completed at least 24 of the 28 days of dosing for each of the 6 cycles

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Days 14, 28, 85, 98, 112, 140, 169, 182, 196, 253, 266, 280, 337, 350, 364, 421, 434 and 448

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

| End point values | Extension Part | | | |
|--------------------------------------|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 ^[20] | | | |
| Units: Log ₁₀ CFU/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 6.289 (\pm 2.8587) | | | |
| Day 14 | -1.196 (\pm 2.0736) | | | |
| Day 28 | -0.416 (\pm 1.8584) | | | |
| Day 85 | 0.154 (\pm 2.4433) | | | |
| Day 98 | -0.623 (\pm 1.9127) | | | |
| Day 112 | -0.781 (\pm 1.1625) | | | |
| Day 140 | -0.266 (\pm 0.2871) | | | |
| Day 169 | -0.144 (\pm 1.2470) | | | |
| Day 182 | -1.087 (\pm 1.9582) | | | |

| | | | | |
|---------|------------------------|--|--|--|
| Day 196 | -0.599 (\pm 1.3450) | | | |
| Day 253 | 0.213 (\pm 1.4059) | | | |
| Day 266 | -0.991 (\pm 2.5040) | | | |
| Day 280 | -0.702 (\pm 1.7419) | | | |
| Day 337 | 0.375 (\pm 1.9924) | | | |
| Day 350 | -0.311 (\pm 1.6342) | | | |
| Day 364 | -0.107 (\pm 1.8027) | | | |
| Day 421 | 0.494 (\pm 2.0058) | | | |
| Day 434 | 0.111 (\pm 1.9098) | | | |
| Day 448 | 0.034 (\pm 2.0020) | | | |

Notes:

[20] - Subjects analysed ranged from 49 to 30.

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Part: Antipseudomonal Rescue Therapy - Duration of Therapy

| | |
|-----------------|--|
| End point title | Extension Part: Antipseudomonal Rescue Therapy - Duration of Therapy ^[21] |
|-----------------|--|

End point description:

The duration of IV and all systemic or inhaled antipseudomonal rescue therapy is presented for the overall safety population and by treatment received.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

18 Months

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

| End point values | Extension Part | | | |
|--------------------------------------|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: Days | | | | |
| arithmetic mean (standard deviation) | 39.7 (\pm 44.57) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Part: Antipseudomonal Rescue Therapy - Time to Therapy

| | |
|-----------------|--|
| End point title | Extension Part: Antipseudomonal Rescue Therapy - Time to Therapy ^[22] |
|-----------------|--|

End point description:

The time to IV and all systemic or inhaled antipseudomonal rescue therapy is presented for the overall safety population and by treatment received.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

18 Months

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

| End point values | Extension Part | | | |
|--------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 | | | |
| Units: Percentage (%) subjects | | | | |
| number (not applicable) | | | | |
| By Day 85 | 2.0 | | | |
| By Day 253 | 17.2 | | | |
| By Day 504 | 32.9 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Extension Part: Analysis of Cystic Fibrosis Questionnaire - Revised (CFQ-R) for Absolute Change in Score

| | |
|-----------------|--|
| End point title | Extension Part: Analysis of Cystic Fibrosis Questionnaire - Revised (CFQ-R) for Absolute Change in Score ^[23] |
|-----------------|--|

End point description:

A summary of absolute change from baseline in the CFQ-R scales at each on treatment assessment between Day 14 and Day 448 is presented for all subjects and by main study treatment group for the safety population. CFQ-R is a disease specific instrument designed to measure impact on overall health, daily life, perceived well-being and symptoms on a scale from 0 to 100 points. Higher values represent a more favorable outcome.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Days 14, 28, 85, 98, 112, 169, 182,196, 253, 266, 280, 337, 350, 364, 421, 434 and 448

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Due to the study design, arms for the baseline period have been split between the Dose Escalation Part and Extension Part of the study. Results will be presented for the applicable arms.

| End point values | Extension Part | | | |
|--------------------------------------|--------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 49 ^[24] | | | |
| Units: Percentage (%) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 14 | 7.616 (± 14.1662) | | | |
| Day 28 | 11.486 (± 14.9347) | | | |
| Day 85 | 9.697 (± 12.9834) | | | |
| Day 98 | 11.235 (± 14.5552) | | | |
| Day 112 | 11.768 (± 13.9321) | | | |
| Day 169 | 5.159 (± 13.6851) | | | |
| Day 182 | 9.233 (± 16.3635) | | | |
| Day 196 | 9.404 (± 12.4334) | | | |
| Day 253 | 7.097 (± 13.7509) | | | |
| Day 266 | 10.041 (± 14.5240) | | | |
| Day 280 | 6.111 (± 11.3611) | | | |
| Day 337 | 9.017 (± 13.8786) | | | |
| Day 350 | 12.108 (± 13.8668) | | | |
| Day 364 | 11.875 (± 12.9679) | | | |
| Day 421 | 11.895 (± 14.1632) | | | |
| Day 434 | 13.718 (± 13.1377) | | | |
| Day 448 | 13.120 (± 14.0144) | | | |

Notes:

[24] - Subjects analysed ranged from 48 to 39.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Dose Escalation Part:

AEs were assessed from the first dose (Visit 2) until the completion of the study follow-up (14 days after 28 days of dosing in cohort 2). The total duration is approximately 84 days.

Extension Part:

18 months

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 15.0 |

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ |
|-----------------------|---|

Reporting group description:

Subjects in this cohort received 280 mg of Arikace™.

| | |
|-----------------------|---|
| Reporting group title | Dose Escalation Part - Cohort 1 - Placebo |
|-----------------------|---|

Reporting group description:

Subjects in this arm of cohort 1 received matching placebo.

| | |
|-----------------------|---|
| Reporting group title | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ |
|-----------------------|---|

Reporting group description:

Subjects in this cohort received 560 mg of Arikace™.

| | |
|-----------------------|---|
| Reporting group title | Dose Escalation Part - Cohort 2 - Placebo |
|-----------------------|---|

Reporting group description:

Subjects in this arm of cohort 2 received matching placebo.

| | |
|-----------------------|----------------|
| Reporting group title | Extension Part |
|-----------------------|----------------|

Reporting group description:

Subjects in the Extension Part received 560 mg of Arikace™.

| Serious adverse events | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ | Dose Escalation Part - Cohort 1 - Placebo | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ |
|---|---|--|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 11 (9.09%) | 2 / 21 (9.52%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Investigations | | | |
| Endoscopy | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 11 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic | | | |

| | | | |
|---|----------------|----------------|----------------|
| disorders | | | |
| Cystic fibrosis lung | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 11 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Drug therapy | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 11 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Testicular appendage torsion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 11 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Lung disorder | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 11 (9.09%) | 2 / 21 (9.52%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Drug abuse | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 11 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Viral infection | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 11 (9.09%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocarditis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 11 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Appendicitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 11 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 11 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 11 (0.00%) | 0 / 21 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Dose Escalation Part - Cohort 2 - Placebo | Extension Part | |
|---|--|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 15 / 49 (30.61%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Endoscopy | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|----------------|------------------|--|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Congenital, familial and genetic disorders | | | |
| Cystic fibrosis lung | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 11 / 49 (22.45%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 17 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Drug therapy | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Testicular appendage torsion | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Lung disorder | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Drug abuse | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|----------------|--|
| Infections and infestations | | | |
| Viral infection | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 49 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Appendicitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 49 (2.04%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Dose Escalation Part - Cohort 1 - 280 mg Arikace™ | Dose Escalation Part - Cohort 1 - Placebo | Dose Escalation Part - Cohort 2 - 560 mg Arikace™ |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 10 / 21 (47.62%) | 6 / 11 (54.55%) | 5 / 21 (23.81%) |
| Investigations | | | |

| | | | |
|---|--|--|--|
| Neutrophil count decreased alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 11 (0.00%) 0 | 2 / 21 (9.52%) 2 |
| Nervous system disorders Headache alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Syncope alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 0 / 21 (0.00%) 0 | 1 / 11 (9.09%) 1 1 / 11 (9.09%) 1 | 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0 |
| General disorders and administration site conditions Pyrexia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 2 / 11 (18.18%) 2 | 0 / 21 (0.00%) 0 |
| Gastrointestinal disorders Aphthous stomatitis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 11 (9.09%) 1 | 0 / 21 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Haemoptysis alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Lung disorder alternative assessment type: Non-systematic | 2 / 21 (9.52%) 2 2 / 21 (9.52%) 2 | 0 / 11 (0.00%) 0 1 / 11 (9.09%) 1 | 0 / 21 (0.00%) 0 0 / 21 (0.00%) 0 |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 11 (9.09%) | 2 / 21 (9.52%) |
| occurrences (all) | 1 | 2 | 2 |
| Productive cough | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 1 / 11 (9.09%) | 0 / 21 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Rhinitis allergic | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 11 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Dyspnoea | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 11 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Asthma | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 11 (9.09%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 11 (9.09%) | 0 / 21 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 11 (9.09%) | 1 / 21 (4.76%) |
| occurrences (all) | 1 | 1 | 1 |
| Pharyngitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 11 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Sinusitis | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 11 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |

| Non-serious adverse events | Dose Escalation Part - Cohort 2 - Placebo | Extension Part | |
|---|--|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 29 / 49 (59.18%) | |
| Investigations | | | |
| Neutrophil count decreased | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 49 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nervous system disorders | | | |
| Headache | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 3 / 49 (6.12%) | |
| occurrences (all) | 0 | 3 | |
| Syncope | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 49 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 5 / 49 (10.20%) | |
| occurrences (all) | 0 | 7 | |
| Gastrointestinal disorders | | | |
| Aphthous stomatitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 49 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 14 / 49 (28.57%) | |
| occurrences (all) | 0 | 33 | |
| Haemoptysis | | | |

| | | | |
|---|----------------|------------------|--|
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 12 / 49 (24.49%) | |
| occurrences (all) | 0 | 20 | |
| Lung disorder | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 49 (2.04%) | |
| occurrences (all) | 0 | 1 | |
| Productive cough | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 11 / 49 (22.45%) | |
| occurrences (all) | 1 | 14 | |
| Rhinitis allergic | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 49 (4.08%) | |
| occurrences (all) | 0 | 2 | |
| Dyspnoea | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 49 (4.08%) | |
| occurrences (all) | 1 | 5 | |
| Asthma | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 49 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 49 (2.04%) | |
| occurrences (all) | 0 | 1 | |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 14 / 49 (28.57%) | |
| occurrences (all) | 1 | 26 | |
| Pharyngitis | | | |
| alternative assessment type: Non-systematic | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 0 / 11 (0.00%) | 5 / 49 (10.20%) | |
| occurrences (all) | 0 | 5 | |
| Sinusitis | | | |
| alternative assessment type: Non-systematic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 4 / 49 (8.16%) | |
| occurrences (all) | 0 | 4 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 18 April 2007 | Summary of key changes: <ul style="list-style-type: none">- Fax number was corrected- Updated the number of subjects planned for enrollment- Added clarification to the inclusion and exclusion criteria- Updated pharmacokinetic (PK) collection schedule- Updated vital sign and oxygen saturation measurement timing details- Updated blood, urine and sputum collection timings- Updated serious adverse event relatedness criteria |
| 08 May 2007 | Summary of key changes: <ul style="list-style-type: none">- Updated the PK collection schedule- Updated the Schedule of In-Clinic Evaluations |
| 27 September 2007 | Summary of key changes: <ul style="list-style-type: none">- Updated the exclusion criteria- Added clarification to the Post-Dose Pulmonary Function Testing schedule- Removed Post-Dose Sputum collection 4 hours post-dose- Added Data and Safety Monitoring Board (DSMB) meeting |
| 16 June 2008 | Summary of key changes: <ul style="list-style-type: none">- Added information regarding the total number of treatment cycles- Added a Secondary Objective- Added treatment supplier details |
| 05 August 2008 | Summary of key changes: <ul style="list-style-type: none">- The treatment follow-up period was extended- Study duration was increased |
| 27 October 2008 | Summary of key changes: <ul style="list-style-type: none">- New text added regarding secondary endpoints- Added new text regarding the Extension Part- Main criteria for inclusion and exclusion was updated- Drug administration table added |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported