



Clinical trial results:

Evaluation of the Therapeutic Efficacy of APD-209 Eye Drops in Treatment of Acute Phase Adenoviral-Induced Epidemic Keratoconjunctivitis (EKC). A Randomised, Double-Masked, Placebo-Controlled, Multi-Centre Proof-of-Concept Study

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2012-005694-31 |
| Trial protocol | SE DE PL |
| Global end of trial date | 12 April 2016 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 02 November 2017 |
| First version publication date | 02 November 2017 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | 2012/ADE002 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01977443 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Adenovir Pharma AB |
| Sponsor organisation address | Kullagatan 8, Helsingborg, Sweden, 25220 |
| Public contact | CEO, Adenovir Pharma AB, +46 4238 74 28, bjorn.dellgren@adenovir.com |
| Scientific contact | CEO, Adenovir Pharma AB, +46 4238 74 28, bjorn.dellgren@adenovir.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 | 02 November 2016 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 31 March 2016 |
| Global end of trial reached? | Yes |
| Global end of trial date | 12 April 2016 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To assess the adenoviral load in epidemic keratokconjunctivitis (EKC) infected eyes following topical treatment with APD-209 Eye drops given 8 times daily for 14 days compared to placebo. Exploratory analyses investigated if there were indications of effects not obvious due to of the small no. of randomized pts in statistical testing. Pts included had symptoms for different lengths; therefore the analysis was adjusted for onset of symptoms. Onset-adjusted analysis of the limited no. of pts that met incl/excl criteria showed a difference in reduction in viral load in favour of APD-209 of 74% (absolute scale) and 12% (log scale) compared with Placebo. Clinical assessments as blurred vision, redness and foreign body sensation showed reductions in symptom scores following treatment with APD-209. Similarly, cumulative proportion analysis of the risk of second eye infection and the risk of opacities showed reductions in favour of APD-209. The differences observed were not statistically significant.

Protection of trial subjects:

A standard physical examination, vital signs and laboratory safety assessments were performed at study visit 1, 5 and 6.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 02 September 2013 |
| 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 | Poland: 3 |
| Country: Number of subjects enrolled | Sweden: 7 |
| Country: Number of subjects enrolled | Germany: 37 |
| Worldwide total number of subjects | 47 |
| EEA total number of subjects | 47 |

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) | 44 |
| From 65 to 84 years | 3 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The initial plan estimated a recruitment of 80-130 subjects, with the exact number to be determined at an interim analysis at 60 recruited subjects. The study was conducted at 10 centers in Germany, Poland and Sweden. Due to slow enrolment the recruitment stopped on March 22 2016.

Pre-assignment

Screening details:

The inclusion and exclusion criteria of the study allowed for inclusion of subjects with EKC infection in either one or both eyes. In total there were 53 subjects screened in the study, out of which 6 were screen failures.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Treatment |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst |

Arms

| | |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | ADP-209 Eye drops |

Arm description:

25 enrolled. 3 lost to follow up, 3 lost due to withdrawal of inform consent. 19 patients completed the period.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | APD-209 |
| Investigational medicinal product code | APD-209 |
| Other name | |
| Pharmaceutical forms | Eye drops |
| Routes of administration | Topical use |

Dosage and administration details:

The active ingredient of APD-209 Eye drops is APD-209. Each dose of 45 µl of APD-209 Eye drops 0.125 mg/ml corresponded to 5.6 µg APD-209. The colourless to bluish, slightly turbid drug product was provided in 10 ml amber glass bottles with a pump, which was especially developed for preservative-free multi-dose eye drops. The pump delivers a dose of 45 µl. The mode of administration was topical administration. The first administration of IMP was done at the clinic at Visit 1 after the subjects had received the corresponding instructions by trained site staff. The IMP was then administered by the subjects at home according to the given instructions.

| | |
|------------------|---------------------------|
| Arm title | APD-209 Placebo Eye drops |
|------------------|---------------------------|

Arm description:

22 enrolled. 1 lost due to prohibited concomitant medication, 1 lost due to diagnosis of other disease than EKC in anterior chamber, 2 lost due to follow-up, 2 lost due to consent withdrawn by subject. 16 completed the period.

| | |
|--|---------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | APD-209 Placebo eye drops |
| Investigational medicinal product code | APD-209 placebo eye drops |
| Other name | |
| Pharmaceutical forms | Eye drops |
| Routes of administration | Topical use |

Dosage and administration details:

APD-209 Placebo Eye drops is a glycerol solution provided in 10 mL amber glass bottles with a pump, which was especially developed for preservative-free multi-dose eye drops. The pump delivered a dose of 45 µL. Each glass bottle was filled with 8 mL (= 8.0 g) and two bottles were to be used per subject

during the study. The mode of administration was topical administration. The first administration of IMP placebo was done at the clinic at Visit 1 after the subjects had received the corresponding instructions by trained site staff. The IMP placebo was then administered by the subjects at home according to the given instructions.

| Number of subjects in period 1 | ADP-209 Eye drops | APD-209 Placebo Eye drops |
|---------------------------------------|-------------------|---------------------------|
| Started | 25 | 22 |
| Completed | 25 | 22 |

Period 2

| | |
|------------------------------|--|
| Period 2 title | Enrollment |
| Is this the baseline period? | Yes ^[1] |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst |

Arms

| | |
|--|-------------------|
| Arm title | Subjects enrolled |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | APD-209 |
| Investigational medicinal product code | APD-209 |
| Other name | |
| Pharmaceutical forms | Eye drops |
| Routes of administration | Topical use |

Dosage and administration details:

The active ingredient of APD-209 Eye drops is APD-209. Each dose of 45 µl of APD-209 Eye drops 0.125 mg/ml corresponded to 5.6 µg APD-209. The colourless to bluish, slightly turbid drug product was provided in 10 ml amber glass bottles with a pump, which was especially developed for preservative-free multi-dose eye drops. The pump delivers a dose of 45 µl. The mode of administration was topical administration. The first administration of IMP was done at the clinic at Visit 1 after the subjects had received the corresponding instructions by trained site staff. The IMP was then administered by the subjects at home according to the given instructions.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Due to manual error treatment period was entered before baseline period.

| Number of subjects in period 2 | Subjects enrolled |
|---------------------------------------|-------------------|
| Started | 47 |
| Completed | 47 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Subjects enrolled |
|-----------------------|-------------------|

Reporting group description: -

| Reporting group values | Subjects enrolled | Total | |
|---|-------------------|-------|--|
| Number of subjects | 47 | 47 | |
| 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 | 45 | | |
| standard deviation | ± 14 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 25 | 25 | |
| Male | 22 | 22 | |
| Sialic acid binding adenovirus | | | |
| Units: Subjects | | | |
| Yes | 16 | 16 | |
| No | 31 | 31 | |
| Virus type | | | |
| Units: Subjects | | | |
| Ad19a | 4 | 4 | |
| Ad3 | 7 | 7 | |
| Ad37 | 2 | 2 | |
| Ad4 | 3 | 3 | |
| Ad42 | 1 | 1 | |
| Ad53 | 2 | 2 | |
| Ad56 | 6 | 6 | |
| Ad8 | 2 | 2 | |
| n.d. | 20 | 20 | |
| Presence of clinical symptoms of EKC infection in the second eye | | | |
| Units: Subjects | | | |
| Yes | 18 | 18 | |
| No | 29 | 29 | |

End points

End points reporting groups

| | |
|---|---------------------------|
| Reporting group title | ADP-209 Eye drops |
| Reporting group description: 25 enrolled. 3 lost to follow up, 3 lost due to withdrawal of inform consent. 19 patients completed the period. | |
| Reporting group title | APD-209 Placebo Eye drops |
| Reporting group description: 22 enrolled. 1 lost due to prohibited concomittant medication, 1 lost due to diagnosis of other disease than EKC in anterior chamber, 2 lost due to follow-up, 2 lost due to consent withdrawn by subject. 16 completed the period. | |
| Reporting group title | Subjects enrolled |
| Reporting group description: - | |

Primary: viral load in tear liquid from EKC infected eyes, as measured by the AUC at 3-14 days from start of treatment.

| | |
|--|--|
| End point title | viral load in tear liquid from EKC infected eyes, as measured by the AUC at 3-14 days from start of treatment. |
| End point description: Statistical analysis (MMRM*) comparing Viral load in tear liquid, mean AUC at 3-14 days. (Modified Intent-to-treat population) | |
| End point type | Primary |
| End point timeframe: Day 3-14 | |

| End point values | ADP-209 Eye drops | APD-209 Placebo Eye drops | | |
|--|-------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: AUC | | | | |
| least squares mean (confidence interval 95%) | 3.3898 (2.141 to 4.638) | 2.65 (0.9 to 4.4) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Comparison vs. Placebo |
| Comparison groups | ADP-209 Eye drops v APD-209 Placebo Eye drops |
| Number of subjects included in analysis | 15 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3785 |
| Method | t-test, 2-sided |
| Parameter estimate | LSmean |
| Point estimate | 0.7398 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.076 |
| upper limit | 2.556 |

Secondary: Viral load in tear liquid from EKC infected eyes, as measured by the AUC at 0-14 days from start of treatment

| | |
|-----------------|---|
| End point title | Viral load in tear liquid from EKC infected eyes, as measured by the AUC at 0-14 days from start of treatment |
|-----------------|---|

End point description:

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

End point timeframe:

Day 0-14

| End point values | ADP-209 Eye drops | APD-209 Placebo Eye drops | | |
|--|-------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: AUC | | | | |
| least squares mean (confidence interval 95%) | 3.9953 (2.716 to 5.274) | 3.3322 (1.6 to 5.064) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: The time point of viral eradication in tear liquid from EKC infected eyes, defined as the time point when viral load=0 or below the lower limit of quantification (LLOQ).

| | |
|-----------------|---|
| End point title | The time point of viral eradication in tear liquid from EKC infected eyes, defined as the time point when viral load=0 or below the lower limit of quantification (LLOQ). |
|-----------------|---|

End point description:

The time point of viral eradication in tear liquid from EKC infected eyes, defined as the time point when viral load=0 or below the lower limit of quantification (LLOQ). The days were plotted into a Kaplan Meier curve, log-rank test). The Kaplan Meier curves for APD-209 and APD-209 placebo were compared with a log rank test statistics of 0.6809 with a p-value of 0.4093.

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

End point timeframe:

Visit day 0 to 16

| End point values | ADP-209 Eye drops | APD-209 Placebo Eye drops | | |
|---|-------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: Day | | | | |
| number (not applicable) | | | | |
| Subjects with viral eradication, visit day 1 | 0 | 0 | | |
| Subjects with viral eradication, visit day 2 | 0 | 0 | | |
| Subjects with viral eradication, visit day 3 | 0 | 0 | | |
| Subjects with viral eradication, visit day 4 | 0 | 0 | | |
| Subjects with viral eradication, visit day 5 | 1 | 0 | | |
| Subjects with viral eradication, visit day 6 | 0 | 0 | | |
| Subjects with viral eradication, visit day 7 | 0 | 1 | | |
| Subjects with viral eradication, visit day 8 | 0 | 0 | | |
| Subjects with viral eradication, visit day 9 | 0 | 1 | | |
| Subjects with viral eradication, visit day 10 | 0 | 0 | | |
| Subjects with viral eradication, visit day 11 | 0 | 0 | | |
| Subjects with viral eradication, visit day 12 | 0 | 0 | | |
| Subjects with viral eradication, visit day 13 | 2 | 0 | | |
| Subjects with viral eradication, visit day 14 | 1 | 1 | | |
| Subjects with viral eradication, visit day 15 | 4 | 0 | | |
| Subjects with viral eradication, visit day 16 | 0 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Resolution of acute ocular symptoms at each time of assessment, as measured by objective (Investigator-based) assessment of conjunctival discharge.

| | |
|---|---|
| End point title | Resolution of acute ocular symptoms at each time of assessment, as measured by objective (Investigator-based) assessment of conjunctival discharge. |
| End point description: | |
| Statistical analysis (Wilcoxon's rank sum test) of difference in resolution of Conjunctival discharge symptoms (investigators assessment) at visit 1-6 (mITT) | |
| End point type | Secondary |
| End point timeframe: | |
| Visit 1 to 6 | |

| End point values | ADP-209 Eye drops | APD-209 Placebo Eye drops | | |
|-----------------------------|-------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: Mean Score | | | | |
| number (not applicable) | | | | |
| Visit 1 Mean score | 7.55 | 8.9 | | |
| Visit 2 Mean Score | 7.11 | 8.2 | | |
| Visit 3 Mean Score | 6.88 | 7.2 | | |
| Visit 4 Mean Score | 7.5 | 6.2 | | |
| Visit 5 Mean Score | 6.75 | 7.4 | | |
| Visit 6 Mean Score | 7.31 | 6.5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Resolution of acute ocular symptoms at each time of assessment, as measured by objective (Investigator-based) assessment of redness.

| | |
|-----------------|--|
| End point title | Resolution of acute ocular symptoms at each time of assessment, as measured by objective (Investigator-based) assessment of redness. |
|-----------------|--|

End point description:

Statistical analysis (Wilcoxon's rank sum test) of difference in resolution of redness symptoms (investigator assessment) at visit 1-6 (mITT)

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

End point timeframe:

Visit 1 to 6

| End point values | ADP-209 Eye drops | APD-209 Placebo Eye drops | | |
|-----------------------------|-------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: Mean score | | | | |
| number (not applicable) | | | | |
| Visit 1 Mean Score | 6.7 | 10.6 | | |
| Visit 2 Mean Score | 6.78 | 8.8 | | |
| Visit 3 Mean Score | 5.88 | 8.8 | | |
| Visit 4 Mean Score | 5.81 | 8.9 | | |
| Visit 5 Mean Score | 6.5 | 7.8 | | |
| Visit 6 Mean Score | 7.38 | 6.4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Resolution of ocular symptoms as measured by subject worksheet assessment of irritation symptoms

| | |
|-----------------|--|
| End point title | Resolution of ocular symptoms as measured by subject worksheet assessment of irritation symptoms |
|-----------------|--|

End point description:

Resolution of ocular symptoms at each time of assessment, as measured by subjective (Subject Worksheet) assessment of irritation symptoms.

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

End point timeframe:

Visit 1 to 6

| End point values | ADP-209 Eye drops | APD-209 Placebo Eye drops | | |
|-----------------------------|-------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: Mean score | | | | |
| number (not applicable) | | | | |
| Visit 1 Mean score | 8.65 | 6.7 | | |
| Visit 2 Mean score | 8.1 | 7.8 | | |
| Visit 3 Mean score | 7.9 | 8.2 | | |
| Visit 4 Mean score | 7.45 | 9.1 | | |
| Visit 5 Mean score | 6.83 | 8.7 | | |
| Visit 6 Mean score | 6.94 | 7.1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Resolution of ocular symptoms as measured by subject worksheet assessment of foreign body sensation

| | |
|-----------------|---|
| End point title | Resolution of ocular symptoms as measured by subject worksheet assessment of foreign body sensation |
|-----------------|---|

End point description:

Resolution of ocular symptoms at each time of assessment, as measured by subjective (Subject Worksheet) assessment foreign body sensation.

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

End point timeframe:

Visit 1 to 6

| End point values | ADP-209 Eye drops | APD-209 Placebo Eye drops | | |
|-----------------------------|-------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: Mean score | | | | |
| number (not applicable) | | | | |
| Visit 1 Mean score | 7.55 | 8.9 | | |
| Visit 2 Mean score | 7.25 | 9.5 | | |
| Visit 3 Mean score | 7.45 | 9.1 | | |
| Visit 4 Mean score | 7.75 | 8.5 | | |
| Visit 5 Mean score | 8.33 | 6 | | |
| Visit 6 Mean score | 6.81 | 7.3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Resolution of ocular symptoms at each time os assessment as measured by subjective assessment of tearing.

| | |
|-----------------|---|
| End point title | Resolution of ocular symptoms at each time os assessment as measured by subjective assessment of tearing. |
|-----------------|---|

End point description:

Resolution of ocular symptoms at each time os assessment, as measured by subjective (Subject Worksheet) assessment of tearing.

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

End point timeframe:

Visit 1-6

| End point values | ADP-209 Eye drops | APD-209 Placebo Eye drops | | |
|-----------------------------|-------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: Mean score | | | | |
| number (not applicable) | | | | |
| Visit 1, mean score | 7.3 | 9.4 | | |
| Visit 2, mean score | 7 | 10 | | |
| Visit 3, mean score | 8.5 | 7 | | |
| Visit 4, mean score | 7 | 10 | | |
| Visit 5, mean score | 6.56 | 9.2 | | |
| Visit 6, mean score | 6.75 | 7.4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Resolution of ocular symptoms at each time of assessment measured by subjective assessment of pain.

| | |
|---|---|
| End point title | Resolution of ocular symptoms at each time of assessment measured by subjective assessment of pain. |
| End point description: Resolution of ocular symptoms at each time of assessment, as measured by subjective (Subject Worksheet) assessment of pain. | |
| End point type | Secondary |
| End point timeframe: Visit 1-6 | |

| End point values | ADP-209 Eye drops | APD-209 Placebo Eye drops | | |
|-----------------------------|-------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: Mean score | | | | |
| number (not applicable) | | | | |
| Visit 1, mean score | 8.3 | 7.4 | | |
| Visit 2, mean score | 7.7 | 8.6 | | |
| Visit 3, mean score | 8.15 | 7.7 | | |
| Visit 4, mean score | 7.8 | 8.4 | | |
| Visit 5, mean score | 7.94 | 6.7 | | |
| Visit 6, mean score | 6.81 | 7.3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Resolution of ocular symptoms at each time of assessment measured by subjective assessment of blurred vision.

| | |
|---|---|
| End point title | Resolution of ocular symptoms at each time of assessment measured by subjective assessment of blurred vision. |
| End point description: Resolution of ocular symptoms at each time of assessment, as measured by subjective (Subject Worksheet) assessment of blurred vision. | |
| End point type | Secondary |

End point timeframe:

Visit 1-6

| End point values | ADP-209 Eye drops | APD-209 Placebo Eye drops | | |
|-----------------------------|-------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: Mean score | | | | |
| number (not applicable) | | | | |
| Visit 1, mean score | 7.6 | 8.8 | | |
| Visit 2, mean score | 7.3 | 9.4 | | |
| Visit 3 mean score | 6.85 | 10.3 | | |
| Visit 4, mean score | 6.05 | 11.9 | | |
| Visit 5, mean score | 6.5 | 9.3 | | |
| Visit 6, mean score | 6.63 | 7.6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Location of opacities at each time of assessment measured by slit lamp examination.

| | |
|-----------------|---|
| End point title | Location of opacities at each time of assessment measured by slit lamp examination. |
|-----------------|---|

End point description:

Location of opacities at each time of assessment, as measured by slit lamp examination. Statistical analysis (Wilcoxon's rank sum test) of difference in quantity of opacities (slit lamp) at visit 1-6 (MITT)

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

End point timeframe:

Visit 1-6

| End point values | ADP-209 Eye drops | APD-209 Placebo Eye drops | | |
|-----------------------------|-------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: Mean score | | | | |
| number (not applicable) | | | | |
| Visit 1, mean score | 7.5 | 9 | | |
| Visit 2, mean score | 7.15 | 9.7 | | |
| Visit 3, mean score | 7.5 | 9 | | |
| Visit 4, mean score | 7.35 | 9.3 | | |
| Visit 5, mean score | 7.17 | 8.1 | | |
| Visit 6, mean score | 7.63 | 6 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Presence of opacities at each time of assessment, as measured by slit lamp examination.

| | |
|-----------------|---|
| End point title | Presence of opacities at each time of assessment, as measured by slit lamp examination. |
|-----------------|---|

End point description:

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

End point timeframe:

Visit 1-6

| End point values | ADP-209 Eye drops | APD-209 Placebo Eye drops | | |
|-----------------------------|-------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: Number | | | | |
| number (not applicable) | | | | |
| Visit 1, No Opacities | 10 | 4 | | |
| Visit 2, No Opacities | 7 | 2 | | |
| Visit 3, No Opacities | 6 | 1 | | |
| Visit 4, No Opacities | 3 | 0 | | |
| Visit 5, No Opacities | 3 | 0 | | |
| Visit 6, No Opacities | 1 | 0 | | |
| Visit 1, Opacities | 0 | 1 | | |
| Visit 2, Opacities | 3 | 3 | | |
| Visit 3, Opacities | 4 | 4 | | |
| Visit 4, Opacities | 7 | 5 | | |
| Visit 5, Opacities | 6 | 5 | | |
| Visit 6, Opacities | 7 | 5 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Visual acuity at each time of assessment by use of the logarithm of the Minimum Angle of Resolution (LogMAR) chart.

| | |
|-----------------|--|
| End point title | Visual acuity at each time of assessment by use of the |
|-----------------|--|

End point description:

The LogMAR score was to be calculated from the data entered into the eCRF as: LogMAR score = LogMAR line value + (0.02 x number of incorrect letters)

End point type Secondary

End point timeframe:

Visit 1-6

| End point values | ADP-209 Eye drops | APD-209 Placebo Eye drops | | |
|-----------------------------|-------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: Mean | | | | |
| number (not applicable) | | | | |
| Visit 1, Mean | 0.175 | 0.024 | | |
| Visit 2, Mean | 0.143 | 0.116 | | |
| Visit 3, Mean | 0.223 | 0.188 | | |
| Visit 4, Mean | 0.195 | 0.148 | | |
| Visit 5, Mean | 0.217 | -0.02 | | |
| Visit 6, Mean | 0.154 | -0.06 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Occurrence of second eye infection

End point title Occurrence of second eye infection

End point description:

Presence of clinical symptoms of EKC infection in the second eye. Statistical analysis (Fisher's exact test) of difference in presence of second eye infection at visit 1-6. (MiTT)

End point type Secondary

End point timeframe:

Visit 1-6

| End point values | ADP-209 Eye drops | APD-209 Placebo Eye drops | | |
|-----------------------------|-------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 10 | 5 | | |
| Units: Presence (Yes/No) | | | | |
| Visit 1, No | 6 | 2 | | |
| Visit 2, No | 5 | 1 | | |
| Visit 3, No | 5 | 0 | | |
| Visit 4, No | 5 | 0 | | |

| | | | | |
|--------------|---|---|--|--|
| Visit 5, No | 5 | 2 | | |
| Visit 6, No | 4 | 2 | | |
| Visit 1, Yes | 4 | 3 | | |
| Visit 2, Yes | 5 | 4 | | |
| Visit 3, Yes | 5 | 5 | | |
| Visit 4, Yes | 5 | 5 | | |
| Visit 5, Yes | 4 | 3 | | |
| Visit 6, Yes | 4 | 3 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

To evaluate the safety of the APD-209 treatment, AEs were reported in the eCRF at the study visits (1-6)

Adverse event reporting additional description:

Safety analyses were performed in the safety population, defined as all subjects who received at least 1 dose of study treatment during the study, which included 25 APD-209 subjects and 22 placebo subjects. Most AE's were considered mild in severity and not related to study treatment. APD-209 Eye Drops was found to be safe and well tolerated.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 16.0 |

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Subjects enrolled |
|-----------------------|-------------------|

Reporting group description:

All safety analyses were performed in the safety population, defined as all subjects who received at least one dose of study treatment during the study.

| Serious adverse events | Subjects enrolled | | |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Gastrointestinal disorders | | | |
| Gastritis | Additional description: There was one SAE (gastritis) reported on day 10 for Subject no. 03-1006 receiving placebo and it was due to a hospitalization. It was not judged as being related to the study drug. The SAE was of mild intensity. | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Subjects enrolled | | |
|---|-------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 25 / 47 (53.19%) | | |
| Investigations | | | |
| Blood pressure abnormal | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | | |
| Injury, poisoning and procedural complications Joint injury subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | | |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 | | |
| Nervous system disorders Migraine subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Sciatica subjects affected / exposed occurrences (all) | 1 / 47 (2.13%) 1 1 / 47 (2.13%) 1 1 / 47 (2.13%) 1 | | |
| General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all) | 2 / 47 (4.26%) 2 | | |
| Eye disorders Conjunctival hyperaemia subjects affected / exposed occurrences (all) Conjunctival irritation subjects affected / exposed occurrences (all) Foreign body sensation in eyes subjects affected / exposed occurrences (all) Vision blurred | 3 / 47 (6.38%) 3 2 / 47 (4.26%) 2 1 / 47 (2.13%) 1 | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences (all) | 1 | | |
| Keratopathy | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences (all) | 1 | | |
| Iritis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences (all) | 1 | | |
| Photophobia | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences (all) | 1 | | |
| Lacrimation increased | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences (all) | 1 | | |
| Eye pain | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences (all) | 1 | | |
| Visual acuity reduced | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences (all) | 1 | | |
| Conjunctival oedema | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences (all) | 1 | | |
| Eye pruritus | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences (all) | 1 | | |
| Lip dry | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences (all) | 1 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences (all) | 1 | | |

| | | | |
|--|--|--|--|
| <p>Dry mouth</p> <p>subjects affected / exposed</p> <p>1 / 47 (2.13%)</p> <p>occurrences (all)</p> <p>1</p> | | | |
| <p>Vomiting</p> <p>subjects affected / exposed</p> <p>1 / 47 (2.13%)</p> <p>occurrences (all)</p> <p>1</p> | | | |
| <p>Abdominal pain upper</p> <p>subjects affected / exposed</p> <p>1 / 47 (2.13%)</p> <p>occurrences (all)</p> <p>1</p> | | | |
| <p>Gastritis</p> <p>subjects affected / exposed</p> <p>1 / 47 (2.13%)</p> <p>occurrences (all)</p> <p>1</p> | | | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Cough</p> <p>subjects affected / exposed</p> <p>1 / 47 (2.13%)</p> <p>occurrences (all)</p> <p>1</p> <p>Oropharyngeal pain</p> <p>subjects affected / exposed</p> <p>1 / 47 (2.13%)</p> <p>occurrences (all)</p> <p>1</p> | | | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Erythema</p> <p>subjects affected / exposed</p> <p>1 / 47 (2.13%)</p> <p>occurrences (all)</p> <p>1</p> <p>Skin burning sensation</p> <p>subjects affected / exposed</p> <p>1 / 47 (2.13%)</p> <p>occurrences (all)</p> <p>1</p> <p>Rash</p> <p>subjects affected / exposed</p> <p>1 / 47 (2.13%)</p> <p>occurrences (all)</p> <p>1</p> | | | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>subjects affected / exposed</p> <p>1 / 47 (2.13%)</p> <p>occurrences (all)</p> <p>1</p> | | | |
| <p>Infections and infestations</p> <p>Adenoviral conjunctivitis</p> | | | |

| | | | |
|--------------------------------|-----------------|--|--|
| subjects affected / exposed | 6 / 47 (12.77%) | | |
| occurrences (all) | 6 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 6 / 47 (12.77%) | | |
| occurrences (all) | 6 | | |
| Asymptomatic bacteriuria | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | | |
| occurrences (all) | 2 | | |
| acute tonsillitis | | | |
| subjects affected / exposed | 2 / 47 (4.26%) | | |
| occurrences (all) | 2 | | |
| Cystitis | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences (all) | 1 | | |
| Infection | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences (all) | 1 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences (all) | 1 | | |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 1 / 47 (2.13%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|---|
| 09 April 2014 | <ul style="list-style-type: none">• Prolongation of the maximum allowed time between first eye symptom and inclusion from 48 to 72 hours• Recording of start of onset of first eye symptom• Addition of exploratory analysis investigating effect of time between first eye symptom and inclusion• Removal of the Ad quick test (AdenoPlus) from the screening visit• Clarification of exclusion criterion 8 (concomitant medication)• Clarification of review of Subject Dosing Cards and return of investigational medicinal product (IMP) at Visit 5 or at Visit 6, depending on which day Visit 5 is performed• Clarification of the LogMAR chart for assessment of visual acuity• Clarification of non-compliance in relation to definition of the per protocol set• Increase of number of study centres in Germany to up to 5 centres• Prolongation of the total study period• Change of project leader at TFS and address of the Danish TFS office• Change of biostatistician |
| 23 April 2015 | <ul style="list-style-type: none">• Prolongation of the maximum allowed time between first eye symptom and inclusion of the subject in the study from 72 hours to 7 days• Additions to the exploratory analyses investigating effect of time between first eye symptom and inclusion of the subject in the study• Change in inclusion criterion 2 to remove the upper age limit• Clarification of exclusion criterion 4 (diagnosis of bacterial or fungal ocular infections) to state that it refers to diagnoses made by the study Investigator only (and not to diagnoses made by other physicians seen by the subject prior to the study)• Clarification of exclusion criterion 5 (use of antibiotics or corticosteroids) to allow ocular antibiotics until 2 hours before first dose• Clarification that tear supplements or saline may be administered in the untreated eye• Increase of number of study centres in Germany to up to 7 centres• Prolongation of the total study period |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|---------------|--|--------------|
| 22 March 2016 | Due to the slow enrolment it was decided to end recruitment on March 22nd 2016 Consequently the planned interim analysis was not done. | - |

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Out of 47 randomised subjects, only 15 were included in the mITT analysis set used to assess the primary efficacy variable. 31 out of the 47 randomised subjects were shown not to have adenovirus of the right type plus one more subject excluded.

Notes: