



Clinical trial results:

Phase III study of adefovir dipivoxil in patients with treatment naïve CHB. Comparator is Lamivudine 100mcg film coated tablets-D2012-7213 Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2015-004890-34 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 16 January 2008 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 22 January 2017 |
| First version publication date | 22 January 2017 |

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | ADF105220 |
|-----------------------|-----------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|------------------------------------------------------------|
| Sponsor organisation name | GlaxoSmithKline |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom, |
| Public contact | GSK Response Center, GlaxoSmithKline, 1 866-435-7343, |
| Scientific contact | GSK Response Center, GlaxoSmithKline, 1 866-435-7343, |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|------------------------------------------------------|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 17 March 2008 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 January 2008 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

TBD

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment | 17 January 2006 |
| 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 | Japan: 105 |
| Worldwide total number of subjects | 105 |
| EEA total number of subjects | 0 |

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) | 105 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In this study, informed consent was obtained from 171 subjects. Of those subjects, 66 were withdrawn for not meeting eligibility criteria at screening, including 2 for consent withdrawn.

Period 1

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

Arms

| | |
|------------------------------|----------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Adefovir (ADV) |

Arm description:

ADV 10 mg orally once daily for 52 weeks

| | |
|----------------------------------------|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Adefovir dipivoxil (ADV) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered one ADV 10 mg tablet and one LAM placebo tablet orally once daily for 52 weeks

| | |
|------------------|------------------|
| Arm title | Lamivudine (LAM) |
|------------------|------------------|

Arm description:

LAM 100 mg orally once daily for 52 weeks

| | |
|----------------------------------------|-------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Lamivudine (LAM) |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects were administered one LAM 100 mg tablet and one ADV placebo tablet orally once daily for 52 weeks

| Number of subjects in period 1 | Adefovir (ADV) | Lamivudine (LAM) |
|---------------------------------------|----------------|------------------|
| Started | 52 | 53 |
| Completed | 50 | 47 |
| Not completed | 2 | 6 |
| Adverse event, non-fatal | - | 6 |
| Consent withdrawn | 2 | - |

Baseline characteristics

Reporting groups

| | |
|---------------------------------------------------------------------------|------------------|
| Reporting group title | Adefovir (ADV) |
| Reporting group description: ADV 10 mg orally once daily for 52 weeks | |
| Reporting group title | Lamivudine (LAM) |
| Reporting group description: LAM 100 mg orally once daily for 52 weeks | |

| Reporting group values | Adefovir (ADV) | Lamivudine (LAM) | Total |
|------------------------------------|----------------|------------------|-------|
| Number of subjects | 52 | 53 | 105 |
| Age categorical Units: Subjects | | | |

| | | | |
|--------------------------------|--------|--------|-----|
| Age continuous | | | |
| Age continuous description | | | |
| Units: years | | | |
| arithmetic mean | 44 | 43.9 | |
| standard deviation | ± 9.73 | ± 9.95 | - |
| Gender categorical | | | |
| Gender categorical description | | | |
| Units: Subjects | | | |
| Female | 9 | 18 | 27 |
| Male | 43 | 35 | 78 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Asian | 52 | 53 | 105 |
| Region of Enrollment | | | |
| Units: Subjects | | | |
| Japan | 52 | 53 | 105 |

End points

End points reporting groups

| | |
|---------------------------------------------------------------------------|------------------|
| Reporting group title | Adefovir (ADV) |
| Reporting group description: ADV 10 mg orally once daily for 52 weeks | |
| Reporting group title | Lamivudine (LAM) |
| Reporting group description: LAM 100 mg orally once daily for 52 weeks | |

Primary: Mean Change from Baseline in Hepatitis B Virus (HBV) DNA at Week 52

| | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|
| End point title | Mean Change from Baseline in Hepatitis B Virus (HBV) DNA at Week 52 |
| End point description: Change from baseline was the difference of the HBV DNA copy numbers (log10) in serum collected by blood draw between baseline and Week 52. Per Protocol Set (PPS): participants in the Full Analysis Set (all subjects who entered the study, received at least one dose of investigational product, and had at least one efficacy assessment after the treatment initiation) population with no major protocol violations. | |
| End point type | Primary |
| End point timeframe: Baseline and Week 52 | |

| End point values | Adefovir (ADV) | Lamivudine (LAM) | | |
|--------------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 50 ^[1] | 52 ^[2] | | |
| Units: log10 copies/mL | | | | |
| arithmetic mean (standard deviation) | -3.69 (± 1.169) | -3.4 (± 1.896) | | |

Notes:

[1] - PPS

[2] - PPS

Statistical analyses

| | |
|-----------------------------------------|-----------------------------------|
| Statistical analysis title | Statistical analysis 1 |
| Comparison groups | Lamivudine (LAM) v Adefovir (ADV) |
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority ^[3] |
| P-value | < 0.001 |
| Method | ANCOVA |
| Parameter estimate | Median difference (net) |
| Point estimate | -0.33 |

| | |
|----------------------|----------------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.94 |
| upper limit | 0.28 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 0.309 |

Notes:

[3] - This is a Non-inferiority Analysis with the margin of -1.0.

Secondary: Percentage of participants with HBV DNA Loss (<400 copies/mL) at Week 52

| | |
|-----------------|--------------------------------------------------------------------------|
| End point title | Percentage of participants with HBV DNA Loss (<400 copies/mL) at Week 52 |
|-----------------|--------------------------------------------------------------------------|

End point description:

The percentages of participants with an HBV DNA level in serum of less than 400 copies/mL, which is the lower limit of detection (HBV DNA loss) at Week 52

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

End point timeframe:

Week 52

| End point values | Adefovir (ADV) | Lamivudine (LAM) | | |
|-----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 50 ^[4] | 52 ^[5] | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| <400 copies/mL | 46 | 50 | | |
| >400 copies/mL | 54 | 50 | | |

Notes:

[4] - PPS

[5] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Hepatitis B e antigen (HBeAg) loss at Week 52

| | |
|-----------------|-------------------------------------------------------------------------------|
| End point title | Percentage of participants with Hepatitis B e antigen (HBeAg) loss at Week 52 |
|-----------------|-------------------------------------------------------------------------------|

End point description:

Participants with loss of Hepatitis B e antigen (HBeAg) in serum collected by blood draw: Chemoluminescent Immuno Assay (CLIA) method

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

End point timeframe:

Week 52

| End point values | Adefovir (ADV) | Lamivudine (LAM) | | |
|-----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 36 ^[6] | 37 ^[7] | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| With loss of HBeAg | 16.7 | 16.2 | | |
| Positive for HBeAg | 93.3 | 93.8 | | |

Notes:

[6] - PPS

[7] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Hepatitis B e antigen/antibody (HBeAg/Ab) Seroconversion at Week 52

| | |
|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of participants with Hepatitis B e antigen/antibody (HBeAg/Ab) Seroconversion at Week 52 |
| End point description: | Participants with loss of Hepatitis B e antigen (HBeAg) and positive for anti-Hepatitis B e antibody (HBeAb) in serum collected by blood draw: CLIA method |
| End point type | Secondary |
| End point timeframe: | Week 52 |

| End point values | Adefovir (ADV) | Lamivudine (LAM) | | |
|-----------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 31 ^[8] | 34 ^[9] | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| With HBeAg/Ab seroconversion | 9.7 | 5.9 | | |
| Without HBeAg/Ab seroconversion | 90.3 | 94.1 | | |

Notes:

[8] - PPS: participants who were positive for HBeAg and negative for HBeAb at baseline

[9] - PPS: participants who were positive for HBeAg and negative for HBeAb at baseline

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Hepatitis B s antigen (HBsAg) loss at Week 52

| | |
|------------------------|-------------------------------------------------------------------------------------------------------|
| End point title | Percentage of participants with Hepatitis B s antigen (HBsAg) loss at Week 52 |
| End point description: | Participants with loss of Hepatitis B s antigen (HBsAg) in serum collected by blood draw: CLIA method |
| End point type | Secondary |

End point timeframe:

Week 52

| End point values | Adefovir (ADV) | Lamivudine (LAM) | | |
|-----------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 50 ^[10] | 52 ^[11] | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| With loss of HBsAg | 0 | 0 | | |
| Positive for HBsAg | 100 | 100 | | |

Notes:

[10] - PPS: participants who were positive for HBeAg at baseline

[11] - PPS: participants who were positive for HBeAg at baseline

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with Hepatitis B s antigen/ antibody (HBsAg/Ab) Seroconversion at Week 52

| | |
|-----------------|------------------------------------------------------------------------------------------------------|
| End point title | Percentage of participants with Hepatitis B s antigen/ antibody (HBsAg/Ab) Seroconversion at Week 52 |
|-----------------|------------------------------------------------------------------------------------------------------|

End point description:

Participants with loss of Hepatitis B s antigen (HBsAg) and positive for anti-Hepatitis B s antibody (HBsAb) in serum collected by blood draw: CLIA method

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

End point timeframe:

Week 52

| End point values | Adefovir (ADV) | Lamivudine (LAM) | | |
|-----------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 46 ^[12] | 45 ^[13] | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| With HBsAg/Ab seroconversion | 0 | 0 | | |
| Without HBsAg/Ab seroconversion | 100 | 100 | | |

Notes:

[12] - PPS: participants who were positive for HBeAg and negative for HBeAb at baseline

[13] - PPS: participants who were positive for HBeAg and negative for HBeAb at baseline

Statistical analyses

No statistical analyses for this end point

Secondary: Mean alanine aminotransferase (ALT) level at Week 52

| | |
|-----------------|------------------------------------------------------|
| End point title | Mean alanine aminotransferase (ALT) level at Week 52 |
|-----------------|------------------------------------------------------|

End point description:

Summary statistics were displayed for serum ALT.

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

End point timeframe:

Week 52

| End point values | Adefovir (ADV) | Lamivudine (LAM) | | |
|--------------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 50 ^[14] | 47 ^[15] | | |
| Units: Units per Liter | | | | |
| arithmetic mean (standard deviation) | 32.3 (± 14.72) | 33 (± 28.12) | | |

Notes:

[14] - PPS

[15] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with alanine aminotransferase (ALT) normalization at Week 52

| | |
|-----------------|-----------------------------------------------------------------------------------------|
| End point title | Percentage of participants with alanine aminotransferase (ALT) normalization at Week 52 |
|-----------------|-----------------------------------------------------------------------------------------|

End point description:

ALT normalization was defined as an ALT value that was in the normal range (≤ 45 IU/L; upper limit of normal [ULN]) at Week 52 of the participants whose ALT values were abnormal (>45 IU/L) at baseline

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

End point timeframe:

Week 52

| End point values | Adefovir (ADV) | Lamivudine (LAM) | | |
|-----------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 46 ^[16] | 51 ^[17] | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| With ALT normalization | 82.6 | 78.4 | | |
| Without ALT normalization | 17.4 | 21.6 | | |

Notes:

[16] - PPS: Participants with abnormal ALT value ($>ULN$) at baseline

[17] - PPS: Participants with abnormal ALT value ($>ULN$) at baseline

Statistical analyses

No statistical analyses for this end point

Secondary: Time to onset of ALT normalization

| | |
|------------------------------------------------------------------------------------------------------------|------------------------------------|
| End point title | Time to onset of ALT normalization |
| End point description: Time to onset of ALT normalization was summarized using the Kaplan-Meier method. | |
| End point type | Secondary |
| End point timeframe: From Baseline to Week 52 | |

| End point values | Adefovir (ADV) | Lamivudine (LAM) | | |
|----------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 46 ^[18] | 51 ^[19] | | |
| Units: Week 52 | | | | |
| median (confidence interval 95%) | 12 (8 to 16) | 12 (12 to 16) | | |

Notes:

[18] - PPS: Participants with abnormal ALT value (>ULN) at baseline

[19] - PPS: Participants with abnormal ALT value (>ULN) at baseline

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Emergence of Resistant Virus at Week 52

| | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------|
| End point title | Rate of Emergence of Resistant Virus at Week 52 |
| End point description: Participants with resistant mutation at Week 52. LAM resistant mutation (enzyme-linked mini-sequencing assay): rtM204I/V; ADV resistant mutation (direct sequencing assay): rtN236T or rtA181T/V in HBV DNA ; rt: reverse transcriptase gene | |
| End point type | Secondary |
| End point timeframe: Week 52 | |

| End point values | Adefovir (ADV) | Lamivudine (LAM) | | |
|-----------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 50 ^[20] | 52 ^[21] | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| With resistant mutation | 0 | 28.8 | | |
| Without resistant mutation | 100 | 71.2 | | |

Notes:

[20] - PPS

[21] - PPS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline to Week 52.

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

Dictionary used

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

| | |
|--------------------|-----|
| Dictionary version | 9.0 |
|--------------------|-----|

Reporting groups

| | |
|-----------------------|----------------|
| Reporting group title | Adefovir (ADV) |
|-----------------------|----------------|

Reporting group description:

ADV 10 mg orally once daily for 52 weeks

| | |
|-----------------------|------------------|
| Reporting group title | Lamivudine (LAM) |
|-----------------------|------------------|

Reporting group description:

LAM 100 mg orally once daily for 52 weeks

| Serious adverse events | Adefovir (ADV) | Lamivudine (LAM) | |
|---------------------------------------------------------------------|----------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 4 / 53 (7.55%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Lymphoma | | | |
| alternative dictionary used: MedDRA 9.0 | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatitis | | | |
| alternative dictionary used: MedDRA 9.0 | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Urinary retention | | | |
| alternative dictionary used: MedDRA 9.0 | | | |

| | | | |
|-------------------------------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 53 (1.89%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia bacterial | | | |
| alternative dictionary used: MedDRA 9.0 | | | |
| subjects affected / exposed | 0 / 52 (0.00%) | 1 / 53 (1.89%) | |
| 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 | Adefovir (ADV) | Lamivudine (LAM) | |
|-------------------------------------------------------|------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 39 / 52 (75.00%) | 47 / 53 (88.68%) | |
| Investigations | | | |
| Blood creatine phosphokinase increased | | | |
| alternative dictionary used: MedDRA 9.0 | | | |
| subjects affected / exposed | 5 / 52 (9.62%) | 4 / 53 (7.55%) | |
| occurrences (all) | 8 | 5 | |
| Nervous system disorders | | | |
| Headache | | | |
| alternative dictionary used: MedDRA 9.0 | | | |
| subjects affected / exposed | 1 / 52 (1.92%) | 4 / 53 (7.55%) | |
| occurrences (all) | 1 | 9 | |
| General disorders and administration site conditions | | | |
| Malaise | | | |
| alternative dictionary used: MedDRA 9.0 | | | |
| subjects affected / exposed | 2 / 52 (3.85%) | 5 / 53 (9.43%) | |
| occurrences (all) | 3 | 5 | |
| Gastrointestinal disorders | | | |
| Diarrhea | | | |
| alternative dictionary used: MedDRA 9.0 | | | |
| subjects affected / exposed | 7 / 52 (13.46%) | 6 / 53 (11.32%) | |
| occurrences (all) | 10 | 6 | |

| | | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------|---------------------------------|--|
| <p>Abdominal pain upper</p> <p>alternative dictionary used: MedDRA 9.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 52 (5.77%)</p> <p>3</p> | <p>2 / 53 (3.77%)</p> <p>2</p> | |
| <p>Nausea</p> <p>alternative dictionary used: MedDRA 9.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 52 (1.92%)</p> <p>1</p> | <p>4 / 53 (7.55%)</p> <p>4</p> | |
| <p>Vomiting</p> <p>alternative dictionary used: MedDRA 9.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 52 (0.00%)</p> <p>1</p> | <p>3 / 53 (5.66%)</p> <p>4</p> | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>Pharyngolaryngeal pain</p> <p>alternative dictionary used: MedDRA 9.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 52 (3.85%)</p> <p>2</p> | <p>5 / 53 (9.43%)</p> <p>5</p> | |
| <p>Cough</p> <p>alternative dictionary used: MedDRA 9.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 52 (3.85%)</p> <p>2</p> | <p>3 / 53 (5.66%)</p> <p>3</p> | |
| <p>Hepatobiliary disorders</p> <p>Hepatitis</p> <p>alternative dictionary used: MedDRA 9.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>0 / 52 (0.00%)</p> <p>0</p> | <p>6 / 53 (11.32%)</p> <p>6</p> | |
| <p>Skin and subcutaneous tissue disorders</p> <p>Eczema</p> <p>alternative dictionary used: MedDRA 9.0</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>5 / 52 (9.62%)</p> <p>5</p> | <p>3 / 53 (5.66%)</p> <p>4</p> | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>Arthralgia</p> <p>alternative dictionary used: MedDRA 9.0</p> | | | |

| | | | |
|--------------------------------------------------------------------------------------------------------------------------------------------------|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 3 / 52 (5.77%) 3 | 0 / 53 (0.00%) 0 | |
| Infections and infestations Nasopharyngitis alternative dictionary used: MedDRA 9.0 subjects affected / exposed occurrences (all) | 11 / 52 (21.15%) 15 | 19 / 53 (35.85%) 27 | |
| Upper respiratory tract inflammation alternative dictionary used: MedDRA 9.0 subjects affected / exposed occurrences (all) | 7 / 52 (13.46%) 11 | 10 / 53 (18.87%) 11 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 01 February 2006 | Revised the description of contraindication medications in the exclusion criteria: transferred the statement "(except ointment and/or cream etc)" to the first sentence, because this statement relates to not only corticosteroid but also entire contraindication medications. |
| 17 March 2006 | Changed the commencement of the period of contraindication medications from the first day of the screening period to the first dosing day. |
| 19 September 2006 | Modified the study administrative structure |
| 16 April 2007 | Modified the study administrative structure |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported