



## Clinical trial results:

**An open-label proof-of-concept study with a double-masked, dose-ranging**

**component to assess the effects of AIN457 in patients with noninfectious uveitis**

### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2011-001243-67    |
| Trial protocol           | DE                |
| Global end of trial date | 13 September 2013 |

### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 13 July 2016 |
| First version publication date | 31 July 2015 |

### Trial information

#### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CAIN457A2208 |
|-----------------------|--------------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00685399 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Novartis Pharma AG  |
| Sponsor organisation address | CH-4002, Basel, Switzerland,                                  |
| Public contact               | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |
| Scientific contact           | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, |

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:

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**Results analysis stage**

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|  |                   |
|--|-------------------|
| Analysis stage                                       | Final             |
| Date of interim/final analysis                       | 13 September 2013 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 13 September 2013 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 13 September 2013 |
| Was the trial ended prematurely?                     | No                |

Notes:

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**General information about the trial**

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Main objective of the trial:

To assess the safety and tolerability of intravenous AIN457 in patients with uveitis.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 10 June 2008 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 72 |
| Country: Number of subjects enrolled | Germany: 7        |
| Worldwide total number of subjects   | 79                |
| EEA total number of subjects         | 7                 |

Notes:

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**Subjects enrolled per age group**

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|   |    |
|---|----|
| 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)                      | 75 |
| From 65 to 84 years                       | 4  |
| 85 years and over                         | 0  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Cohort 4 was originally comprised of patients from all other core cohorts of this study whose uveitis was in remission at the end of study observation (Cohorts 1, 2, and 3).

### Period 1

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

### Arms

|                              |          |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes      |
| <b>Arm title</b>             | Cohort 1 |

Arm description:

Cohort 1-300mg s.c. bi-weekly (q2wks)

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Sekukinumab                      |
| Investigational medicinal product code | AIN457                           |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Cohort 1-300mg s.c. bi-weekly (q2wks)

|                  |          |
|------------------|----------|
| <b>Arm title</b> | Cohort 2 |
|------------------|----------|

Arm description:

(300mg s.c. bi-weekly (q2wks)), 3 patients from cohort 1 rolled into this cohort

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Sekukinumab                      |
| Investigational medicinal product code | AIN457                           |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

(300mg s.c. bi-weekly (q2wks)), 3 patients from cohort 1 rolled into this cohort

|                  |          |
|------------------|----------|
| <b>Arm title</b> | Cohort 3 |
|------------------|----------|

Arm description:

10 mg/kg i.v. every 4 weeks (q4 wks)

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Sekukinumab                      |
| Investigational medicinal product code | AIN457                           |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:  
10 mg/kg i.v. every 4 weeks (q4 wks)

|                  |          |
|------------------|----------|
| <b>Arm title</b> | Cohort 5 |
|------------------|----------|

Arm description:

30 mg/kg AIN457 IV q4 weeks

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Sekukinumab                      |
| Investigational medicinal product code | AIN457                           |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

30 mg/kg AIN457 IV q4 weeks

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Cohort 6 Arm 1 |
|------------------|----------------|

Arm description:

300mg sc q 2wks

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Sekukinumab                      |
| Investigational medicinal product code | AIN457                           |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

300mg sc q 2wks

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Cohort 6 Arm 2 |
|------------------|----------------|

Arm description:

10mg/kg i.v. q2wks

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Sekukinumab                      |
| Investigational medicinal product code | AIN457                           |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

10mg/kg i.v. q2wks

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Cohort 6 Arm 3 |
|------------------|----------------|

Arm description:

30mg/kg i.v. q4wks

|  |                                  |
|--|----------------------------------|
| Arm type                               | Experimental                     |
| Investigational medicinal product name | Sekukinumab                      |
| Investigational medicinal product code | AIN457                           |
| Other name                             |                                  |
| Pharmaceutical forms                   | Powder for solution for infusion |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

30mg/kg i.v. q4wks

| <b>Number of subjects in period 1</b> | Cohort 1 | Cohort 2 | Cohort 3 |
|---------------------------------------|----------|----------|----------|
| Started                               | 16       | 17       | 5        |
| Completed                             | 10       | 3        | 2        |
| Not completed                         | 6        | 14       | 3        |
| Consent withdrawn by subject          | 2        | 1        | -        |
| Adverse event, non-fatal              | -        | -        | -        |
| Administrative Problems               | 2        | 2        | 1        |
| Protocol deviation                    | 1        | -        | -        |
| Lack of efficacy                      | 1        | 11       | 2        |

| <b>Number of subjects in period 1</b> | Cohort 5 | Cohort 6 Arm 1 | Cohort 6 Arm 2 |
|---------------------------------------|----------|----------------|----------------|
| Started                               | 4        | 12             | 13             |
| Completed                             | 4        | 10             | 13             |
| Not completed                         | 0        | 2              | 0              |
| Consent withdrawn by subject          | -        | -              | -              |
| Adverse event, non-fatal              | -        | 1              | -              |
| Administrative Problems               | -        | -              | -              |
| Protocol deviation                    | -        | -              | -              |
| Lack of efficacy                      | -        | 1              | -              |

| <b>Number of subjects in period 1</b> | Cohort 6 Arm 3 |
|---------------------------------------|----------------|
| Started                               | 12             |
| Completed                             | 10             |
| Not completed                         | 2              |
| Consent withdrawn by subject          | 2              |
| Adverse event, non-fatal              | -              |
| Administrative Problems               | -              |
| Protocol deviation                    | -              |
| Lack of efficacy                      | -              |

## Period 2

|                              |                |
|------------------------------|----------------|
| Period 2 title               | Extension      |
| Is this the baseline period? | No             |
| Allocation method            | Not applicable |
| Blinding used                | Not blinded    |

## Arms

|  |                     |
|--|---------------------|
| <b>Arm title</b>   | Cohort 4            |
| Arm description:<br>Extension- All patients are rollover patients from other cohorts. AIN457 10 mg/kg iv PRN no more than once per month. COHORT 4 not added to total mean as they are already included. |                     |
| Arm type   | Experimental        |
| Investigational medicinal product name   | Secukinumab         |
| Investigational medicinal product code   | AIN457              |
| Other name   |                     |
| Pharmaceutical forms   | Powder for infusion |
| Routes of administration   | Intravenous use     |

### Dosage and administration details:

Extension- All patients are rollover patients from other cohorts. AIN457 10 mg/kg iv PRN no more than once per month. COHORT 4 not added to total mean as they are already included.

| <b>Number of subjects in period 2</b> | Cohort 4 |
|---------------------------------------|----------|
| Started                               | 28       |
| Completed                             | 21       |
| Not completed                         | 7        |
| Consent withdrawn by subject          | 1        |
| Adverse event, non-fatal              | 2        |
| Administrative Issues                 | 1        |
| Protocol deviation                    | 1        |
| Lack of efficacy                      | 2        |

## Baseline characteristics

| Reporting groups   |                |
|--|----------------|
| Reporting group title  | Cohort 1       |
| Reporting group description:<br>Cohort 1-300mg s.c. bi-weekly (q2wks)  |                |
| Reporting group title  | Cohort 2       |
| Reporting group description:<br>(300mg s.c. bi-weekly (q2wks)), 3 patients from cohort 1 rolled into this cohort |                |
| Reporting group title  | Cohort 3       |
| Reporting group description:<br>10 mg/kg i.v. every 4 weeks (q4 wks)   |                |
| Reporting group title  | Cohort 5       |
| Reporting group description:<br>30 mg/kg AIN457 IV q4 weeks  |                |
| Reporting group title  | Cohort 6 Arm 1 |
| Reporting group description:<br>300mg sc q 2wks  |                |
| Reporting group title  | Cohort 6 Arm 2 |
| Reporting group description:<br>10mg/kg i.v. q2wks   |                |
| Reporting group title  | Cohort 6 Arm 3 |
| Reporting group description:<br>30mg/kg i.v. q4wks   |                |

| Reporting group values                     | Cohort 1 | Cohort 2 | Cohort 3 |
|--|----------|----------|----------|
| Number of subjects                         | 16       | 17       | 5        |
| Age categorical<br>Units: Subjects         |          |          |          |
| 18y < 65y                                  | 15       | 16       | 5        |
| 65y < 85y                                  | 1        | 1        | 0        |
| Gender, Male/Female<br>Units: Participants |          |          |          |
| male                                       | 4        | 5        | 2        |
| Female                                     | 12       | 12       | 3        |

| Reporting group values                     | Cohort 5 | Cohort 6 Arm 1 | Cohort 6 Arm 2 |
|--|----------|----------------|----------------|
| Number of subjects                         | 4        | 12             | 13             |
| Age categorical<br>Units: Subjects         |          |                |                |
| 18y < 65y                                  | 4        | 11             | 12             |
| 65y < 85y                                  | 0        | 1              | 1              |
| Gender, Male/Female<br>Units: Participants |          |                |                |
| male                                       | 1        | 4              | 4              |
| Female                                     | 3        | 8              | 9              |

| Reporting group values | Cohort 6 Arm 3 | Total |  |
|------------------------|----------------|-------|--|
| Number of subjects     | 12             | 79    |  |

|  |    |    |  |
|--|----|----|--|
| Age categorical<br>Units: Subjects         |    |    |  |
| 18y < 65y                                  | 12 | 75 |  |
| 65y < 85y                                  | 0  | 4  |  |
| Gender, Male/Female<br>Units: Participants |    |    |  |
| male                                       | 3  | 23 |  |
| Female                                     | 9  | 56 |  |

## Subject analysis sets

|   |                         |
|---|-------------------------|
| Subject analysis set title  | Adverse Events          |
| Subject analysis set type   | Safety analysis         |
| Subject analysis set description:<br>Found in Adverse Event Section   |                         |
| Subject analysis set title  | Intermediate Uveitis    |
| Subject analysis set type   | Full analysis           |
| Subject analysis set description:<br>Intermediate uveitis is a form of uveitis localized to the vitreous and peripheral retina.   |                         |
| Subject analysis set title  | Posterior uveitis       |
| Subject analysis set type   | Full analysis           |
| Subject analysis set description:<br>Inflammation in the back of the eye is commonly characterized by: Floaters, Blurred vision, Photopsia or seeing flashing lights  |                         |
| Subject analysis set title  | Responders              |
| Subject analysis set type   | Full analysis           |
| Subject analysis set description:<br>Total number of responders   |                         |
| Subject analysis set title  | Pan Uveitis             |
| Subject analysis set type   | Full analysis           |
| Subject analysis set description:<br>Panuveitis is a generalized inflammation of not only the whole of the uveal tract but also involves the retina and vitreous humor  |                         |
| Subject analysis set title  | Anterior Uveitis        |
| Subject analysis set type   | Full analysis           |
| Subject analysis set description:<br>Anterior uveitis includes iridocyclitis and iritis. Iritis is the inflammation of the anterior chamber and iris. Iridocyclitis presents the same symptoms as iritis, but also includes inflammation in the vitreous cavity |                         |
| Subject analysis set title  | Birdshot                |
| Subject analysis set type   | Full analysis           |
| Subject analysis set description:<br>Birdshot chorioretinopathy is a rare form of bilateral posterior uveitis affecting the eye. It causes severe, progressive inflammation of both the choroid and retina  |                         |
| Subject analysis set title  | Sympathetic Ophthalmia  |
| Subject analysis set type   | Full analysis           |
| Subject analysis set description:<br>Sympathetic ophthalmia (SO) is a bilateral diffuse granulomatous uveitis (a kind of inflammation) of both eyes following trauma to one eye.  |                         |
| Subject analysis set title  | Multi-focal Choroiditis |
| Subject analysis set type   | Full analysis           |
| Subject analysis set description:<br>MCP is a condition characterized by intraocular inflammation and multifocal choroidal lesions occurring in the absence of any known ocular or systemic disease   |                         |



| Reporting group values                     | Adverse Events | Intermediate Uveitis | Posterior uveitis |
|--|----------------|----------------------|-------------------|
| Number of subjects                         | 79             | 79                   | 79                |
| Age categorical<br>Units: Subjects         |                |                      |                   |
| 18y < 65y                                  | 75             | 75                   | 75                |
| 65y < 85y                                  | 4              | 4                    | 4                 |
| Gender, Male/Female<br>Units: Participants |                |                      |                   |
| male                                       |                |                      |                   |
| Female                                     |                |                      |                   |

| Reporting group values                     | Responders | Pan Uveitis | Anterior Uveitis |
|--|------------|-------------|------------------|
| Number of subjects                         | 79         | 79          | 79               |
| Age categorical<br>Units: Subjects         |            |             |                  |
| 18y < 65y                                  | 75         | 75          | 75               |
| 65y < 85y                                  | 4          | 4           | 4                |
| Gender, Male/Female<br>Units: Participants |            |             |                  |
| male                                       |            |             |                  |
| Female                                     |            |             |                  |

| Reporting group values                     | Birdshot | Sympathetic Ophthalmia | Multi-focal Choroiditis |
|--|----------|------------------------|-------------------------|
| Number of subjects                         | 79       | 79                     | 79                      |
| Age categorical<br>Units: Subjects         |          |                        |                         |
| 18y < 65y                                  | 75       | 75                     | 75                      |
| 65y < 85y                                  | 4        | 4                      | 4                       |
| Gender, Male/Female<br>Units: Participants |          |                        |                         |
| male                                       |          |                        |                         |
| Female                                     |          |                        |                         |

## End points

### End points reporting groups

|  |                      |
|--|----------------------|
| Reporting group title  | Cohort 1             |
| Reporting group description:<br>Cohort 1-300mg s.c. bi-weekly (q2wks)  |                      |
| Reporting group title  | Cohort 2             |
| Reporting group description:<br>(300mg s.c. bi-weekly (q2wks)), 3 patients from cohort 1 rolled into this cohort   |                      |
| Reporting group title  | Cohort 3             |
| Reporting group description:<br>10 mg/kg i.v. every 4 weeks (q4 wks)   |                      |
| Reporting group title  | Cohort 5             |
| Reporting group description:<br>30 mg/kg AIN457 IV q4 weeks  |                      |
| Reporting group title  | Cohort 6 Arm 1       |
| Reporting group description:<br>300mg sc q 2wks  |                      |
| Reporting group title  | Cohort 6 Arm 2       |
| Reporting group description:<br>10mg/kg i.v. q2wks   |                      |
| Reporting group title  | Cohort 6 Arm 3       |
| Reporting group description:<br>30mg/kg i.v. q4wks   |                      |
| Reporting group title  | Cohort 4             |
| Reporting group description:<br>Extension- All patients are rollover patients from other cohorts. AIN457 10 mg/kg iv PRN no more than once per month. COHORT 4 not added to total mean as they are already included. |                      |
| Subject analysis set title   | Adverse Events       |
| Subject analysis set type  | Safety analysis      |
| Subject analysis set description:<br>Found in Adverse Event Section  |                      |
| Subject analysis set title   | Intermediate Uveitis |
| Subject analysis set type  | Full analysis        |
| Subject analysis set description:<br>Intermediate uveitis is a form of uveitis localized to the vitreous and peripheral retina.  |                      |
| Subject analysis set title   | Posterior uveitis    |
| Subject analysis set type  | Full analysis        |
| Subject analysis set description:<br>Inflammation in the back of the eye is commonly characterized by: Floaters, Blurred vision, Photopsia or seeing flashing lights   |                      |
| Subject analysis set title   | Responders           |
| Subject analysis set type  | Full analysis        |
| Subject analysis set description:<br>Total number of responders  |                      |
| Subject analysis set title   | Pan Uveitis          |
| Subject analysis set type  | Full analysis        |
| Subject analysis set description:<br>Panuveitis is a generalized inflammation of not only the whole of the uveal tract but also involves the retina and vitreous humor   |                      |
| Subject analysis set title   | Anterior Uveitis     |

|  |                         |
|--|-------------------------|
| Subject analysis set type  | Full analysis           |
| Subject analysis set description:  |                         |
| Anterior uveitis includes iridocyclitis and iritis. Iritis is the inflammation of the anterior chamber and iris. Iridocyclitis presents the same symptoms as iritis, but also includes inflammation in the vitreous cavity |                         |
| Subject analysis set title   | Birdshot                |
| Subject analysis set type  | Full analysis           |
| Subject analysis set description:  |                         |
| Birdshot chorioretinopathy is a rare form of bilateral posterior uveitis affecting the eye. It causes severe, progressive inflammation of both the choroid and retina  |                         |
| Subject analysis set title   | Sympathetic Ophthalmia  |
| Subject analysis set type  | Full analysis           |
| Subject analysis set description:  |                         |
| Sympathetic ophthalmia (SO) is a bilateral diffuse granulomatous uveitis (a kind of inflammation) of both eyes following trauma to one eye.  |                         |
| Subject analysis set title   | Multi-focal Choroiditis |
| Subject analysis set type  | Full analysis           |
| Subject analysis set description:  |                         |
| MCP is a condition characterized by intraocular inflammation and multifocal choroidal lesions occurring in the absence of any known ocular or systemic disease   |                         |

### Primary: Number of participants with ocular examinations, physical examination, and adverse events

|   |  |
|---|--|
| End point title   | Number of participants with ocular examinations, physical examination, and adverse events <sup>[1]</sup> |
| End point description:  |  |
| All safety measures are described in the adverse event section. |  |
| End point type  | Primary  |
| End point timeframe:  |  |
| Baseline day through end of study                               |  |

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: insufficient number of participants with events and so there were no statistics performed

| End point values            | Adverse Events       |  |  |  |
|-----------------------------|----------------------|--|--|--|
| Subject group type          | Subject analysis set |  |  |  |
| Number of subjects analysed | 0 <sup>[2]</sup>     |  |  |  |
| Units: participants         |                      |  |  |  |

Notes:

[2] - See Safety

### Statistical analyses

No statistical analyses for this end point

### Secondary: Reduction in ocular inflammation Responders at day 57

|  |   |
|--|---|
| End point title  | Reduction in ocular inflammation Responders at day 57 |
| End point description:   |   |
| Patients from cohorts 1 and 3 participated in an open-label, single sequence, proof-of-concept study to evaluate the effects of 2 intravenous doses of 10 mg/kg of AIN457. Patients from cohort 2 participated in a randomized, double-masked study to evaluate the effects of a single initial dose of 10 mg/kg of Sp2/0-derived AIN457, 3 mg/kg CHO-derived AIN457, or 1 mg/kg of CHO-derived AIN457, followed, if deemed necessary, by a second dose at 10 mg/kg 2 or 3 weeks after the initial dose. Cohort 5 was an open-label single-dose safety study of 30 mg/kg AIN457 delivered in a single 2 hour i.v. infusion. Cohort |   |

6 patients received both subcutaneous and intravenous study drug administration in a double-masked, double dummy design. Patients who responded to AIN457 therapy while in cohorts 1, 2, 3, 5 or 6 and who passed the end of study visit in these cohorts could be enrolled into cohort 4 in which they could continue to receive AIN457 as needed

|                              |           |
|------------------------------|-----------|
| End point type               | Secondary |
| End point timeframe:         |           |
| One week through nine months |           |

| End point values            | Responders           | Intermediate Uveitis | Posterior uveitis    | Pan Uveitis          |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type          | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 79                   | 79                   | 79                   | 79                   |
| Units: Participants         |                      |                      |                      |                      |
| Cohort 1 10mg/Kg Sp2/0      | 11                   | 0                    | 3                    | 5                    |
| Cohort 2 10mg/Kg Sp2/0      | 1                    | 0                    | 0                    | 1                    |
| Cohort 2 10mg/Kg CHO        | 5                    | 1                    | 0                    | 3                    |
| Cohort 2 3mg/Kg CHO         | 0                    | 0                    | 0                    | 0                    |
| Cohort 2 1mg/Kg CHO         | 0                    | 0                    | 0                    | 0                    |
| Cohort 3 10mg/Kg CHO        | 3                    | 0                    | 0                    | 0                    |

| End point values            | Anterior Uveitis     | Birdshot             | Sympathetic Ophthalmia | Multi-focal Choroiditis |
|-----------------------------|----------------------|----------------------|------------------------|-------------------------|
| Subject group type          | Subject analysis set | Subject analysis set | Subject analysis set   | Subject analysis set    |
| Number of subjects analysed | 79                   | 79                   | 79                     | 79 <sup>[3]</sup>       |
| Units: Participants         |                      |                      |                        |                         |
| Cohort 1 10mg/Kg Sp2/0      | 3                    | 0                    | 0                      | 0                       |
| Cohort 2 10mg/Kg Sp2/0      | 0                    | 0                    | 0                      | 0                       |
| Cohort 2 10mg/Kg CHO        | 1                    | 0                    | 0                      | 0                       |
| Cohort 2 3mg/Kg CHO         | 0                    | 0                    | 0                      | 0                       |
| Cohort 2 1mg/Kg CHO         | 0                    | 0                    | 0                      | 0                       |
| Cohort 3 10mg/Kg CHO        | 0                    | 2                    | 1                      | 0                       |

Notes:

[3] - insufficient number of participants with events

## Statistical analyses

No statistical analyses for this end point

## Secondary: Reduction in ocular inflammation Complete Responders at day 57

|                 |  |
|-----------------|--|
| End point title | Reduction in ocular inflammation Complete Responders at day 57 |
|-----------------|--|

End point description:

Patients from cohorts 1 and 3 participated in an open-label, single sequence, proof-of-concept study to evaluate the effects of 2 intravenous doses of 10 mg/kg of AIN457. Patients from cohort 2 participated in a randomized, double-masked study to evaluate the effects of a single initial dose of 10 mg/kg of Sp2/0-derived AIN457, 3 mg/kg CHO-derived AIN457, or 1 mg/kg of CHO-derived AIN457, followed, if deemed necessary, by a second dose at 10 mg/kg 2 or 3 weeks after the initial dose. Cohort 5 was an open-label single-dose safety study of 30 mg/kg AIN457 delivered in a single 2 hour i.v. infusion. Cohort 6 patients received both subcutaneous and intravenous study drug administration in a double-masked,

double dummy design. Patients who responded to AIN457 therapy while in cohorts 1, 2, 3, 5 or 6 and who passed the end of study visit in these cohorts could be enrolled into cohort 4 in which they could continue to receive AIN457 as needed

|                              |           |
|------------------------------|-----------|
| End point type               | Secondary |
| End point timeframe:         |           |
| One week through nine months |           |

| End point values            | Responders           | Intermediate Uveitis | Posterior uveitis    | Pan Uveitis          |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type          | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 79                   | 79                   | 79                   | 79                   |
| Units: Participants         |                      |                      |                      |                      |
| Cohort 2 10mg/Kg Sp2/0      | 0                    | 0                    | 0                    | 0                    |
| Cohort 2 10mg/Kg CHO        | 2                    | 0                    | 0                    | 1                    |
| Cohort 2 3mg/Kg CHO         | 0                    | 0                    | 0                    | 0                    |
| Cohort 2 1mg/Kg CHO         | 0                    | 0                    | 0                    | 0                    |
| Cohort 3 10mg/Kg CHO        | 3                    | 0                    | 0                    | 0                    |
| Cohort 6 300 mg SC          | 2                    | 0                    | 1                    | 1                    |
| Cohort 6 10 mg/Kg iv        | 5                    | 1                    | 2                    | 2                    |
| Cohort 6 30 mg/Kg iv        | 3                    | 1                    | 0                    | 2                    |

| End point values            | Anterior Uveitis     | Birdshot             | Sympathetic Ophthalmia | Multi-focal Choroiditis |
|-----------------------------|----------------------|----------------------|------------------------|-------------------------|
| Subject group type          | Subject analysis set | Subject analysis set | Subject analysis set   | Subject analysis set    |
| Number of subjects analysed | 79                   | 79                   | 79                     | 79                      |
| Units: Participants         |                      |                      |                        |                         |
| Cohort 2 10mg/Kg Sp2/0      | 0                    | 0                    | 0                      | 0                       |
| Cohort 2 10mg/Kg CHO        | 1                    | 0                    | 0                      | 0                       |
| Cohort 2 3mg/Kg CHO         | 0                    | 0                    | 0                      | 0                       |
| Cohort 2 1mg/Kg CHO         | 0                    | 0                    | 0                      | 0                       |
| Cohort 3 10mg/Kg CHO        | 0                    | 2                    | 1                      | 0                       |
| Cohort 6 300 mg SC          | 0                    | 0                    | 0                      | 0                       |
| Cohort 6 10 mg/Kg iv        | 0                    | 0                    | 0                      | 0                       |
| Cohort 6 30 mg/Kg iv        | 0                    | 0                    | 0                      | 0                       |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with ability to induce a remission in uveitis

|  |  |
|--|--|
| End point title  | Number of participants with ability to induce a remission in uveitis |
| End point description:   |  |
| Not enough patients for analysis...only a few that are detailed by narrative in study report |  |
| End point type   | Secondary  |

End point timeframe:  
one week through nine months

| End point values            | Cohort 1         | Cohort 2         | Cohort 3         | Cohort 5         |
|-----------------------------|------------------|------------------|------------------|------------------|
| Subject group type          | Reporting group  | Reporting group  | Reporting group  | Reporting group  |
| Number of subjects analysed | 0 <sup>[4]</sup> | 0 <sup>[5]</sup> | 0 <sup>[6]</sup> | 0 <sup>[7]</sup> |
| Units: Participants         |                  |                  |                  |                  |

Notes:

[4] - insufficient number of participants with events

[5] - insufficient number of participants with events

[6] - insufficient number of participants with events

[7] - insufficient number of participants with events

| End point values            | Cohort 6 Arm 1   | Cohort 6 Arm 2   | Cohort 6 Arm 3    |  |
|-----------------------------|------------------|------------------|-------------------|--|
| Subject group type          | Reporting group  | Reporting group  | Reporting group   |  |
| Number of subjects analysed | 0 <sup>[8]</sup> | 0 <sup>[9]</sup> | 0 <sup>[10]</sup> |  |
| Units: Participants         |                  |                  |                   |  |

Notes:

[8] - insufficient number of participants with events

[9] - insufficient number of participants with events

[10] - insufficient number of participants with events

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with Reduction in other immunosuppressant drugs

|                 |  |
|-----------------|--|
| End point title | Number of participants with Reduction in other immunosuppressant drugs |
|-----------------|--|

End point description:

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

End point timeframe:

One week through nine months

| End point values            | Cohort 1          | Cohort 2          | Cohort 3          | Cohort 5          |
|-----------------------------|-------------------|-------------------|-------------------|-------------------|
| Subject group type          | Reporting group   | Reporting group   | Reporting group   | Reporting group   |
| Number of subjects analysed | 0 <sup>[11]</sup> | 0 <sup>[12]</sup> | 0 <sup>[13]</sup> | 0 <sup>[14]</sup> |
| Units: participants         |                   |                   |                   |                   |

Notes:

[11] - insufficient number of participants with events

[12] - insufficient number of participants with events

[13] - insufficient number of participants with events

[14] - insufficient number of participants with events

| End point values            | Cohort 6 Arm 1    | Cohort 6 Arm 2    | Cohort 6 Arm 3    |  |
|-----------------------------|-------------------|-------------------|-------------------|--|
| Subject group type          | Reporting group   | Reporting group   | Reporting group   |  |
| Number of subjects analysed | 0 <sup>[15]</sup> | 0 <sup>[16]</sup> | 0 <sup>[17]</sup> |  |
| Units: participants         |                   |                   |                   |  |

Notes:

[15] - insufficient number of participants with events

[16] - insufficient number of participants with events

[17] - insufficient number of participants with events

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with remission in uveitis

|  |  |
|--|--|
| End point title  | Number of participants with remission in uveitis |
| End point description:<br>Not enough patients for analysis...only a few that are detailed by narrative in study report |  |
| End point type   | Secondary  |
| End point timeframe:<br>one week through nine months   |  |

| End point values            | Cohort 1          | Cohort 2          | Cohort 3          | Cohort 5          |
|-----------------------------|-------------------|-------------------|-------------------|-------------------|
| Subject group type          | Reporting group   | Reporting group   | Reporting group   | Reporting group   |
| Number of subjects analysed | 0 <sup>[18]</sup> | 0 <sup>[19]</sup> | 0 <sup>[20]</sup> | 0 <sup>[21]</sup> |
| Units: Participants         |                   |                   |                   |                   |

Notes:

[18] - insufficient number of participants with events

[19] - insufficient number of participants with events

[20] - insufficient number of participants with events

[21] - insufficient number of participants with events

| End point values            | Cohort 6 Arm 1    | Cohort 6 Arm 2    | Cohort 6 Arm 3    |  |
|-----------------------------|-------------------|-------------------|-------------------|--|
| Subject group type          | Reporting group   | Reporting group   | Reporting group   |  |
| Number of subjects analysed | 0 <sup>[22]</sup> | 0 <sup>[23]</sup> | 0 <sup>[24]</sup> |  |
| Units: Participants         |                   |                   |                   |  |

Notes:

[22] - insufficient number of participants with events

[23] - insufficient number of participants with events

[24] - insufficient number of participants with events

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants able to re-induce a remission if a flare-up occurs

|                 |   |
|-----------------|---|
| End point title | Number of participants able to re-induce a remission if a flare-up occurs |
|-----------------|---|

End point description:

Not enough patients for analysis...only a few that are detailed by narrative in study report

|                              |           |
|------------------------------|-----------|
| End point type               | Secondary |
| End point timeframe:         |           |
| One week through nine months |           |

| End point values            | Cohort 1          | Cohort 2          | Cohort 3          | Cohort 5          |
|-----------------------------|-------------------|-------------------|-------------------|-------------------|
| Subject group type          | Reporting group   | Reporting group   | Reporting group   | Reporting group   |
| Number of subjects analysed | 0 <sup>[25]</sup> | 0 <sup>[26]</sup> | 0 <sup>[27]</sup> | 0 <sup>[28]</sup> |
| Units: Participants         |                   |                   |                   |                   |

Notes:

[25] - Not enough patients for analysis

[26] - Not enough patients for analysis

[27] - Not enough patients for analysis

[28] - Not enough patients for analysis

| End point values            | Cohort 6 Arm 1    | Cohort 6 Arm 2    | Cohort 6 Arm 3    |  |
|-----------------------------|-------------------|-------------------|-------------------|--|
| Subject group type          | Reporting group   | Reporting group   | Reporting group   |  |
| Number of subjects analysed | 0 <sup>[29]</sup> | 0 <sup>[30]</sup> | 0 <sup>[31]</sup> |  |
| Units: Participants         |                   |                   |                   |  |

Notes:

[29] - Not enough patients for analysis

[30] - Not enough patients for analysis

[31] - Not enough patients for analysis

## Statistical analyses

No statistical analyses for this end point



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All other adverse events are monitored from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

AE additional description

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 16.0 |
|--------------------|------|

### Reporting groups

|                       |   |
|-----------------------|---|
| Reporting group title | Cohort 1 - AIN457 10mg/kg SP2/0 10mg/kg SP2/0 |
|-----------------------|---|

Reporting group description:

Cohort 1 - AIN457 10mg/kg SP2/0 10mg/kg SP2/0

|                       |   |
|-----------------------|---|
| Reporting group title | Cohort 2 - AIN457 10mg/kg SP2/0 10mg/kg SP2/0 |
|-----------------------|---|

Reporting group description:

Cohort 2 - AIN457 10mg/kg SP2/0 10mg/kg SP2/0

|                       |   |
|-----------------------|---|
| Reporting group title | Cohort 2 - AIN457 10mg/kg CHO 10mg/kg CHO |
|-----------------------|---|

Reporting group description:

Cohort 2 - AIN457 10mg/kg CHO 10mg/kg CHO

|                       |  |
|-----------------------|--|
| Reporting group title | Cohort 2 - AIN457 3mg/kg CHO 10mg/kg CHO |
|-----------------------|--|

Reporting group description:

Cohort 2 - AIN457 3mg/kg CHO 10mg/kg CHO

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | Cohort 2 - AIN457 1mg/kg CHO None |
|-----------------------|-----------------------------------|

Reporting group description:

Cohort 2 - AIN457 1mg/kg CHO None

|                       |  |
|-----------------------|--|
| Reporting group title | Cohort 2 - AIN457 1mg/kg CHO 10mg/kg CHO |
|-----------------------|--|

Reporting group description:

Cohort 2 - AIN457 1mg/kg CHO 10mg/kg CHO

|                       |   |
|-----------------------|---|
| Reporting group title | Cohort 3 - AIN457 10mg/kg CHO 10mg/kg CHO |
|-----------------------|---|

Reporting group description:

Cohort 3 - AIN457 10mg/kg CHO 10mg/kg CHO

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Cohort 5 - AIN457 30mg/kg i.v. q4wks |
|-----------------------|--------------------------------------|

Reporting group description:

Cohort 5 - AIN457 30mg/kg i.v. q4wks

|                       |                                  |
|-----------------------|----------------------------------|
| Reporting group title | Cohort 6 - AIN457 300mg sc q2wks |
|-----------------------|----------------------------------|

Reporting group description:

Cohort 6 - AIN457 300mg sc q2wks

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Cohort 6 - AIN457 10mg/kg i.v. q2wks |
|-----------------------|--------------------------------------|

Reporting group description:

Cohort 6 - AIN457 10mg/kg i.v. q2wks

|                       |                                      |
|-----------------------|--------------------------------------|
| Reporting group title | Cohort 6 - AIN457 30mg/kg i.v. q4wks |
|-----------------------|--------------------------------------|

Reporting group description:

Cohort 6 - AIN457 30mg/kg i.v. q4wks

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Cohort 4 (extension) - AIN457 |
|-----------------------|-------------------------------|

Reporting group description:

Cohort 4 (extension) - AIN457

| <b>Serious adverse events</b>                                       | Cohort 1 - AIN457<br>10mg/kg SP2/0<br>10mg/kg SP2/0 | Cohort 2 - AIN457<br>10mg/kg SP2/0<br>10mg/kg SP2/0 | Cohort 2 - AIN457<br>10mg/kg CHO<br>10mg/kg CHO |
|---|---|---|---|
| Total subjects affected by serious adverse events                   |   |   |   |
| subjects affected / exposed   | 0 / 15 (0.00%)                                      | 0 / 1 (0.00%)                                       | 0 / 5 (0.00%)                                   |
| number of deaths (all causes)                                       | 0   | 0   | 0   |
| number of deaths resulting from adverse events                      | 0   | 0   | 0   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |   |   |
| Uterine cancer  |   |   |   |
| subjects affected / exposed   | 0 / 15 (0.00%)                                      | 0 / 1 (0.00%)                                       | 0 / 5 (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   |
| Injury, poisoning and procedural complications                      |   |   |   |
| Tibia fracture  |   |   |   |
| subjects affected / exposed   | 0 / 15 (0.00%)                                      | 0 / 1 (0.00%)                                       | 0 / 5 (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   |   |   |   |
| Pyelonephritis  |   |   |   |
| subjects affected / exposed   | 0 / 15 (0.00%)                                      | 0 / 1 (0.00%)                                       | 0 / 5 (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   |
| Urinary tract infection   |   |   |   |
| subjects affected / exposed   | 0 / 15 (0.00%)                                      | 0 / 1 (0.00%)                                       | 0 / 5 (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   |
| Metabolism and nutrition disorders                                  |   |   |   |
| Hypokalaemia  |   |   |   |
| subjects affected / exposed   | 0 / 15 (0.00%)                                      | 0 / 1 (0.00%)                                       | 0 / 5 (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   |

| <b>Serious adverse events</b>      | Cohort 2 - AIN457<br>3mg/kg CHO<br>10mg/kg CHO | Cohort 2 - AIN457<br>1mg/kg CHO None | Cohort 2 - AIN457<br>1mg/kg CHO<br>10mg/kg CHO |
|------------------------------------|--|--------------------------------------|--|
| Total subjects affected by serious |  |                                      |  |

|   |               |               |               |
|---|---------------|---------------|---------------|
| adverse events  |               |               |               |
| subjects affected / exposed   | 0 / 5 (0.00%) | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| number of deaths (all causes)                                       | 0             | 0             | 0             |
| number of deaths resulting from adverse events                      | 0             | 0             | 0             |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |               |               |               |
| Uterine cancer  |               |               |               |
| subjects affected / exposed   | 0 / 5 (0.00%) | 0 / 2 (0.00%) | 0 / 4 (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         |
| Injury, poisoning and procedural complications                      |               |               |               |
| Tibia fracture  |               |               |               |
| subjects affected / exposed   | 0 / 5 (0.00%) | 0 / 2 (0.00%) | 0 / 4 (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   |               |               |               |
| Pyelonephritis  |               |               |               |
| subjects affected / exposed   | 0 / 5 (0.00%) | 0 / 2 (0.00%) | 0 / 4 (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         |
| Urinary tract infection   |               |               |               |
| subjects affected / exposed   | 0 / 5 (0.00%) | 0 / 2 (0.00%) | 0 / 4 (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         |
| Metabolism and nutrition disorders                                  |               |               |               |
| Hypokalaemia  |               |               |               |
| subjects affected / exposed   | 0 / 5 (0.00%) | 0 / 2 (0.00%) | 0 / 4 (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         |

|   |   |   |                                     |
|---|---|---|-------------------------------------|
| <b>Serious adverse events</b>                                       | Cohort 3 - AIN457<br>10mg/kg CHO<br>10mg/kg CHO | Cohort 5 - AIN457<br>30mg/kg i.v. q4wks | Cohort 6 - AIN457<br>300mg sc q2wks |
| Total subjects affected by serious adverse events                   |   |   |                                     |
| subjects affected / exposed   | 1 / 5 (20.00%)                                  | 0 / 4 (0.00%)                           | 1 / 12 (8.33%)                      |
| number of deaths (all causes)                                       | 0   | 0                                       | 0                                   |
| number of deaths resulting from adverse events                      | 0   | 0                                       | 0                                   |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |   |                                     |

|   |                |               |                |
|---|----------------|---------------|----------------|
| Uterine cancer                                  |                |               |                |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Injury, poisoning and procedural complications  |                |               |                |
| Tibia fracture                                  |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (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                     |                |               |                |
| Pyelonephritis                                  |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Urinary tract infection                         |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 1 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |
| Metabolism and nutrition disorders              |                |               |                |
| Hypokalaemia                                    |                |               |                |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 1 / 12 (8.33%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0          |

| <b>Serious adverse events</b>                                       | Cohort 6 - AIN457<br>10mg/kg i.v. q2wks | Cohort 6 - AIN457<br>30mg/kg i.v. q4wks | Cohort 4 (extension)<br>- AIN457 |
|---|---|---|----------------------------------|
| Total subjects affected by serious adverse events                   |   |   |                                  |
| subjects affected / exposed   | 0 / 13 (0.00%)                          | 0 / 12 (0.00%)                          | 1 / 28 (3.57%)                   |
| number of deaths (all causes)                                       | 0                                       | 0                                       | 0                                |
| number of deaths resulting from adverse events                      | 0                                       | 0                                       | 0                                |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |   |                                  |
| Uterine cancer  |   |   |                                  |
| subjects affected / exposed   | 0 / 13 (0.00%)                          | 0 / 12 (0.00%)                          | 0 / 28 (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                            |
| Injury, poisoning and procedural                                    |   |   |                                  |

|   |                |                |                |
|---|----------------|----------------|----------------|
| complications                                   |                |                |                |
| Tibia fracture                                  |                |                |                |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 1 / 28 (3.57%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Pyelonephritis                                  |                |                |                |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (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          |
| Urinary tract infection                         |                |                |                |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (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          |
| Metabolism and nutrition disorders              |                |                |                |
| Hypokalaemia                                    |                |                |                |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (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          |

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

| <b>Non-serious adverse events</b>                                   | Cohort 1 - AIN457<br>10mg/kg SP2/0<br>10mg/kg SP2/0 | Cohort 2 - AIN457<br>10mg/kg SP2/0<br>10mg/kg SP2/0 | Cohort 2 - AIN457<br>10mg/kg CHO<br>10mg/kg CHO |
|---|---|---|---|
| Total subjects affected by non-serious adverse events               |   |   |   |
| subjects affected / exposed   | 15 / 15 (100.00%)                                   | 1 / 1 (100.00%)                                     | 4 / 5 (80.00%)                                  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |   |   |
| Fibroadenoma of breast  |   |   |   |
| subjects affected / exposed   | 1 / 15 (6.67%)                                      | 0 / 1 (0.00%)                                       | 0 / 5 (0.00%)                                   |
| occurrences (all)   | 1   | 0   | 0   |
| Vascular disorders  |   |   |   |
| Hot flush   |   |   |   |
| subjects affected / exposed   | 1 / 15 (6.67%)                                      | 0 / 1 (0.00%)                                       | 0 / 5 (0.00%)                                   |
| occurrences (all)   | 1   | 0   | 0   |
| General disorders and administration site conditions                |   |   |   |

|   |                 |               |                |
|---|-----------------|---------------|----------------|
| Fatigue   |                 |               |                |
| subjects affected / exposed                     | 2 / 15 (13.33%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 2               | 0             | 0              |
| Infusion site extravasation                     |                 |               |                |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0               | 0             | 0              |
| Irritability                                    |                 |               |                |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0               | 0             | 0              |
| Oedema peripheral                               |                 |               |                |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0               | 0             | 0              |
| Pain  |                 |               |                |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0               | 0             | 0              |
| Pyrexia   |                 |               |                |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0               | 0             | 0              |
| Immune system disorders                         |                 |               |                |
| Seasonal allergy                                |                 |               |                |
| subjects affected / exposed                     | 2 / 15 (13.33%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 2               | 0             | 0              |
| Reproductive system and breast disorders        |                 |               |                |
| Uterine haemorrhage                             |                 |               |                |
| subjects affected / exposed                     | 1 / 15 (6.67%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 1               | 0             | 0              |
| Uterine spasm                                   |                 |               |                |
| subjects affected / exposed                     | 1 / 15 (6.67%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 1               | 0             | 0              |
| Respiratory, thoracic and mediastinal disorders |                 |               |                |
| Cough   |                 |               |                |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)                               | 0               | 0             | 1              |
| Nasal congestion                                |                 |               |                |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)                               | 0               | 0             | 1              |

|  |                     |                    |                     |
|--|---------------------|--------------------|---------------------|
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 15 (6.67%)<br>1 | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 15 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 | 1 / 5 (20.00%)<br>1 |
| Sinus congestion<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 15 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Vocal cord disorder<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 15 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Psychiatric disorders  |                     |                    |                     |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                              | 0 / 15 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Anxiety disorder<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 15 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Depression<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 15 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 15 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Nervousness<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 15 (6.67%)<br>1 | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Investigations   |                     |                    |                     |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 0 / 15 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 | 1 / 5 (20.00%)<br>1 |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0 | 0 / 1 (0.00%)<br>0 | 1 / 5 (20.00%)<br>1 |
| Blood bilirubin increased  |                     |                    |                     |

|  |                 |               |                |
|--|-----------------|---------------|----------------|
| subjects affected / exposed            | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                      | 0               | 0             | 0              |
| Blood creatine phosphokinase increased |                 |               |                |
| subjects affected / exposed            | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)                      | 0               | 0             | 1              |
| Blood lactate dehydrogenase increased  |                 |               |                |
| subjects affected / exposed            | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)                      | 0               | 0             | 1              |
| Blood pressure increased               |                 |               |                |
| subjects affected / exposed            | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                      | 0               | 0             | 0              |
| Blood triglycerides increased          |                 |               |                |
| subjects affected / exposed            | 2 / 15 (13.33%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                      | 2               | 0             | 0              |
| Blood urine present                    |                 |               |                |
| subjects affected / exposed            | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)                      | 0               | 0             | 1              |
| Intraocular pressure increased         |                 |               |                |
| subjects affected / exposed            | 5 / 15 (33.33%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                      | 5               | 0             | 0              |
| Lipase increased                       |                 |               |                |
| subjects affected / exposed            | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)                      | 0               | 0             | 1              |
| Lymphocyte count decreased             |                 |               |                |
| subjects affected / exposed            | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                      | 0               | 0             | 0              |
| Lymphocyte percentage decreased        |                 |               |                |
| subjects affected / exposed            | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                      | 0               | 0             | 0              |
| Neutrophil percentage increased        |                 |               |                |
| subjects affected / exposed            | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                      | 0               | 0             | 0              |
| Protein urine                          |                 |               |                |



|  |                      |                    |                     |
|--|----------------------|--------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                 | 1 / 15 (6.67%)<br>1  | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)             | 0 / 15 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Injury, poisoning and procedural complications                                   |                      |                    |                     |
| Back injury<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 15 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Joint injury<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 15 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 | 1 / 5 (20.00%)<br>1 |
| Laceration<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 15 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Muscle strain<br>subjects affected / exposed<br>occurrences (all)                | 0 / 15 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Post procedural complication<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Radius fracture<br>subjects affected / exposed<br>occurrences (all)              | 0 / 15 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Cardiac disorders  |                      |                    |                     |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 15 (6.67%)<br>1  | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Nervous system disorders   |                      |                    |                     |
| Aphonia<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 15 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 | 1 / 5 (20.00%)<br>1 |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                    | 3 / 15 (20.00%)<br>4 | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Headache   |                      |                    |                     |

|                             |                  |               |                |
|-----------------------------|------------------|---------------|----------------|
| subjects affected / exposed | 10 / 15 (66.67%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 30               | 0             | 0              |
| Hyperaesthesia              |                  |               |                |
| subjects affected / exposed | 0 / 15 (0.00%)   | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0                | 0             | 0              |
| Migraine                    |                  |               |                |
| subjects affected / exposed | 1 / 15 (6.67%)   | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 2                | 0             | 0              |
| Paraesthesia                |                  |               |                |
| subjects affected / exposed | 0 / 15 (0.00%)   | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0                | 0             | 0              |
| Presyncope                  |                  |               |                |
| subjects affected / exposed | 1 / 15 (6.67%)   | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 1                | 0             | 0              |
| Sinus headache              |                  |               |                |
| subjects affected / exposed | 2 / 15 (13.33%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 2                | 0             | 0              |
| Somnolence                  |                  |               |                |
| subjects affected / exposed | 1 / 15 (6.67%)   | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 1                | 0             | 0              |
| Syncope                     |                  |               |                |
| subjects affected / exposed | 1 / 15 (6.67%)   | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 1                | 0             | 0              |
| Tension headache            |                  |               |                |
| subjects affected / exposed | 0 / 15 (0.00%)   | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0                | 0             | 0              |
| Ear and labyrinth disorders |                  |               |                |
| Ear pain                    |                  |               |                |
| subjects affected / exposed | 0 / 15 (0.00%)   | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0                | 0             | 0              |
| Eye disorders               |                  |               |                |
| Abnormal sensation in eye   |                  |               |                |
| subjects affected / exposed | 0 / 15 (0.00%)   | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)           | 0                | 0             | 1              |
| Anterior chamber flare      |                  |               |                |

|                             |                 |               |                |
|-----------------------------|-----------------|---------------|----------------|
| subjects affected / exposed | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0             | 0              |
| Cataract                    |                 |               |                |
| subjects affected / exposed | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0             | 0              |
| Chalazion                   |                 |               |                |
| subjects affected / exposed | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0             | 0              |
| Colour blindness acquired   |                 |               |                |
| subjects affected / exposed | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0             | 0              |
| Conjunctival hyperaemia     |                 |               |                |
| subjects affected / exposed | 1 / 15 (6.67%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 2               | 0             | 0              |
| Conjunctivitis allergic     |                 |               |                |
| subjects affected / exposed | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0             | 0              |
| Corneal disorder            |                 |               |                |
| subjects affected / exposed | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0             | 0              |
| Dry eye                     |                 |               |                |
| subjects affected / exposed | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0             | 0              |
| Eye irritation              |                 |               |                |
| subjects affected / exposed | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0             | 0              |
| Eye pain                    |                 |               |                |
| subjects affected / exposed | 3 / 15 (20.00%) | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)           | 8               | 0             | 1              |
| Eye pruritus                |                 |               |                |
| subjects affected / exposed | 1 / 15 (6.67%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 1               | 0             | 0              |
| Eye swelling                |                 |               |                |
| subjects affected / exposed | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0             | 0              |
| Eyelid oedema               |                 |               |                |

|                                |                 |                 |                |
|--------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed    | 1 / 15 (6.67%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)              | 1               | 0               | 0              |
| Foreign body sensation in eyes |                 |                 |                |
| subjects affected / exposed    | 1 / 15 (6.67%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)              | 1               | 0               | 0              |
| Iridocyclitis                  |                 |                 |                |
| subjects affected / exposed    | 0 / 15 (0.00%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)              | 0               | 0               | 0              |
| Iris adhesions                 |                 |                 |                |
| subjects affected / exposed    | 0 / 15 (0.00%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)              | 0               | 0               | 0              |
| Iris bombe                     |                 |                 |                |
| subjects affected / exposed    | 1 / 15 (6.67%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)              | 1               | 0               | 0              |
| Keratoconjunctivitis sicca     |                 |                 |                |
| subjects affected / exposed    | 1 / 15 (6.67%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)              | 1               | 0               | 0              |
| Lacrimation increased          |                 |                 |                |
| subjects affected / exposed    | 0 / 15 (0.00%)  | 0 / 1 (0.00%)   | 1 / 5 (20.00%) |
| occurrences (all)              | 0               | 0               | 1              |
| Macular fibrosis               |                 |                 |                |
| subjects affected / exposed    | 0 / 15 (0.00%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)              | 0               | 0               | 0              |
| Macular oedema                 |                 |                 |                |
| subjects affected / exposed    | 1 / 15 (6.67%)  | 1 / 1 (100.00%) | 1 / 5 (20.00%) |
| occurrences (all)              | 1               | 1               | 1              |
| Ocular hyperaemia              |                 |                 |                |
| subjects affected / exposed    | 2 / 15 (13.33%) | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)              | 2               | 0               | 0              |
| Papilloedema                   |                 |                 |                |
| subjects affected / exposed    | 0 / 15 (0.00%)  | 0 / 1 (0.00%)   | 1 / 5 (20.00%) |
| occurrences (all)              | 0               | 0               | 1              |
| Photophobia                    |                 |                 |                |
| subjects affected / exposed    | 0 / 15 (0.00%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)              | 0               | 0               | 0              |
| Photopsia                      |                 |                 |                |

|                             |                 |                 |                |
|-----------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 15 (6.67%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0              |
| Pupillary reflex impaired   |                 |                 |                |
| subjects affected / exposed | 0 / 15 (0.00%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0               | 0              |
| Retinal detachment          |                 |                 |                |
| subjects affected / exposed | 1 / 15 (6.67%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0              |
| Retinal tear                |                 |                 |                |
| subjects affected / exposed | 0 / 15 (0.00%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0               | 0              |
| Scleritis                   |                 |                 |                |
| subjects affected / exposed | 1 / 15 (6.67%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0              |
| Uveitis                     |                 |                 |                |
| subjects affected / exposed | 1 / 15 (6.67%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0              |
| Vision blurred              |                 |                 |                |
| subjects affected / exposed | 3 / 15 (20.00%) | 0 / 1 (0.00%)   | 1 / 5 (20.00%) |
| occurrences (all)           | 3               | 0               | 1              |
| Visual acuity reduced       |                 |                 |                |
| subjects affected / exposed | 2 / 15 (13.33%) | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 2               | 0               | 0              |
| Vitreous detachment         |                 |                 |                |
| subjects affected / exposed | 0 / 15 (0.00%)  | 1 / 1 (100.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 1               | 0              |
| Vitreous floaters           |                 |                 |                |
| subjects affected / exposed | 1 / 15 (6.67%)  | 0 / 1 (0.00%)   | 1 / 5 (20.00%) |
| occurrences (all)           | 3               | 0               | 1              |
| Vitreous haemorrhage        |                 |                 |                |
| subjects affected / exposed | 0 / 15 (0.00%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 0               | 0               | 0              |
| Gastrointestinal disorders  |                 |                 |                |
| Abdominal distension        |                 |                 |                |
| subjects affected / exposed | 1 / 15 (6.67%)  | 0 / 1 (0.00%)   | 0 / 5 (0.00%)  |
| occurrences (all)           | 1               | 0               | 0              |

|  |                      |                    |                     |
|--|----------------------|--------------------|---------------------|
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 15 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Abdominal pain lower<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 15 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Abdominal pain upper<br>subjects affected / exposed<br>occurrences (all)                                     | 3 / 15 (20.00%)<br>4 | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)   | 1 / 15 (6.67%)<br>1  | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)  | 0 / 15 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 | 1 / 5 (20.00%)<br>1 |
| Inguinal hernia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 15 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Mouth ulceration<br>subjects affected / exposed<br>occurrences (all)   | 1 / 15 (6.67%)<br>2  | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 1 / 15 (6.67%)<br>1  | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Tooth disorder<br>subjects affected / exposed<br>occurrences (all)   | 1 / 15 (6.67%)<br>1  | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 2 / 15 (13.33%)<br>5 | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Hepatobiliary disorders<br>Non-alcoholic steatohepatitis<br>subjects affected / exposed<br>occurrences (all) | 0 / 15 (0.00%)<br>0  | 0 / 1 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  |
| Skin and subcutaneous tissue disorders   |                      |                    |                     |

|                             |                |               |                |
|-----------------------------|----------------|---------------|----------------|
| Acne                        |                |               |                |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Alopecia                    |                |               |                |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)           | 0              | 0             | 1              |
| Dermatitis acneiform        |                |               |                |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Dermatitis contact          |                |               |                |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Eczema                      |                |               |                |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Madarosis                   |                |               |                |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 1              | 0             | 0              |
| Pruritus                    |                |               |                |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Pruritus generalised        |                |               |                |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Psoriasis                   |                |               |                |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Rash                        |                |               |                |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)           | 3              | 0             | 1              |
| Rash pruritic               |                |               |                |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Skin odour abnormal         |                |               |                |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)           | 1              | 0             | 0              |

|   |                 |               |                |
|---|-----------------|---------------|----------------|
| Renal and urinary disorders                     |                 |               |                |
| Nephrolithiasis                                 |                 |               |                |
| subjects affected / exposed                     | 1 / 15 (6.67%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 1               | 0             | 0              |
| Endocrine disorders                             |                 |               |                |
| Hypothyroidism                                  |                 |               |                |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)                               | 0               | 0             | 1              |
| Musculoskeletal and connective tissue disorders |                 |               |                |
| Arthralgia                                      |                 |               |                |
| subjects affected / exposed                     | 2 / 15 (13.33%) | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)                               | 3               | 0             | 1              |
| Back pain                                       |                 |               |                |
| subjects affected / exposed                     | 2 / 15 (13.33%) | 0 / 1 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all)                               | 3               | 0             | 1              |
| Exostosis                                       |                 |               |                |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0               | 0             | 0              |
| Flank pain                                      |                 |               |                |
| subjects affected / exposed                     | 1 / 15 (6.67%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 3               | 0             | 0              |
| Joint swelling                                  |                 |               |                |
| subjects affected / exposed                     | 1 / 15 (6.67%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 1               | 0             | 0              |
| Limb discomfort                                 |                 |               |                |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0               | 0             | 0              |
| Muscle spasms                                   |                 |               |                |
| subjects affected / exposed                     | 2 / 15 (13.33%) | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 3               | 0             | 0              |
| Musculoskeletal pain                            |                 |               |                |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0               | 0             | 0              |
| Musculoskeletal stiffness                       |                 |               |                |
| subjects affected / exposed                     | 0 / 15 (0.00%)  | 0 / 1 (0.00%) | 0 / 5 (0.00%)  |
| occurrences (all)                               | 0               | 0             | 0              |



|                             |                |               |               |
|-----------------------------|----------------|---------------|---------------|
| Myalgia                     |                |               |               |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 1              | 0             | 0             |
| Pain in extremity           |                |               |               |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0             | 0             |
| Spondylitis                 |                |               |               |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 1              | 0             | 0             |
| Infections and infestations |                |               |               |
| Cellulitis                  |                |               |               |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0             | 0             |
| Ear infection               |                |               |               |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0             | 0             |
| Gastroenteritis             |                |               |               |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0             | 0             |
| Herpes zoster               |                |               |               |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0             | 0             |
| Hordeolum                   |                |               |               |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0             | 0             |
| Lice infestation            |                |               |               |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0             | 0             |
| Nasopharyngitis             |                |               |               |
| subjects affected / exposed | 1 / 15 (6.67%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 1              | 0             | 0             |
| Oral herpes                 |                |               |               |
| subjects affected / exposed | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)           | 0              | 0             | 0             |
| Pharyngitis streptococcal   |                |               |               |

|   |                |               |               |
|---|----------------|---------------|---------------|
| subjects affected / exposed             | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                       | 0              | 0             | 0             |
| Respiratory tract infection             |                |               |               |
| subjects affected / exposed             | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                       | 0              | 0             | 0             |
| Sinusitis                               |                |               |               |
| subjects affected / exposed             | 1 / 15 (6.67%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                       | 1              | 0             | 0             |
| Upper respiratory tract infection       |                |               |               |
| subjects affected / exposed             | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                       | 0              | 0             | 0             |
| Urinary tract infection                 |                |               |               |
| subjects affected / exposed             | 1 / 15 (6.67%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                       | 1              | 0             | 0             |
| Vaginitis bacterial                     |                |               |               |
| subjects affected / exposed             | 1 / 15 (6.67%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                       | 1              | 0             | 0             |
| Viral upper respiratory tract infection |                |               |               |
| subjects affected / exposed             | 1 / 15 (6.67%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                       | 1              | 0             | 0             |
| Vulvovaginal mycotic infection          |                |               |               |
| subjects affected / exposed             | 1 / 15 (6.67%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                       | 1              | 0             | 0             |
| Metabolism and nutrition disorders      |                |               |               |
| Gout                                    |                |               |               |
| subjects affected / exposed             | 1 / 15 (6.67%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                       | 1              | 0             | 0             |
| Increased appetite                      |                |               |               |
| subjects affected / exposed             | 0 / 15 (0.00%) | 0 / 1 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all)                       | 0              | 0             | 0             |

| <b>Non-serious adverse events</b>                                   | Cohort 2 - AIN457<br>3mg/kg CHO<br>10mg/kg CHO | Cohort 2 - AIN457<br>1mg/kg CHO None | Cohort 2 - AIN457<br>1mg/kg CHO<br>10mg/kg CHO |
|---|--|--------------------------------------|--|
| Total subjects affected by non-serious adverse events               |  |                                      |  |
| subjects affected / exposed   | 2 / 5 (40.00%)                                 | 2 / 2 (100.00%)                      | 3 / 4 (75.00%)                                 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |  |                                      |  |

|  |                     |                    |                    |
|--|---------------------|--------------------|--------------------|
| Fibroadenoma of breast<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Vascular disorders<br>Hot flush<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| General disorders and administration<br>site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Infusion site extravasation<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Irritability<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5 (20.00%)<br>1 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Immune system disorders<br>Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Reproductive system and breast<br>disorders<br>Uterine haemorrhage<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Uterine spasm  |                     |                    |                    |

|  |                    |                    |                    |
|--|--------------------|--------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Respiratory, thoracic and mediastinal disorders  |                    |                    |                    |
| Cough  |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 1 / 4 (25.00%)     |
| occurrences (all)                                | 0                  | 0                  | 1                  |
| Nasal congestion                                 |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Oropharyngeal pain                               |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Rhinorrhoea                                      |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Sinus congestion                                 |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Vocal cord disorder                              |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Psychiatric disorders                            |                    |                    |                    |
| Anxiety  |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Anxiety disorder                                 |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Depression                                       |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Insomnia   |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Nervousness                                      |                    |                    |                    |

|  |                    |                    |                    |
|--|--------------------|--------------------|--------------------|
| subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Investigations   |                    |                    |                    |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)     | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)              | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Blood creatine phosphokinase increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Blood lactate dehydrogenase increased<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Blood pressure increased<br>subjects affected / exposed<br>occurrences (all)               | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Blood triglycerides increased<br>subjects affected / exposed<br>occurrences (all)          | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Blood urine present<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Intraocular pressure increased<br>subjects affected / exposed<br>occurrences (all)         | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Lipase increased<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Lymphocyte count decreased   |                    |                    |                    |

|  |                |               |               |
|--|----------------|---------------|---------------|
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| Lymphocyte percentage decreased                |                |               |               |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| Neutrophil percentage increased                |                |               |               |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| Protein urine                                  |                |               |               |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| Weight decreased                               |                |               |               |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| Injury, poisoning and procedural complications |                |               |               |
| Back injury                                    |                |               |               |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| Joint injury                                   |                |               |               |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| Laceration                                     |                |               |               |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| Muscle strain                                  |                |               |               |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| Post procedural complication                   |                |               |               |
| subjects affected / exposed                    | 1 / 5 (20.00%) | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                              | 1              | 0             | 0             |
| Radius fracture                                |                |               |               |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| Cardiac disorders                              |                |               |               |

|                             |                |               |                |
|-----------------------------|----------------|---------------|----------------|
| Palpitations                |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Nervous system disorders    |                |               |                |
| Aphonia                     |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Dizziness                   |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Headache                    |                |               |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 2 (0.00%) | 3 / 4 (75.00%) |
| occurrences (all)           | 1              | 0             | 4              |
| Hyperaesthesia              |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Migraine                    |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Paraesthesia                |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Presyncope                  |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Sinus headache              |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Somnolence                  |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Syncope                     |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Tension headache            |                |               |                |

|  |                    |                    |                    |
|--|--------------------|--------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 |
| Ear and labyrinth disorders                      |                    |                    |                    |
| Ear pain   |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Eye disorders                                    |                    |                    |                    |
| Abnormal sensation in eye                        |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Anterior chamber flare                           |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Cataract   |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Chalazion  |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Colour blindness acquired                        |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Conjunctival hyperaemia                          |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Conjunctivitis allergic                          |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Corneal disorder                                 |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Dry eye  |                    |                    |                    |
| subjects affected / exposed                      | 0 / 5 (0.00%)      | 0 / 2 (0.00%)      | 0 / 4 (0.00%)      |
| occurrences (all)                                | 0                  | 0                  | 0                  |
| Eye irritation                                   |                    |                    |                    |



|                                |                |               |                |
|--------------------------------|----------------|---------------|----------------|
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0              |
| Eye pain                       |                |               |                |
| subjects affected / exposed    | 1 / 5 (20.00%) | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)              | 1              | 0             | 0              |
| Eye pruritus                   |                |               |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0              |
| Eye swelling                   |                |               |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 1 / 4 (25.00%) |
| occurrences (all)              | 0              | 0             | 1              |
| Eyelid oedema                  |                |               |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0              |
| Foreign body sensation in eyes |                |               |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0              |
| Iridocyclitis                  |                |               |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0              |
| Iris adhesions                 |                |               |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0              |
| Iris bombe                     |                |               |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0              |
| Keratoconjunctivitis sicca     |                |               |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0              |
| Lacrimation increased          |                |               |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0              |
| Macular fibrosis               |                |               |                |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0              |
| Macular oedema                 |                |               |                |

|                             |               |                |               |
|-----------------------------|---------------|----------------|---------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Ocular hyperaemia           |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Papilloedema                |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Photophobia                 |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Photopsia                   |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Pupillary reflex impaired   |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Retinal detachment          |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Retinal tear                |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Scleritis                   |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Uveitis                     |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Vision blurred              |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Visual acuity reduced       |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 2 (50.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Vitreous detachment         |               |                |               |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 2 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Vitreous floaters           |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 2 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Vitreous haemorrhage        |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 2 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Gastrointestinal disorders  |                |                |                |
| Abdominal distension        |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 2 (50.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 3              | 0              |
| Abdominal pain              |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 2 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Abdominal pain lower        |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 2 (50.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 3              | 0              |
| Abdominal pain upper        |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 2 (0.00%)  | 1 / 4 (25.00%) |
| occurrences (all)           | 0              | 0              | 1              |
| Constipation                |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 2 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Diarrhoea                   |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Inguinal hernia             |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 2 (50.00%) | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0              |
| Mouth ulceration            |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 2 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Nausea                      |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |

|  |                     |                    |                     |
|--|---------------------|--------------------|---------------------|
| Tooth disorder<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 1 / 5 (20.00%)<br>1 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Hepatobiliary disorders<br>Non-alcoholic steatohepatitis<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Skin and subcutaneous tissue disorders<br>Acne<br>subjects affected / exposed<br>occurrences (all)           | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Dermatitis acneiform<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Dermatitis contact<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Eczema<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Madarosis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 1 / 4 (25.00%)<br>1 |
| Pruritus generalised<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 5 (0.00%)<br>0  | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Psoriasis  |                     |                    |                     |

|   |                    |                    |                     |
|---|--------------------|--------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Rash<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 1 / 4 (25.00%)<br>1 |
| Rash pruritic<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Skin odour abnormal<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Renal and urinary disorders<br>Nephrolithiasis<br>subjects affected / exposed<br>occurrences (all)                | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Endocrine disorders<br>Hypothyroidism<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Exostosis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Flank pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Joint swelling<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0 | 0 / 2 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0  |
| Limb discomfort   |                    |                    |                     |

|                             |               |                |               |
|-----------------------------|---------------|----------------|---------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Muscle spasms               |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Musculoskeletal pain        |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Musculoskeletal stiffness   |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Myalgia                     |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Pain in extremity           |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Spondylitis                 |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Infections and infestations |               |                |               |
| Cellulitis                  |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Ear infection               |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Gastroenteritis             |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 2 (50.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Herpes zoster               |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Hordeolum                   |               |                |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%)  | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |

|   |                |               |               |
|---|----------------|---------------|---------------|
| Lice infestation                        |                |               |               |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                       | 0              | 0             | 0             |
| Nasopharyngitis                         |                |               |               |
| subjects affected / exposed             | 1 / 5 (20.00%) | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                       | 1              | 0             | 0             |
| Oral herpes                             |                |               |               |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                       | 0              | 0             | 0             |
| Pharyngitis streptococcal               |                |               |               |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                       | 0              | 0             | 0             |
| Respiratory tract infection             |                |               |               |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                       | 0              | 0             | 0             |
| Sinusitis                               |                |               |               |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                       | 0              | 0             | 0             |
| Upper respiratory tract infection       |                |               |               |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                       | 0              | 0             | 0             |
| Urinary tract infection                 |                |               |               |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                       | 0              | 0             | 0             |
| Vaginitis bacterial                     |                |               |               |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                       | 0              | 0             | 0             |
| Viral upper respiratory tract infection |                |               |               |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                       | 0              | 0             | 0             |
| Vulvovaginal mycotic infection          |                |               |               |
| subjects affected / exposed             | 0 / 5 (0.00%)  | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)                       | 0              | 0             | 0             |
| Metabolism and nutrition disorders      |                |               |               |
| Gout                                    |                |               |               |

|                             |               |               |               |
|-----------------------------|---------------|---------------|---------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Increased appetite          |               |               |               |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 2 (0.00%) | 0 / 4 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |

| <b>Non-serious adverse events</b>                                   | Cohort 3 - AIN457<br>10mg/kg CHO<br>10mg/kg CHO | Cohort 5 - AIN457<br>30mg/kg i.v. q4wks | Cohort 6 - AIN457<br>300mg sc q2wks |
|---|---|---|-------------------------------------|
| Total subjects affected by non-serious adverse events               |   |   |                                     |
| subjects affected / exposed   | 5 / 5 (100.00%)                                 | 3 / 4 (75.00%)                          | 9 / 12 (75.00%)                     |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |   |   |                                     |
| Fibroadenoma of breast  |   |   |                                     |
| subjects affected / exposed   | 0 / 5 (0.00%)                                   | 0 / 4 (0.00%)                           | 0 / 12 (0.00%)                      |
| occurrences (all)   | 0   | 0                                       | 0                                   |
| Vascular disorders  |   |   |                                     |
| Hot flush   |   |   |                                     |
| subjects affected / exposed   | 0 / 5 (0.00%)                                   | 0 / 4 (0.00%)                           | 0 / 12 (0.00%)                      |
| occurrences (all)   | 0   | 0                                       | 0                                   |
| General disorders and administration site conditions                |   |   |                                     |
| Fatigue   |   |   |                                     |
| subjects affected / exposed   | 0 / 5 (0.00%)                                   | 0 / 4 (0.00%)                           | 1 / 12 (8.33%)                      |
| occurrences (all)   | 0   | 0                                       | 2                                   |
| Infusion site extravasation   |   |   |                                     |
| subjects affected / exposed   | 0 / 5 (0.00%)                                   | 0 / 4 (0.00%)                           | 0 / 12 (0.00%)                      |
| occurrences (all)   | 0   | 0                                       | 0                                   |
| Irritability  |   |   |                                     |
| subjects affected / exposed   | 0 / 5 (0.00%)                                   | 0 / 4 (0.00%)                           | 0 / 12 (0.00%)                      |
| occurrences (all)   | 0   | 0                                       | 0                                   |
| Oedema peripheral   |   |   |                                     |
| subjects affected / exposed   | 2 / 5 (40.00%)                                  | 0 / 4 (0.00%)                           | 0 / 12 (0.00%)                      |
| occurrences (all)   | 2   | 0                                       | 0                                   |
| Pain  |   |   |                                     |
| subjects affected / exposed   | 0 / 5 (0.00%)                                   | 0 / 4 (0.00%)                           | 0 / 12 (0.00%)                      |
| occurrences (all)   | 0   | 0                                       | 0                                   |
| Pyrexia   |   |   |                                     |



|  |  |  |   |
|--|--|--|---|
| subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0   | 0 / 4 (0.00%)<br>0   | 0 / 12 (0.00%)<br>0   |
| Immune system disorders<br>Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0   | 0 / 4 (0.00%)<br>0   | 0 / 12 (0.00%)<br>0   |
| Reproductive system and breast disorders<br>Uterine haemorrhage<br>subjects affected / exposed<br>occurrences (all)<br><br>Uterine spasm<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0<br><br>0 / 5 (0.00%)<br>0   | 0 / 4 (0.00%)<br>0<br><br>0 / 4 (0.00%)<br>0   | 0 / 12 (0.00%)<br>0<br><br>0 / 12 (0.00%)<br>0  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Nasal congestion<br>subjects affected / exposed<br>occurrences (all)<br><br>Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)<br><br>Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Sinus congestion<br>subjects affected / exposed<br>occurrences (all)<br><br>Vocal cord disorder<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0<br><br>0 / 5 (0.00%)<br>0<br><br>0 / 5 (0.00%)<br>0<br><br>0 / 5 (0.00%)<br>0<br><br>1 / 5 (20.00%)<br>1<br><br>1 / 5 (20.00%)<br>1 | 0 / 4 (0.00%)<br>0<br><br>0 / 4 (0.00%)<br>0<br><br>0 / 4 (0.00%)<br>0<br><br>0 / 4 (0.00%)<br>0<br><br>0 / 4 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0<br><br>0 / 12 (0.00%)<br>0<br><br>0 / 12 (0.00%)<br>0<br><br>0 / 12 (0.00%)<br>0<br><br>0 / 12 (0.00%)<br>0 |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0   | 0 / 4 (0.00%)<br>0   | 1 / 12 (8.33%)<br>1   |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Anxiety disorder<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1 |
| Depression<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 5 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 | 0 / 12 (0.00%)<br>0 |
| Nervousness<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 |
| Investigations   |                     |                     |                     |
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)     | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 |
| Aspartate aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 |
| Blood bilirubin increased<br>subjects affected / exposed<br>occurrences (all)              | 1 / 5 (20.00%)<br>1 | 0 / 4 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 |
| Blood creatine phosphokinase increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 |
| Blood lactate dehydrogenase increased<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 |
| Blood pressure increased<br>subjects affected / exposed<br>occurrences (all)               | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 |
| Blood triglycerides increased<br>subjects affected / exposed<br>occurrences (all)          | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 |
| Blood urine present  |                     |                     |                     |

|  |                |               |                |
|--|----------------|---------------|----------------|
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0              |
| Intraocular pressure increased                 |                |               |                |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0              |
| Lipase increased                               |                |               |                |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0              |
| Lymphocyte count decreased                     |                |               |                |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0              |
| Lymphocyte percentage decreased                |                |               |                |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0              |
| Neutrophil percentage increased                |                |               |                |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0              |
| Protein urine                                  |                |               |                |
| subjects affected / exposed                    | 1 / 5 (20.00%) | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                              | 1              | 0             | 0              |
| Weight decreased                               |                |               |                |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0              |
| Injury, poisoning and procedural complications |                |               |                |
| Back injury                                    |                |               |                |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0              |
| Joint injury                                   |                |               |                |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0              |
| Laceration                                     |                |               |                |
| subjects affected / exposed                    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0              |
| Muscle strain                                  |                |               |                |

|                              |                |                |                 |
|------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed  | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)            | 2              | 0              | 0               |
| Post procedural complication |                |                |                 |
| subjects affected / exposed  | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)            | 0              | 0              | 0               |
| Radius fracture              |                |                |                 |
| subjects affected / exposed  | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)            | 1              | 0              | 0               |
| Cardiac disorders            |                |                |                 |
| Palpitations                 |                |                |                 |
| subjects affected / exposed  | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)            | 0              | 0              | 0               |
| Nervous system disorders     |                |                |                 |
| Aphonia                      |                |                |                 |
| subjects affected / exposed  | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)            | 0              | 0              | 0               |
| Dizziness                    |                |                |                 |
| subjects affected / exposed  | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)            | 0              | 0              | 0               |
| Headache                     |                |                |                 |
| subjects affected / exposed  | 3 / 5 (60.00%) | 2 / 4 (50.00%) | 5 / 12 (41.67%) |
| occurrences (all)            | 4              | 3              | 12              |
| Hyperaesthesia               |                |                |                 |
| subjects affected / exposed  | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)            | 0              | 0              | 0               |
| Migraine                     |                |                |                 |
| subjects affected / exposed  | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)            | 0              | 0              | 0               |
| Paraesthesia                 |                |                |                 |
| subjects affected / exposed  | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)            | 0              | 0              | 0               |
| Presyncope                   |                |                |                 |
| subjects affected / exposed  | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)            | 0              | 0              | 0               |
| Sinus headache               |                |                |                 |

|                             |                |               |                |
|-----------------------------|----------------|---------------|----------------|
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 1              | 0             | 0              |
| Somnolence                  |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0             | 0              |
| Syncope                     |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0             | 0              |
| Tension headache            |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0             | 0              |
| Ear and labyrinth disorders |                |               |                |
| Ear pain                    |                |               |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 1              | 0             | 0              |
| Eye disorders               |                |               |                |
| Abnormal sensation in eye   |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0             | 0              |
| Anterior chamber flare      |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all)           | 0              | 0             | 1              |
| Cataract                    |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0             | 0              |
| Chalazion                   |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0             | 0              |
| Colour blindness acquired   |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0             | 0              |
| Conjunctival hyperaemia     |                |               |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0             | 0              |
| Conjunctivitis allergic     |                |               |                |

|                                |                |               |                 |
|--------------------------------|----------------|---------------|-----------------|
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0               |
| Corneal disorder               |                |               |                 |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0               |
| Dry eye                        |                |               |                 |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0               |
| Eye irritation                 |                |               |                 |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0               |
| Eye pain                       |                |               |                 |
| subjects affected / exposed    | 1 / 5 (20.00%) | 0 / 4 (0.00%) | 1 / 12 (8.33%)  |
| occurrences (all)              | 1              | 0             | 1               |
| Eye pruritus                   |                |               |                 |
| subjects affected / exposed    | 1 / 5 (20.00%) | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)              | 1              | 0             | 0               |
| Eye swelling                   |                |               |                 |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0               |
| Eyelid oedema                  |                |               |                 |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0               |
| Foreign body sensation in eyes |                |               |                 |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0               |
| Iridocyclitis                  |                |               |                 |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all)              | 0              | 0             | 2               |
| Iris adhesions                 |                |               |                 |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0               |
| Iris bombe                     |                |               |                 |
| subjects affected / exposed    | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)              | 0              | 0             | 0               |
| Keratoconjunctivitis sicca     |                |               |                 |

|                             |               |                |                |
|-----------------------------|---------------|----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Lacrimation increased       |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Macular fibrosis            |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Macular oedema              |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 4 (25.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 0             | 1              | 0              |
| Ocular hyperaemia           |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 4 (0.00%)  | 1 / 12 (8.33%) |
| occurrences (all)           | 0             | 0              | 1              |
| Papilloedema                |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Photophobia                 |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Photopsia                   |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Pupillary reflex impaired   |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Retinal detachment          |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Retinal tear                |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Scleritis                   |               |                |                |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0             | 0              | 0              |
| Uveitis                     |               |                |                |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 2 / 12 (16.67%) |
| occurrences (all)           | 0              | 0              | 2               |
| Vision blurred              |                |                |                 |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Visual acuity reduced       |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Vitreous detachment         |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Vitreous floaters           |                |                |                 |
| subjects affected / exposed | 2 / 5 (40.00%) | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 3              | 0              | 0               |
| Vitreous haemorrhage        |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Gastrointestinal disorders  |                |                |                 |
| Abdominal distension        |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Abdominal pain              |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 1 / 4 (25.00%) | 0 / 12 (0.00%)  |
| occurrences (all)           | 0              | 2              | 0               |
| Abdominal pain lower        |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Abdominal pain upper        |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Constipation                |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Diarrhoea                   |                |                |                 |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 1 / 12 (8.33%)  |
| occurrences (all)           | 0              | 0              | 1               |



|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Inguinal hernia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 |
| Mouth ulceration<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 |
| Nausea<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 |
| Tooth disorder<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 |
| Hepatobiliary disorders<br>Non-alcoholic steatohepatitis<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 |
| Skin and subcutaneous tissue disorders<br>Acne<br>subjects affected / exposed<br>occurrences (all)           | 1 / 5 (20.00%)<br>1 | 0 / 4 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1 |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 |
| Dermatitis acneiform<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 |
| Dermatitis contact<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 5 (0.00%)<br>0  | 1 / 4 (25.00%)<br>1 | 0 / 12 (0.00%)<br>0 |
| Eczema<br>subjects affected / exposed<br>occurrences (all)   | 0 / 5 (0.00%)<br>0  | 0 / 4 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 |
| Madarosis  |                     |                     |                     |

|   |                |               |                 |
|---|----------------|---------------|-----------------|
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0               |
| Pruritus  |                |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0               |
| Pruritus generalised                            |                |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 2 / 12 (16.67%) |
| occurrences (all)                               | 0              | 0             | 2               |
| Psoriasis                                       |                |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0               |
| Rash  |                |               |                 |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                               | 3              | 0             | 0               |
| Rash pruritic                                   |                |               |                 |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                               | 1              | 0             | 0               |
| Skin odour abnormal                             |                |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0               |
| Renal and urinary disorders                     |                |               |                 |
| Nephrolithiasis                                 |                |               |                 |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                               | 1              | 0             | 0               |
| Endocrine disorders                             |                |               |                 |
| Hypothyroidism                                  |                |               |                 |
| subjects affected / exposed                     | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                               | 0              | 0             | 0               |
| Musculoskeletal and connective tissue disorders |                |               |                 |
| Arthralgia                                      |                |               |                 |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                               | 1              | 0             | 0               |
| Back pain                                       |                |               |                 |
| subjects affected / exposed                     | 1 / 5 (20.00%) | 0 / 4 (0.00%) | 0 / 12 (0.00%)  |
| occurrences (all)                               | 3              | 0             | 0               |
| Exostosis                                       |                |               |                 |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 1 / 12 (8.33%) |
| occurrences (all)           | 0              | 0              | 1              |
| Flank pain                  |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Joint swelling              |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Limb discomfort             |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Muscle spasms               |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Musculoskeletal pain        |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 1 / 12 (8.33%) |
| occurrences (all)           | 1              | 0              | 1              |
| Musculoskeletal stiffness   |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Myalgia                     |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 2              | 0              | 0              |
| Pain in extremity           |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Spondylitis                 |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Infections and infestations |                |                |                |
| Cellulitis                  |                |                |                |
| subjects affected / exposed | 0 / 5 (0.00%)  | 0 / 4 (0.00%)  | 0 / 12 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Ear infection               |                |                |                |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 4 (25.00%) | 0 / 12 (0.00%) |
| occurrences (all)           | 1              | 1              | 0              |

|                                   |                |               |                |
|-----------------------------------|----------------|---------------|----------------|
| Gastroenteritis                   |                |               |                |
| subjects affected / exposed       | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                 | 0              | 0             | 0              |
| Herpes zoster                     |                |               |                |
| subjects affected / exposed       | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                 | 0              | 0             | 0              |
| Hordeolum                         |                |               |                |
| subjects affected / exposed       | 1 / 5 (20.00%) | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                 | 1              | 0             | 0              |
| Lice infestation                  |                |               |                |
| subjects affected / exposed       | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                 | 0              | 0             | 0              |
| Nasopharyngitis                   |                |               |                |
| subjects affected / exposed       | 1 / 5 (20.00%) | 0 / 4 (0.00%) | 1 / 12 (8.33%) |
| occurrences (all)                 | 1              | 0             | 1              |
| Oral herpes                       |                |               |                |
| subjects affected / exposed       | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                 | 0              | 0             | 0              |
| Pharyngitis streptococcal         |                |               |                |
| subjects affected / exposed       | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                 | 0              | 0             | 0              |
| Respiratory tract infection       |                |               |                |
| subjects affected / exposed       | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                 | 0              | 0             | 0              |
| Sinusitis                         |                |               |                |
| subjects affected / exposed       | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                 | 0              | 0             | 0              |
| Upper respiratory tract infection |                |               |                |
| subjects affected / exposed       | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                 | 0              | 0             | 0              |
| Urinary tract infection           |                |               |                |
| subjects affected / exposed       | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                 | 0              | 0             | 0              |
| Vaginitis bacterial               |                |               |                |
| subjects affected / exposed       | 0 / 5 (0.00%)  | 0 / 4 (0.00%) | 0 / 12 (0.00%) |
| occurrences (all)                 | 0              | 0             | 0              |

|   |                    |                    |                     |
|---|--------------------|--------------------|---------------------|
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 5 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |
| Vulvovaginal mycotic infection<br>subjects affected / exposed<br>occurrences (all)          | 0 / 5 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |
| Metabolism and nutrition disorders  |                    |                    |                     |
| Gout<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 5 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |
| Increased appetite<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 5 (0.00%)<br>0 | 0 / 4 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 |

| <b>Non-serious adverse events</b>  | Cohort 6 - AIN457<br>10mg/kg i.v. q2wks | Cohort 6 - AIN457<br>30mg/kg i.v. q4wks | Cohort 4 (extension)<br>- AIN457 |
|--|---|---|----------------------------------|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed  | 10 / 13 (76.92%)                        | 12 / 12 (100.00%)                       | 20 / 28 (71.43%)                 |
| Neoplasms benign, malignant and<br>unspecified (incl cysts and polyps)<br>Fibroadenoma of breast<br>subjects affected / exposed<br>occurrences (all) | 0 / 13 (0.00%)<br>0                     | 0 / 12 (0.00%)<br>0                     | 0 / 28 (0.00%)<br>0              |
| Vascular disorders<br>Hot flush<br>subjects affected / exposed<br>occurrences (all)  | 0 / 13 (0.00%)<br>0                     | 0 / 12 (0.00%)<br>0                     | 0 / 28 (0.00%)<br>0              |
| General disorders and administration<br>site conditions<br>Fatigue<br>subjects affected / exposed<br>occurrences (all)                               | 2 / 13 (15.38%)<br>2                    | 2 / 12 (16.67%)<br>2                    | 1 / 28 (3.57%)<br>1              |
| Infusion site extravasation<br>subjects affected / exposed<br>occurrences (all)  | 0 / 13 (0.00%)<br>0                     | 1 / 12 (8.33%)<br>2                     | 0 / 28 (0.00%)<br>0              |
| Irritability<br>subjects affected / exposed<br>occurrences (all)   | 1 / 13 (7.69%)<br>1                     | 0 / 12 (0.00%)<br>0                     | 1 / 28 (3.57%)<br>1              |
| Oedema peripheral  |   |   |                                  |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)  | 1 / 13 (7.69%)<br>1 | 0 / 12 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0 |
| Pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 13 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1 | 1 / 28 (3.57%)<br>1 |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 13 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1 | 0 / 28 (0.00%)<br>0 |
| Immune system disorders<br>Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 13 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 2 / 28 (7.14%)<br>2 |
| Reproductive system and breast disorders<br>Uterine haemorrhage<br>subjects affected / exposed<br>occurrences (all) | 0 / 13 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0 |
| Uterine spasm<br>subjects affected / exposed<br>occurrences (all)   | 0 / 13 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0 |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)        | 1 / 13 (7.69%)<br>1 | 0 / 12 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0 |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)  | 0 / 13 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0 |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)  | 1 / 13 (7.69%)<br>1 | 0 / 12 (0.00%)<br>0 | 1 / 28 (3.57%)<br>1 |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)   | 0 / 13 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0 |
| Sinus congestion<br>subjects affected / exposed<br>occurrences (all)  | 0 / 13 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0 |
| Vocal cord disorder   |                     |                     |                     |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 13 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 28 (0.00%)<br>0 |
| Psychiatric disorders                            |                     |                     |                     |
| Anxiety  |                     |                     |                     |
| subjects affected / exposed                      | 2 / 13 (15.38%)     | 0 / 12 (0.00%)      | 0 / 28 (0.00%)      |
| occurrences (all)                                | 3                   | 0                   | 0                   |
| Anxiety disorder                                 |                     |                     |                     |
| subjects affected / exposed                      | 0 / 13 (0.00%)      | 0 / 12 (0.00%)      | 0 / 28 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Depression                                       |                     |                     |                     |
| subjects affected / exposed                      | 1 / 13 (7.69%)      | 0 / 12 (0.00%)      | 0 / 28 (0.00%)      |
| occurrences (all)                                | 1                   | 0                   | 0                   |
| Insomnia   |                     |                     |                     |
| subjects affected / exposed                      | 0 / 13 (0.00%)      | 1 / 12 (8.33%)      | 0 / 28 (0.00%)      |
| occurrences (all)                                | 0                   | 1                   | 0                   |
| Nervousness                                      |                     |                     |                     |
| subjects affected / exposed                      | 0 / 13 (0.00%)      | 0 / 12 (0.00%)      | 1 / 28 (3.57%)      |
| occurrences (all)                                | 0                   | 0                   | 1                   |
| Investigations                                   |                     |                     |                     |
| Alanine aminotransferase increased               |                     |                     |                     |
| subjects affected / exposed                      | 0 / 13 (0.00%)      | 0 / 12 (0.00%)      | 0 / 28 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Aspartate aminotransferase increased             |                     |                     |                     |
| subjects affected / exposed                      | 0 / 13 (0.00%)      | 0 / 12 (0.00%)      | 0 / 28 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Blood bilirubin increased                        |                     |                     |                     |
| subjects affected / exposed                      | 0 / 13 (0.00%)      | 0 / 12 (0.00%)      | 0 / 28 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Blood creatine phosphokinase increased           |                     |                     |                     |
| subjects affected / exposed                      | 0 / 13 (0.00%)      | 0 / 12 (0.00%)      | 0 / 28 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Blood lactate dehydrogenase increased            |                     |                     |                     |
| subjects affected / exposed                      | 0 / 13 (0.00%)      | 0 / 12 (0.00%)      | 0 / 28 (0.00%)      |
| occurrences (all)                                | 0                   | 0                   | 0                   |
| Blood pressure increased                         |                     |                     |                     |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                    | 0 / 13 (0.00%) | 1 / 12 (8.33%) | 0 / 28 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| Blood triglycerides increased                  |                |                |                |
| subjects affected / exposed                    | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Blood urine present                            |                |                |                |
| subjects affected / exposed                    | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Intraocular pressure increased                 |                |                |                |
| subjects affected / exposed                    | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 2 / 28 (7.14%) |
| occurrences (all)                              | 1              | 0              | 4              |
| Lipase increased                               |                |                |                |
| subjects affected / exposed                    | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                              | 0              | 0              | 0              |
| Lymphocyte count decreased                     |                |                |                |
| subjects affected / exposed                    | 0 / 13 (0.00%) | 1 / 12 (8.33%) | 0 / 28 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| Lymphocyte percentage decreased                |                |                |                |
| subjects affected / exposed                    | 0 / 13 (0.00%) | 1 / 12 (8.33%) | 0 / 28 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| Neutrophil percentage increased                |                |                |                |
| subjects affected / exposed                    | 0 / 13 (0.00%) | 1 / 12 (8.33%) | 0 / 28 (0.00%) |
| occurrences (all)                              | 0              | 1              | 0              |
| Protein urine                                  |                |                |                |
| subjects affected / exposed                    | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                              | 1              | 0              | 0              |
| Weight decreased                               |                |                |                |
| subjects affected / exposed                    | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 2 / 28 (7.14%) |
| occurrences (all)                              | 0              | 0              | 2              |
| Injury, poisoning and procedural complications |                |                |                |
| Back injury                                    |                |                |                |
| subjects affected / exposed                    | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                              | 1              | 0              | 0              |
| Joint injury                                   |                |                |                |



|                              |                 |                 |                |
|------------------------------|-----------------|-----------------|----------------|
| subjects affected / exposed  | 0 / 13 (0.00%)  | 0 / 12 (0.00%)  | 0 / 28 (0.00%) |
| occurrences (all)            | 0               | 0               | 0              |
| Laceration                   |                 |                 |                |
| subjects affected / exposed  | 0 / 13 (0.00%)  | 0 / 12 (0.00%)  | 2 / 28 (7.14%) |
| occurrences (all)            | 0               | 0               | 2              |
| Muscle strain                |                 |                 |                |
| subjects affected / exposed  | 0 / 13 (0.00%)  | 0 / 12 (0.00%)  | 0 / 28 (0.00%) |
| occurrences (all)            | 0               | 0               | 0              |
| Post procedural complication |                 |                 |                |
| subjects affected / exposed  | 0 / 13 (0.00%)  | 0 / 12 (0.00%)  | 0 / 28 (0.00%) |
| occurrences (all)            | 0               | 0               | 0              |
| Radius fracture              |                 |                 |                |
| subjects affected / exposed  | 0 / 13 (0.00%)  | 0 / 12 (0.00%)  | 0 / 28 (0.00%) |
| occurrences (all)            | 0               | 0               | 0              |
| Cardiac disorders            |                 |                 |                |
| Palpitations                 |                 |                 |                |
| subjects affected / exposed  | 0 / 13 (0.00%)  | 0 / 12 (0.00%)  | 0 / 28 (0.00%) |
| occurrences (all)            | 0               | 0               | 0              |
| Nervous system disorders     |                 |                 |                |
| Aphonia                      |                 |                 |                |
| subjects affected / exposed  | 0 / 13 (0.00%)  | 0 / 12 (0.00%)  | 0 / 28 (0.00%) |
| occurrences (all)            | 0               | 0               | 0              |
| Dizziness                    |                 |                 |                |
| subjects affected / exposed  | 1 / 13 (7.69%)  | 0 / 12 (0.00%)  | 0 / 28 (0.00%) |
| occurrences (all)            | 1               | 0               | 0              |
| Headache                     |                 |                 |                |
| subjects affected / exposed  | 3 / 13 (23.08%) | 4 / 12 (33.33%) | 1 / 28 (3.57%) |
| occurrences (all)            | 5               | 7               | 1              |
| Hyperaesthesia               |                 |                 |                |
| subjects affected / exposed  | 1 / 13 (7.69%)  | 0 / 12 (0.00%)  | 1 / 28 (3.57%) |
| occurrences (all)            | 1               | 0               | 1              |
| Migraine                     |                 |                 |                |
| subjects affected / exposed  | 0 / 13 (0.00%)  | 0 / 12 (0.00%)  | 0 / 28 (0.00%) |
| occurrences (all)            | 0               | 0               | 0              |
| Paraesthesia                 |                 |                 |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 2 / 28 (7.14%) |
| occurrences (all)           | 1              | 0              | 2              |
| Presyncope                  |                |                |                |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Sinus headache              |                |                |                |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Somnolence                  |                |                |                |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Syncope                     |                |                |                |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Tension headache            |                |                |                |
| subjects affected / exposed | 1 / 13 (7.69%) | 1 / 12 (8.33%) | 1 / 28 (3.57%) |
| occurrences (all)           | 1              | 1              | 1              |
| Ear and labyrinth disorders |                |                |                |
| Ear pain                    |                |                |                |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Eye disorders               |                |                |                |
| Abnormal sensation in eye   |                |                |                |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all)           | 0              | 0              | 1              |
| Anterior chamber flare      |                |                |                |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Cataract                    |                |                |                |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 2 / 28 (7.14%) |
| occurrences (all)           | 0              | 0              | 2              |
| Chalazion                   |                |                |                |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | 0 / 28 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Colour blindness acquired   |                |                |                |

|                                |                 |                |                 |
|--------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed    | 1 / 13 (7.69%)  | 0 / 12 (0.00%) | 0 / 28 (0.00%)  |
| occurrences (all)              | 1               | 0              | 0               |
| Conjunctival hyperaemia        |                 |                |                 |
| subjects affected / exposed    | 1 / 13 (7.69%)  | 0 / 12 (0.00%) | 0 / 28 (0.00%)  |
| occurrences (all)              | 1               | 0              | 0               |
| Conjunctivitis allergic        |                 |                |                 |
| subjects affected / exposed    | 0 / 13 (0.00%)  | 0 / 12 (0.00%) | 3 / 28 (10.71%) |
| occurrences (all)              | 0               | 0              | 3               |
| Corneal disorder               |                 |                |                 |
| subjects affected / exposed    | 1 / 13 (7.69%)  | 0 / 12 (0.00%) | 0 / 28 (0.00%)  |
| occurrences (all)              | 1               | 0              | 0               |
| Dry eye                        |                 |                |                 |
| subjects affected / exposed    | 2 / 13 (15.38%) | 0 / 12 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)              | 2               | 0              | 2               |
| Eye irritation                 |                 |                |                 |
| subjects affected / exposed    | 0 / 13 (0.00%)  | 0 / 12 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)              | 0               | 0              | 2               |
| Eye pain                       |                 |                |                 |
| subjects affected / exposed    | 1 / 13 (7.69%)  | 1 / 12 (8.33%) | 3 / 28 (10.71%) |
| occurrences (all)              | 1               | 1              | 6               |
| Eye pruritus                   |                 |                |                 |
| subjects affected / exposed    | 0 / 13 (0.00%)  | 1 / 12 (8.33%) | 0 / 28 (0.00%)  |
| occurrences (all)              | 0               | 1              | 0               |
| Eye swelling                   |                 |                |                 |
| subjects affected / exposed    | 0 / 13 (0.00%)  | 0 / 12 (0.00%) | 0 / 28 (0.00%)  |
| occurrences (all)              | 0               | 0              | 0               |
| Eyelid oedema                  |                 |                |                 |
| subjects affected / exposed    | 0 / 13 (0.00%)  | 1 / 12 (8.33%) | 2 / 28 (7.14%)  |
| occurrences (all)              | 0               | 1              | 2               |
| Foreign body sensation in eyes |                 |                |                 |
| subjects affected / exposed    | 1 / 13 (7.69%)  | 0 / 12 (0.00%) | 0 / 28 (0.00%)  |
| occurrences (all)              | 1               | 0              | 0               |
| Iridocyclitis                  |                 |                |                 |
| subjects affected / exposed    | 0 / 13 (0.00%)  | 0 / 12 (0.00%) | 0 / 28 (0.00%)  |
| occurrences (all)              | 0               | 0              | 0               |
| Iris adhesions                 |                 |                |                 |

|                             |                |                |                 |
|-----------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 28 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Iris bombe                  |                |                |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Keratoconjunctivitis sicca  |                |                |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Lacrimation increased       |                |                |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Macular fibrosis            |                |                |                 |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 1 / 28 (3.57%)  |
| occurrences (all)           | 1              | 0              | 1               |
| Macular oedema              |                |                |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 1 / 28 (3.57%)  |
| occurrences (all)           | 0              | 0              | 1               |
| Ocular hyperaemia           |                |                |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 3 / 28 (10.71%) |
| occurrences (all)           | 0              | 0              | 4               |
| Papilloedema                |                |                |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Photophobia                 |                |                |                 |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 2 / 28 (7.14%)  |
| occurrences (all)           | 1              | 0              | 2               |
| Photopsia                   |                |                |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 1 / 28 (3.57%)  |
| occurrences (all)           | 0              | 0              | 1               |
| Pupillary reflex impaired   |                |                |                 |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 28 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0               |
| Retinal detachment          |                |                |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0               |
| Retinal tear                |                |                |                 |

|                             |                |                 |                 |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%)  | 0 / 28 (0.00%)  |
| occurrences (all)           | 1              | 0               | 0               |
| Scleritis                   |                |                 |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%)  | 0 / 28 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |
| Uveitis                     |                |                 |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%)  | 1 / 28 (3.57%)  |
| occurrences (all)           | 0              | 0               | 1               |
| Vision blurred              |                |                 |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 3 / 12 (25.00%) | 1 / 28 (3.57%)  |
| occurrences (all)           | 0              | 3               | 1               |
| Visual acuity reduced       |                |                 |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%)  | 1 / 28 (3.57%)  |
| occurrences (all)           | 0              | 0               | 1               |
| Vitreous detachment         |                |                 |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%)  | 1 / 28 (3.57%)  |
| occurrences (all)           | 0              | 0               | 2               |
| Vitreous floaters           |                |                 |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%)  | 4 / 28 (14.29%) |
| occurrences (all)           | 0              | 1               | 4               |
| Vitreous haemorrhage        |                |                 |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%)  | 0 / 28 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0               |
| Gastrointestinal disorders  |                |                 |                 |
| Abdominal distension        |                |                 |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%)  | 0 / 28 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |
| Abdominal pain              |                |                 |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%)  | 0 / 28 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |
| Abdominal pain lower        |                |                 |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%)  | 0 / 28 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |
| Abdominal pain upper        |                |                 |                 |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%)  | 0 / 28 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0               |

|  |                |                |                |
|--|----------------|----------------|----------------|
| Constipation                           |                |                |                |
| subjects affected / exposed            | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Diarrhoea                              |                |                |                |
| subjects affected / exposed            | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Inguinal hernia                        |                |                |                |
| subjects affected / exposed            | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Mouth ulceration                       |                |                |                |
| subjects affected / exposed            | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Nausea                                 |                |                |                |
| subjects affected / exposed            | 0 / 13 (0.00%) | 1 / 12 (8.33%) | 0 / 28 (0.00%) |
| occurrences (all)                      | 0              | 1              | 0              |
| Tooth disorder                         |                |                |                |
| subjects affected / exposed            | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Vomiting                               |                |                |                |
| subjects affected / exposed            | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Hepatobiliary disorders                |                |                |                |
| Non-alcoholic steatohepatitis          |                |                |                |
| subjects affected / exposed            | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                      | 1              | 0              | 0              |
| Skin and subcutaneous tissue disorders |                |                |                |
| Acne                                   |                |                |                |
| subjects affected / exposed            | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0              |
| Alopecia                               |                |                |                |
| subjects affected / exposed            | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all)                      | 0              | 0              | 1              |
| Dermatitis acneiform                   |                |                |                |
| subjects affected / exposed            | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                      | 1              | 0              | 0              |
| Dermatitis contact                     |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Eczema  |                |                |                |
| subjects affected / exposed                     | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0              |
| Madarosis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Pruritus  |                |                |                |
| subjects affected / exposed                     | 1 / 13 (7.69%) | 1 / 12 (8.33%) | 2 / 28 (7.14%) |
| occurrences (all)                               | 3              | 1              | 2              |
| Pruritus generalised                            |                |                |                |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Psoriasis                                       |                |                |                |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 2 / 28 (7.14%) |
| occurrences (all)                               | 0              | 0              | 2              |
| Rash  |                |                |                |
| subjects affected / exposed                     | 1 / 13 (7.69%) | 1 / 12 (8.33%) | 1 / 28 (3.57%) |
| occurrences (all)                               | 1              | 1              | 3              |
| Rash pruritic                                   |                |                |                |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Skin odour abnormal                             |                |                |                |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Renal and urinary disorders                     |                |                |                |
| Nephrolithiasis                                 |                |                |                |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all)                               | 0              | 0              | 1              |
| Endocrine disorders                             |                |                |                |
| Hypothyroidism                                  |                |                |                |
| subjects affected / exposed                     | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0              |
| Musculoskeletal and connective tissue disorders |                |                |                |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Arthralgia                  |                |                |                |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Back pain                   |                |                |                |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Exostosis                   |                |                |                |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Flank pain                  |                |                |                |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all)           | 0              | 0              | 1              |
| Joint swelling              |                |                |                |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Limb discomfort             |                |                |                |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Muscle spasms               |                |                |                |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Musculoskeletal pain        |                |                |                |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |
| Musculoskeletal stiffness   |                |                |                |
| subjects affected / exposed | 1 / 13 (7.69%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)           | 1              | 0              | 0              |
| Myalgia                     |                |                |                |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 1 / 28 (3.57%) |
| occurrences (all)           | 0              | 0              | 1              |
| Pain in extremity           |                |                |                |
| subjects affected / exposed | 0 / 13 (0.00%) | 1 / 12 (8.33%) | 0 / 28 (0.00%) |
| occurrences (all)           | 0              | 1              | 0              |
| Spondylitis                 |                |                |                |
| subjects affected / exposed | 0 / 13 (0.00%) | 0 / 12 (0.00%) | 0 / 28 (0.00%) |
| occurrences (all)           | 0              | 0              | 0              |



|                                   |                |                 |                 |
|-----------------------------------|----------------|-----------------|-----------------|
| Infections and infestations       |                |                 |                 |
| Cellulitis                        |                |                 |                 |
| subjects affected / exposed       | 0 / 13 (0.00%) | 1 / 12 (8.33%)  | 0 / 28 (0.00%)  |
| occurrences (all)                 | 0              | 1               | 0               |
| Ear infection                     |                |                 |                 |
| subjects affected / exposed       | 0 / 13 (0.00%) | 0 / 12 (0.00%)  | 1 / 28 (3.57%)  |
| occurrences (all)                 | 0              | 0               | 2               |
| Gastroenteritis                   |                |                 |                 |
| subjects affected / exposed       | 0 / 13 (0.00%) | 0 / 12 (0.00%)  | 0 / 28 (0.00%)  |
| occurrences (all)                 | 0              | 0               | 0               |
| Herpes zoster                     |                |                 |                 |
| subjects affected / exposed       | 0 / 13 (0.00%) | 0 / 12 (0.00%)  | 2 / 28 (7.14%)  |
| occurrences (all)                 | 0              | 0               | 2               |
| Hordeolum                         |                |                 |                 |
| subjects affected / exposed       | 0 / 13 (0.00%) | 0 / 12 (0.00%)  | 0 / 28 (0.00%)  |
| occurrences (all)                 | 0              | 0               | 0               |
| Lice infestation                  |                |                 |                 |
| subjects affected / exposed       | 1 / 13 (7.69%) | 0 / 12 (0.00%)  | 0 / 28 (0.00%)  |
| occurrences (all)                 | 1              | 0               | 0               |
| Nasopharyngitis                   |                |                 |                 |
| subjects affected / exposed       | 1 / 13 (7.69%) | 3 / 12 (25.00%) | 6 / 28 (21.43%) |
| occurrences (all)                 | 2              | 3               | 14              |
| Oral herpes                       |                |                 |                 |
| subjects affected / exposed       | 1 / 13 (7.69%) | 0 / 12 (0.00%)  | 0 / 28 (0.00%)  |
| occurrences (all)                 | 1              | 0               | 0               |
| Pharyngitis streptococcal         |                |                 |                 |
| subjects affected / exposed       | 0 / 13 (0.00%) | 1 / 12 (8.33%)  | 0 / 28 (0.00%)  |
| occurrences (all)                 | 0              | 1               | 0               |
| Respiratory tract infection       |                |                 |                 |
| subjects affected / exposed       | 0 / 13 (0.00%) | 1 / 12 (8.33%)  | 0 / 28 (0.00%)  |
| occurrences (all)                 | 0              | 1               | 0               |
| Sinusitis                         |                |                 |                 |
| subjects affected / exposed       | 0 / 13 (0.00%) | 0 / 12 (0.00%)  | 0 / 28 (0.00%)  |
| occurrences (all)                 | 0              | 0               | 0               |
| Upper respiratory tract infection |                |                 |                 |

|   |                |                 |                |
|---|----------------|-----------------|----------------|
| subjects affected / exposed             | 0 / 13 (0.00%) | 0 / 12 (0.00%)  | 2 / 28 (7.14%) |
| occurrences (all)                       | 0              | 0               | 2              |
| Urinary tract infection                 |                |                 |                |
| subjects affected / exposed             | 0 / 13 (0.00%) | 2 / 12 (16.67%) | 1 / 28 (3.57%) |
| occurrences (all)                       | 0              | 2               | 1              |
| Vaginitis bacterial                     |                |                 |                |
| subjects affected / exposed             | 0 / 13 (0.00%) | 0 / 12 (0.00%)  | 0 / 28 (0.00%) |
| occurrences (all)                       | 0              | 0               | 0              |
| Viral upper respiratory tract infection |                |                 |                |
| subjects affected / exposed             | 0 / 13 (0.00%) | 0 / 12 (0.00%)  | 0 / 28 (0.00%) |
| occurrences (all)                       | 0              | 0               | 0              |
| Vulvovaginal mycotic infection          |                |                 |                |
| subjects affected / exposed             | 1 / 13 (7.69%) | 1 / 12 (8.33%)  | 0 / 28 (0.00%) |
| occurrences (all)                       | 1              | 1               | 0              |
| Metabolism and nutrition disorders      |                |                 |                |
| Gout                                    |                |                 |                |
| subjects affected / exposed             | 0 / 13 (0.00%) | 0 / 12 (0.00%)  | 0 / 28 (0.00%) |
| occurrences (all)                       | 0              | 0               | 0              |
| Increased appetite                      |                |                 |                |
| subjects affected / exposed             | 1 / 13 (7.69%) | 0 / 12 (0.00%)  | 0 / 28 (0.00%) |
| occurrences (all)                       | 1              | 0               | 0              |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 12 June 2008     | Patients were randomized prior to this date. Amendment 1 modified key secondary efficacy outcomes and key efficacy variables, to use a 15-letter change in BCVA rather than a 10-letter change, as one of the criteria for declaring a patient as responding to therapy with AIN457, to use a 2- grade improvement in vitreous haze as an outcome criterion, and to delete the secondary efficacy variable "change in macular edema". The exclusion criteria were modified to add aqueous tap to ocular surgeries allowed in the study eye, to allow "up to every hour while awake" use of topical corticosteroids, and to allow patients to be on any dose of prednisone before baseline day. Additionally, it modified the section on Rescue medication so that clinical assessments continued after rescue.)  |
| 01 August 2008   | This amendment was issued when 4 patients had been randomized, introduced the following change: removal of the weight inclusion criterion that specified a range of masses (45 –100 kg, or 99 to 220 pounds).  |
| 17 February 2009 | This amendment introduced the following changes: Addition of two new cohorts of patients, designated cohort 2 and cohort 3. The study of cohort 2 had the following objectives: - determine if a single dose of AIN457 was sufficient to induce a remission of uveitis within 3 weeks, -determine if AIN457 produced from Sp2/0 cells was similar in efficacy to AIN457 produced from CHO cells, -determine the time to flare-up once a remission was achieved, -determine if remission can be re-induced with AIN457 once a flare-up occurred, -determine if continued periodic doses of AIN457 maintain a remission. Cohort 3 was to determine whether AIN457 was efficacious in treating forms of uveitis that often progress to blindness with all currently available immunosuppressive therapies. The amendment also revised certain inclusion and exclusion criteria. For example, the 3-week washout period for oral low-molecular weight immunosuppressant drugs was eliminated. Patients with active uveitis were allowed to continue their oral immunosuppressant drugs throughout the interval between the screening visit and the baseline visit when the first dose of AIN457 was given, thereby improving the safety of enrolled patients as it minimized the deleterious effects of up to 3 weeks of untreated uveitis or the need to start corticosteroids during this interval. Another inclusion criterion that was revised was the requirement for visual acuity of 20/40 or less. Many eyes with active uveitis have visual acuity better than 20/40, and it was reasonable to determine how well AIN457 suppressed uveitis in these eyes. Finally, an exclusion criterion was added for patients whose disease had resolved between screening and baseline visits. |
| 06 April 2009    | This amendment was to clarify and emphasize that the patients and all assessing personnel (e.g., the investigators and clinical coordinators) would be masked to the treatment arm assigned to patients randomized to Cohort 2. Additionally, patients from Cohort 1 who proceeded to participate in Cohort 2 were randomized to only the 3 mg/kg and 1 mg/kg initial doses, not the 10 mg/kg dose that was given to cohort 1. The following changes were also introduced -physical examinations at screening and at various time points during the trial,-clarification on testing for tuberculosis required for patients, AIN457 doses of 10 mg/kg would not be given more frequently than every 4 weeks (lower doses of 3 mg/kg or 1 mg/kg could be given as frequently as every 3 weeks), mentions in the synopsis that AIN457 comes in 150-mg vials as well as 50-mg vials, reduction in the exclusion period after ocular surgery before enrollment to 4 months from 6 months , elimination of the contingency of dosing patients in cohort 2 with the Sp2/0-derived AIN457 in an unblinded manner prior to the availability of CHO-derived AIN457, and provides for emergency unblinding of treatment assignment in cohort 2.   |

|                  |   |
|------------------|---|
| 18 May 2009      | This amendment was made to add exploratory pharmacogenetic studies with the objective of identifying genetic variants that may be associated with the etiology of uveitis that may predict the response to therapy with AIN457, susceptibility to interactions between AIN457 and other therapies and the risk for side effects. The logistics and consent processes of pharmacogenetic data collection were detailed. These pharmacogenetic analyses are not part of this study report because they are planned to be combined with other studies of AIN457 to increase the number of patients and thereby the power of the analyses. The synopsis and assessment schedule were revised as well to change the current serum pregnancy test, conducted at study completion, to a urine pregnancy test. In addition, exclusion criteria were revised to increase the washout period to 12 months for two immunosuppressive agents, Raptiva and Rituxan, and to correct some minor clerical errors in language.   |
| 13 July 2009     | This amendment introduced the following: AIN457 could be used as a rescue medication in patients whose uveitis responded after receiving two doses of 10 mg/kg while enrolled in Cohort 1 but whose uveitis did not subside for up to 8 weeks after a single dose of 1 or 3 mg/kg while enrolled in Cohort 2. Such patients, if their uveitis was active within 8-16 weeks after that single dose while in cohort 2, would be given one or two doses of 10 mg/kg iv. If their uveitis responded to these doses, then the patient would be provided periodic doses of AIN457 as specified in the protocol. Observing the efficacy of 10 mg/kg in comparison with 1 and 3 mg/kg AIN457 in the same patient would allow the selection of the optimal dose for the treatment of uveitis.  |
| 23 February 2010 | This amendment allowed the continued treatment of study patients from Cohorts 1-3 who responded well with AIN457 and who preferred this therapy to any other uveitis therapy. These patients were enrolled into Cohort 4.   |
| 01 December 2010 | This amendment was made to test for the first time in humans, a higher dose of AIN457, 30 mg/kg, given intravenously, and tested a subcutaneous route at a dose of AIN457 (300 mg), and updated inclusion/exclusion criteria to be consistent with other uveitis studies.   |
| 13 May 2011      | This amendment explained the retreatment sequence for patients in Safety Cohort 5. Although the critical data for patients in this cohort is the safety of a single 30 mg/kg iv infusion of AIN457, the protocol provided the opportunity for continued AIN457 treatment for these patients following confirmation of safety of this dose. Criteria for continued treatment were intended to be identical to those used for patients in Cohort 6. However, it was clearly stated in the protocol that no patient in this cohort was to receive a second dose of AIN457 30 mg/kg until all 4 patients in Cohort 5 had demonstrated that the dose was safe for a minimum of 29 days. As an unintended consequence of this stipulation, for all patients of this cohort, the second dose of study medication was delayed beyond Day 29. This amendment addressed the resultant changes in the visit and assessment schedule, as well as clarifying the institution of therapeutic intervention to maintain the patient's response until they could be re-treated. Cohort 4 was comprised of patients from all other cohorts of this study whose uveitis was in remission at the end of study observation. These patients are offered open-label access to AIN457 on a PRN basis. In this amendment Cohort 4 was extended to include open-label treatment for complete responders in Cohort 5 and Cohort 6 as well as to stipulate a firm end date for this open-label extension cohort as 1 year following last patient last visit date of Cohort 6. Cohort 4 efficacy assessment collections will be discontinued with safety being the key variable, after finalization of the current amendment. These amendments were not considered to have affected the interpretation of study results as they were minor and occurred prior to study unblinding. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported