



Clinical trial results:

A phase II a , Multicenter, Randomized , Third -party Unblinded , Long-term Extension study to Determine Safety, Tolerability and Immunogenicity of ACC-001 with and without QS21 Adjuvant in Subjects with Mild to Moderate Alzheimer's Disease

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2009-010922-21 |
| Trial protocol | DE FR ES |
| Global end of trial date | 17 December 2013 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 23 May 2016 |
| First version publication date | 05 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | 3134K1-2203-EU |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00955409 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Pfizer, Inc. |
| Sponsor organisation address | 235 E 42nd St, New York, United States, |
| Public contact | Pfizer ClinicalTrials.gov Call Center , Pfizer, Inc., 1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer ClinicalTrials.gov Call Center , Pfizer, Inc., 1 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 03 October 2014 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 December 2013 |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 December 2013 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the long-term safety and tolerability of doses of 3, 10, and 30 µg of ACC-001 (CRM-conjugated A-beta [1-7] antigen alone and in combination with QS-21 adjuvant) in subjects with mild to moderate AD. The Basic Results disclose pooled data from the extension studies 3134K1-2203-EU (B2571007) and 3434K1-2205-US (B2571008).

Protection of trial subjects:

These studies were conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonisation Good Clinical Practice guidelines. Pfizer/Janssen Alzheimer's Immunotherapy (AI) data monitoring committee (DMC) and external DMC were involved for the ongoing monitoring of participants' safety. The table 'Number of subjects enrolled per age group' below reflects the number of enrolled subjects in the extension study.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 05 November 2009 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 110 |
| Country: Number of subjects enrolled | Spain: 9 |
| Country: Number of subjects enrolled | France: 15 |
| Country: Number of subjects enrolled | Germany: 26 |
| Worldwide total number of subjects | 160 |
| EEA total number of subjects | 50 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |

| | |
|---------------------------|-----|
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 40 |
| From 65 to 84 years | 117 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details:

Planned duration was approximately 2 years (including 18 months of treatment + 6 months of follow-up). Participants who completed the lead-in 3134K1-200-EU (B2571004) study through Week 78 (Week 104 for Cohort 1 and 2) had the option to stay in the lead-in study or to roll-over into the extension protocol 3134K1-2203-EU (B2571007).

Pre-assignment

Screening details:

This extension study enrolled participants who completed lead-in study 3134K1-200-EU. All participants received active treatment in this extension study (ACC-001 with QS-21 adjuvant). Basic Results disclose pooled data from extension studies 3134K1-2203-EU (B2571007) and 3134K1-2205-US (B2571008). The row 'completed'=completed study in below table.

Period 1

| | |
|------------------------------|---|
| Period 1 title | Including treatment and follow up period (overall 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 |
| Arm title | ACC 3 µg+QS-21 /ACC 3 µg+QS-21 |

Arm description:

Participants received 3 µg of ACC-001 and 50 µg of QS-21 in the lead-in study and in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ACC-001 + QS-21 Adjuvant |
| Investigational medicinal product code | ACC-001 + QS-21 Adjuvant |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Lead-in study and extension study: ACC-001 3 µg and QS-21 50 µg. Intramuscular use.

| | |
|------------------|------------------------|
| Arm title | QS-21 / ACC 3 µg+QS-21 |
|------------------|------------------------|

Arm description:

Participants received 50 µg of QS-21 in the lead-in study and 3 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ACC-001 + QS-21 Adjuvant |
| Investigational medicinal product code | ACC-001 + QS-21 Adjuvant |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Lead-in study: QS-21 - 50 µg. Extension study: ACC-001 - 3 µg and QS-21 - 50 µg. Intramuscular use.

| | |
|------------------|----------------------------------|
| Arm title | ACC 10 µg+QS-21 /ACC 10 µg+QS-21 |
|------------------|----------------------------------|

Arm description:

Participants received 10 µg of ACC-001 and 50 µg of QS-21 in the lead-in study and in the extension

study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ACC-001 + QS-21 Adjuvant |
| Investigational medicinal product code | ACC-001 + QS-21 Adjuvant |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

In both lead-in study and extension study: ACC-001 - 10 µg and QS-21 - 50 µg. Intramuscular use.

| | |
|------------------|-----------------------------|
| Arm title | ACC 10 µg / ACC 10 µg+QS-21 |
|------------------|-----------------------------|

Arm description:

Participants received 10 µg of ACC-001 in the lead-in study and 10 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ACC-001 + QS-21 Adjuvant |
| Investigational medicinal product code | ACC-001 + QS-21 Adjuvant |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Lead-in study: ACC-001 - 10 µg. Extension study: 10 µg ACC-001 and 50 µg QS-21. Intramuscular use.

| | |
|------------------|-------------------------|
| Arm title | QS-21 / ACC 10 µg+QS-21 |
|------------------|-------------------------|

Arm description:

Participants received 50 µg of QS-21 in the lead-in study and 10 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ACC-001 + QS-21 Adjuvant |
| Investigational medicinal product code | ACC-001 + QS-21 Adjuvant |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Lead-in study: 50 µg QS-21. Extension study: 10 µg ACC-001 and 50 µg QS-21. Intramuscular use.

| | |
|------------------|-----------------------|
| Arm title | PBS / ACC 10 µg+QS-21 |
|------------------|-----------------------|

Arm description:

Participants received Phosphate buffered Saline (PBS) in the lead-in study and 10 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ACC-001 + QS-21 Adjuvant |
| Investigational medicinal product code | ACC-001 + QS-21 Adjuvant |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Lead-in study: PBS. Extension study: 10 µg ACC-001 and 50 µg QS-21. Intramuscular use.

| | |
|------------------|---------------------------------|
| Arm title | ACC 30 µg+QS-21/ACC 30 µg+QS-21 |
|------------------|---------------------------------|

Arm description:

Participants received 30 µg of ACC-001 and 50 µg of QS-21 in the lead-in study and in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18

months.

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ACC-001 + QS-21 Adjuvant |
| Investigational medicinal product code | ACC-001 + QS-21 Adjuvant |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Lead-in study and in extension study: 30 µg ACC-001 and 50 µg QS-21. Intramuscular use.

| | |
|------------------|-----------------------------|
| Arm title | ACC 30 µg / ACC 30 µg+QS-21 |
|------------------|-----------------------------|

Arm description:

Participants received 30 µg of ACC-001 in the lead-in study and 30 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ACC-001 + QS-21 Adjuvant |
| Investigational medicinal product code | ACC-001 + QS-21 Adjuvant |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Lead-in study: 30 µg ACC-001. Extension study: 30 µg ACC-001 and 50 µg QS-21. Intramuscular use.

| | |
|------------------|-------------------------|
| Arm title | QS-21 / ACC 30 µg+QS-21 |
|------------------|-------------------------|

Arm description:

Participants received 50 µg of QS-21 in the lead-in study and 30 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ACC-001 + QS-21 Adjuvant |
| Investigational medicinal product code | ACC-001 + QS-21 Adjuvant |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Lead-in study: 50 µg QS-21. Extension study: 30 µg ACC-001 and 50 µg QS-21. Intramuscular use.

| | |
|------------------|-----------------------|
| Arm title | PBS / ACC 30 µg+QS-21 |
|------------------|-----------------------|

Arm description:

Participants received PBS in the lead-in study and 30 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | ACC-001 + QS-21 Adjuvant |
| Investigational medicinal product code | ACC-001 + QS-21 Adjuvant |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Lead-in study: PBS. Extension study: 30 µg ACC-001 and 50 µg QS-21 . Intramuscular use.

| Number of subjects in period 1 | ACC 3 µg+QS-21 / ACC 3 µg+QS-21 | QS-21 / ACC 3 µg+QS-21 | ACC 10 µg+QS-21 / ACC 10 µg+QS-21 |
|---|---------------------------------|------------------------|-----------------------------------|
| Started | 21 | 6 | 41 |
| Completed Treatment | 12 | 5 | 15 |
| Completed | 11 | 5 | 15 |
| Not completed | 10 | 1 | 26 |
| Consent withdrawn by subject | 1 | - | 5 |
| Physician decision | - | - | 1 |
| Adverse Event | 2 | - | - |
| Discontinuation of Study by Sponsor | - | - | - |
| Caregiver Request | 2 | - | 6 |
| Lost to follow-up | 2 | - | 1 |
| Retrieval subjects; impacted by sponsor disc. | 2 | 1 | 13 |
| Lack of efficacy | 1 | - | - |

| Number of subjects in period 1 | ACC 10 µg / ACC 10 µg+QS-21 | QS-21 / ACC 10 µg+QS-21 | PBS / ACC 10 µg+QS-21 |
|---|-----------------------------|-------------------------|-----------------------|
| Started | 25 | 5 | 9 |
| Completed Treatment | 17 | 3 | 7 |
| Completed | 17 | 3 | 6 |
| Not completed | 8 | 2 | 3 |
| Consent withdrawn by subject | 2 | - | - |
| Physician decision | - | - | - |
| Adverse Event | - | - | 1 |
| Discontinuation of Study by Sponsor | - | - | - |
| Caregiver Request | 5 | - | 2 |
| Lost to follow-up | - | - | - |
| Retrieval subjects; impacted by sponsor disc. | 1 | 2 | - |
| Lack of efficacy | - | - | - |

| Number of subjects in period 1 | ACC 30 µg+QS-21/ACC 30 µg+QS-21 | ACC 30 µg / ACC 30 µg+QS-21 | QS-21 / ACC 30 µg+QS-21 |
|-------------------------------------|---------------------------------|-----------------------------|-------------------------|
| Started | 27 | 6 | 16 |
| Completed Treatment | 4 | 3 | 2 |
| Completed | 3 | 2 | 2 |
| Not completed | 24 | 4 | 14 |
| Consent withdrawn by subject | 2 | - | 1 |
| Physician decision | - | - | - |
| Adverse Event | 2 | - | 2 |
| Discontinuation of Study by Sponsor | - | 1 | - |
| Caregiver Request | 3 | 1 | 3 |
| Lost to follow-up | 1 | 2 | - |

| | | | |
|---|----|---|---|
| Retrieval subjects; impacted by sponsor disc. | 16 | - | 8 |
| Lack of efficacy | - | - | - |

| Number of subjects in period 1 | PBS / ACC 30 µg+QS-21 |
|---|--------------------------|
| Started | 4 |
| Completed Treatment | 4 |
| Completed | 3 |
| Not completed | 1 |
| Consent withdrawn by subject | - |
| Physician decision | - |
| Adverse Event | - |
| Discontinuation of Study by Sponsor | - |
| Caregiver Request | - |
| Lost to follow-up | - |
| Retrieval subjects; impacted by sponsor disc. | 1 |
| Lack of efficacy | - |

Baseline characteristics

Reporting groups

| | |
|--|----------------------------------|
| Reporting group title | ACC 3 µg+QS-21 /ACC 3 µg+QS-21 |
| Reporting group description: Participants received 3 µg of ACC-001 and 50 µg of QS-21 in the lead-in study and in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Reporting group title | QS-21 / ACC 3 µg+QS-21 |
| Reporting group description: Participants received 50 µg of QS-21 in the lead-in study and 3 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Reporting group title | ACC 10 µg+QS-21 /ACC 10 µg+QS-21 |
| Reporting group description: Participants received 10 µg of ACC-001 and 50 µg of QS-21 in the lead-in study and in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Reporting group title | ACC 10 µg / ACC 10 µg+QS-21 |
| Reporting group description: Participants received 10 µg of ACC-001 in the lead-in study and 10 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Reporting group title | QS-21 / ACC 10 µg+QS-21 |
| Reporting group description: Participants received 50 µg of QS-21 in the lead-in study and 10 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Reporting group title | PBS / ACC 10 µg+QS-21 |
| Reporting group description: Participants received Phosphate buffered Saline (PBS) in the lead-in study and 10 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Reporting group title | ACC 30 µg+QS-21/ACC 30 µg+QS-21 |
| Reporting group description: Participants received 30 µg of ACC-001 and 50 µg of QS-21 in the lead-in study and in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Reporting group title | ACC 30 µg / ACC 30 µg+QS-21 |
| Reporting group description: Participants received 30 µg of ACC-001 in the lead-in study and 30 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Reporting group title | QS-21 / ACC 30 µg+QS-21 |
| Reporting group description: Participants received 50 µg of QS-21 in the lead-in study and 30 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Reporting group title | PBS / ACC 30 µg+QS-21 |
| Reporting group description: Participants received PBS in the lead-in study and 30 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |

| Reporting group values | ACC 3 µg+QS-21 /ACC 3 µg+QS-21 | QS-21 / ACC 3 µg+QS-21 | ACC 10 µg+QS-21 /ACC 10 µg+QS-21 |
|---------------------------------------|-----------------------------------|---------------------------|-------------------------------------|
| Number of subjects | 21 | 6 | 41 |
| Age categorical Units: Subjects | | | |
| 50 - 64 Years | 4 | 2 | 14 |
| ≥ 65 years | 17 | 4 | 27 |
| Age continuous Units: years | | | |
| arithmetic mean | 68.7 | 67.7 | 69.7 |
| standard deviation | ± 6.94 | ± 9.52 | ± 9.29 |
| Gender categorical Units: Subjects | | | |
| Female | 11 | 4 | 21 |
| Male | 10 | 2 | 20 |
| Race/Ethnicity Units: Subjects | | | |
| Asian | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 1 |
| Other | 1 | 0 | 0 |
| White | 20 | 6 | 40 |
| MMSE Ranges Units: Subjects | | | |
| MMSE score >26 | 0 | 0 | 5 |
| MMSE score 21-26 | 5 | 2 | 9 |
| MMSE score 16-20 | 5 | 2 | 12 |
| MMSE score 10-15 | 10 | 2 | 15 |
| MMSE score <10 | 1 | 0 | 0 |
| MMSE Score Units: Score | | | |
| arithmetic mean | 16.7 | 18.3 | 18.4 |
| standard deviation | ± 4.64 | ± 5.61 | ± 5.92 |

| Reporting group values | ACC 10 µg / ACC 10 µg+QS-21 | QS-21 / ACC 10 µg+QS-21 | PBS / ACC 10 µg+QS-21 |
|---------------------------------------|--------------------------------|----------------------------|--------------------------|
| Number of subjects | 25 | 5 | 9 |
| Age categorical Units: Subjects | | | |
| 50 - 64 Years | 5 | 1 | 3 |
| ≥ 65 years | 20 | 4 | 6 |
| Age continuous Units: years | | | |
| arithmetic mean | 72.4 | 75.2 | 69.6 |
| standard deviation | ± 9.12 | ± 8.23 | ± 7.94 |
| Gender categorical Units: Subjects | | | |
| Female | 12 | 3 | 8 |
| Male | 13 | 2 | 1 |
| Race/Ethnicity Units: Subjects | | | |
| Asian | 0 | 0 | 0 |
| Black or African American | 0 | 1 | 0 |

| | | | |
|--------------------|--------|--------|--------|
| Other | 0 | 0 | 0 |
| White | 25 | 4 | 9 |
| MMSE Ranges | | | |
| Units: Subjects | | | |
| MMSE score >26 | 3 | 1 | 1 |
| MMSE score 21-26 | 7 | 2 | 3 |
| MMSE score 16-20 | 10 | 2 | 3 |
| MMSE score 10-15 | 5 | 0 | 2 |
| MMSE score <10 | 0 | 0 | 0 |
| MMSE Score | | | |
| Units: Score | | | |
| arithmetic mean | 19.6 | 21.8 | 20 |
| standard deviation | ± 5.45 | ± 4.21 | ± 6.14 |

| Reporting group values | ACC 30 µg+QS-21/ACC 30 µg+QS-21 | ACC 30 µg / ACC 30 µg+QS-21 | QS-21 / ACC 30 µg+QS-21 |
|---------------------------|---------------------------------|-----------------------------|-------------------------|
| Number of subjects | 27 | 6 | 16 |
| Age categorical | | | |
| Units: Subjects | | | |
| 50 - 64 Years | 6 | 2 | 3 |
| ≥ 65 years | 21 | 4 | 13 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 71.3 | 66.3 | 69.5 |
| standard deviation | ± 9.2 | ± 9.42 | ± 6.95 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 16 | 3 | 14 |
| Male | 11 | 3 | 2 |
| Race/Ethnicity | | | |
| Units: Subjects | | | |
| Asian | 0 | 0 | 0 |
| Black or African American | 1 | 0 | 0 |
| Other | 0 | 0 | 0 |
| White | 26 | 6 | 16 |
| MMSE Ranges | | | |
| Units: Subjects | | | |
| MMSE score >26 | 1 | 0 | 1 |
| MMSE score 21-26 | 8 | 3 | 6 |
| MMSE score 16-20 | 11 | 2 | 6 |
| MMSE score 10-15 | 7 | 1 | 3 |
| MMSE score <10 | 0 | 0 | 0 |
| MMSE Score | | | |
| Units: Score | | | |
| arithmetic mean | 18.7 | 20.5 | 19.1 |
| standard deviation | ± 4.98 | ± 4.76 | ± 4.84 |

| Reporting group values | PBS / ACC 30 µg+QS-21 | Total | |
|------------------------|-----------------------|-------|--|
| Number of subjects | 4 | 160 | |

| | | | |
|---------------------------------------|--------|-----|--|
| Age categorical Units: Subjects | | | |
| 50 - 64 Years | 0 | 40 | |
| ≥ 65 years | 4 | 120 | |
| Age continuous Units: years | | | |
| arithmetic mean | 75.8 | | |
| standard deviation | ± 7.89 | - | |
| Gender categorical Units: Subjects | | | |
| Female | 2 | 94 | |
| Male | 2 | 66 | |
| Race/Ethnicity Units: Subjects | | | |
| Asian | 0 | 0 | |
| Black or African American | 0 | 3 | |
| Other | 0 | 1 | |
| White | 4 | 156 | |
| MMSE Ranges Units: Subjects | | | |
| MMSE score >26 | 0 | 12 | |
| MMSE score 21-26 | 3 | 48 | |
| MMSE score 16-20 | 0 | 53 | |
| MMSE score 10-15 | 1 | 46 | |
| MMSE score <10 | 0 | 1 | |
| MMSE Score Units: Score | | | |
| arithmetic mean | 20 | | |
| standard deviation | ± 4.69 | - | |

End points

End points reporting groups

| | |
|--|----------------------------------|
| Reporting group title | ACC 3 µg+QS-21 /ACC 3 µg+QS-21 |
| Reporting group description: Participants received 3 µg of ACC-001 and 50 µg of QS-21 in the lead-in study and in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Reporting group title | QS-21 / ACC 3 µg+QS-21 |
| Reporting group description: Participants received 50 µg of QS-21 in the lead-in study and 3 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Reporting group title | ACC 10 µg+QS-21 /ACC 10 µg+QS-21 |
| Reporting group description: Participants received 10 µg of ACC-001 and 50 µg of QS-21 in the lead-in study and in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Reporting group title | ACC 10 µg / ACC 10 µg+QS-21 |
| Reporting group description: Participants received 10 µg of ACC-001 in the lead-in study and 10 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Reporting group title | QS-21 / ACC 10 µg+QS-21 |
| Reporting group description: Participants received 50 µg of QS-21 in the lead-in study and 10 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Reporting group title | PBS / ACC 10 µg+QS-21 |
| Reporting group description: Participants received Phosphate buffered Saline (PBS) in the lead-in study and 10 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Reporting group title | ACC 30 µg+QS-21/ACC 30 µg+QS-21 |
| Reporting group description: Participants received 30 µg of ACC-001 and 50 µg of QS-21 in the lead-in study and in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Reporting group title | ACC 30 µg / ACC 30 µg+QS-21 |
| Reporting group description: Participants received 30 µg of ACC-001 in the lead-in study and 30 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Reporting group title | QS-21 / ACC 30 µg+QS-21 |
| Reporting group description: Participants received 50 µg of QS-21 in the lead-in study and 30 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Reporting group title | PBS / ACC 30 µg+QS-21 |
| Reporting group description: Participants received PBS in the lead-in study and 30 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months. | |
| Subject analysis set title | ACC 3 µg+QS-21 / ACC 3 µg+QS-21 |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All subjects who received at least one dose of the study drug were included in the safety population. Subjects in this group received 3 µg of ACC-001 and 50 µg of QS-21 in the lead-in study and in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|----------------------------|------------------------|
| Subject analysis set title | QS-21 / ACC 3 µg+QS-21 |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All subjects who received at least one dose of the study drug were included in the safety population. Subjects in this group received 50 µg of QS-21 in the lead-in study and 3 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|----------------------------|--------------------------|
| Subject analysis set title | Active / ACC 10 µg+QS-21 |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All subjects who received at least one dose of the study drug were included in the safety population. Subjects in this group received 10 µg of ACC-001 and 50 µg of QS-21 or 10 µg of ACC-001 alone in the lead-in study and 10 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|----------------------------|---------------------------|
| Subject analysis set title | Control / ACC 10 µg+QS-21 |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All subjects who received at least one dose of the study drug were included in the safety population. Subjects received 50 µg of QS-21 or PBS in the lead-in study and 10 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|----------------------------|--------------------------|
| Subject analysis set title | Active / ACC 30 µg+QS-21 |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All subjects who received at least one dose of the study drug were included in the safety population. Subjects received 30 µg of ACC-001 and 50 µg of QS-21 or 30 µg of ACC-001 alone in the lead-in study and 30 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|----------------------------|---------------------------|
| Subject analysis set title | Control / ACC 30 µg+QS-21 |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

All subjects who received at least one dose of the study drug were included in the safety population. Subjects in this group received 50 µg of QS-21 or PBS in the lead-in study and 30 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

Primary: Percentage of Participants With Treatment-emergent adverse events (AEs) or serious adverse events (SAEs)

| | |
|-----------------|---|
| End point title | Percentage of Participants With Treatment-emergent adverse events (AEs) or serious adverse events (SAEs) ^[1] |
|-----------------|---|

End point description:

An AE was any untoward, undesired, or unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given study drug or in a sponsor's clinical study. The event did not need to be causally related to the study drug or the clinical studies. A treatment emergent AE was defined as an event that emerged during the treatment period that was absent before treatment, or worsened during the treatment period relative to the pretreatment state. An SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly.

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

End point timeframe:

24 months

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: No statistical analysis was performed for this endpoint.

| End point values | ACC 3 µg+QS-21 / ACC 3 µg+QS-21 | QS-21 / ACC 3 µg+QS-21 | Active / ACC 10 µg+QS-21 | Control / ACC 10 µg+QS-21 |
|-----------------------------------|---------------------------------|------------------------|--------------------------|---------------------------|
| Subject group type | Subject analysis set | Subject analysis set | Subject analysis set | Subject analysis set |
| Number of subjects analysed | 21 | 6 | 65 | 14 |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| With TEAEs | 100 | 100 | 93.8 | 92.9 |
| With serious TEAEs | 28.6 | 0 | 24.6 | 14.3 |

| End point values | Active / ACC 30 µg+QS-21 | Control / ACC 30 µg+QS-21 | | |
|-----------------------------------|--------------------------|---------------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 33 | 20 | | |
| Units: Percentage of participants | | | | |
| number (not applicable) | | | | |
| With TEAEs | 78.8 | 90 | | |
| With serious TEAEs | 12.1 | 20 | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Geometric Mean Titers (GMTs) of Anti-A-beta Immunoglobulin G (IgG) Total Using an Enzyme-linked Immunosorbent Assay (ELISA) at Weeks 0, 4, 12, 24, 30, 36, 50, 56, 66, 76, 82, and 104

| | |
|-----------------|--|
| End point title | Geometric Mean Titers (GMTs) of Anti-A-beta Immunoglobulin G (IgG) Total Using an Enzyme-linked Immunosorbent Assay (ELISA) at Weeks 0, 4, 12, 24, 30, 36, 50, 56, 66, 76, 82, and 104 |
|-----------------|--|

End point description:

The lower limit of quantification (LLOQ) was 100 U/mL and when the assay result was below LLOQ (100 U/mL), 50 U/mL was imputed for IgG.

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Weeks 0, 4, 12, 24, 30, 36, 50, 56, 66, 76, 82, and 104

| End point values | ACC 3 µg+QS-21 /ACC 3 µg+QS-21 | QS-21 / ACC 3 µg+QS-21 | ACC 10 µg+QS-21 /ACC 10 µg+QS-21 | ACC 10 µg / ACC 10 µg+QS-21 |
|---|--------------------------------|---------------------------|----------------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 21 | 6 | 41 | 24 |
| Units: U/ml | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Screening Lead-in (N:21,6,41,24,5,9,27,6,16,4) | 50 (-99999 to 99999) | 50 (-99999 to 99999) | 50 (-99999 to 99999) | 50 (575.1 to 3808.2) |
| Screening Extension (N:21,6,41,24,5,9,27,6,16,4) | 836.5 (362.2 to 1932.3) | 50 (-99999 to 99999) | 1623.4 (1015.3 to 2595.7) | 180.2 (-99999 to 99999) |
| Week 4 (N:21,6,41,24,5,9,27,5,16,4) | 4523.7 (2070.2 to 9885) | 50 (-99999 to 99999) | 6219.3 (3853.2 to 10038.2) | 517.9 (76.4 to 425.3) |
| Week 12 (N:21,6,41,23,4,9,27,5,16,4) | 2540.3 (1060.5 to 6084.8) | 50 (-99999 to 99999) | 4251 (2709.7 to 6669.2) | 425.4 (166.8 to 1607.6) |
| Week 24 (N:21,6,39,24,4,9,27,5,15,3) | 1466.6 (607.2 to 3542.4) | 50 (-99999 to 99999) | 3058.1 (1887.1 to 4955.9) | 280.3 (137 to 1320.6) |
| Week 30 (N:18,6,38,20,4,6,24,5,14,3) | 3780.6 (1941.7 to 7360.9) | 477.1 (85.4 to 2664.5) | 8682 (5670.1 to 13293.8) | 1574.5 (100.2 to 784.4) |
| Week 36 (N:18,6,36,20,4,9,25,5,14,3) | 2927.8 (1368.7 to 6262.8) | 267.1 (53.6 to 1331.2) | 5946.6 (3807.1 to 9288.6) | 1029.4 (568.2 to 4363.1) |
| Week 50 (N:17,6,37,20,4,8,20,5,13,3) | 1843.8 (776.1 to 4380) | 141.3 (24.5 to 813.2) | 3146.6 (1945.8 to 5088.4) | 512.4 (346.4 to 3059.1) |
| Week 56 (N:17,6,32,19,4,8,12,4,5,3) | 4958.8 (2257.8 to 10891) | 1441.4 (159.3 to 13045.1) | 10412.4 (6365.4 to 17032.7) | 4562.2 (176.5 to 1487.4) |
| Week 66 (N:17,6,30,19,4,7,8,5,3,3) | 2765 (1190.8 to 6420.3) | 701.5 (86 to 5719.3) | 6627.7 (3946.1 to 11131.5) | 2049.2 (2233.3 to 9319.8) |
| Week 76 (N:14,5,23,19,4,7,5,5,3,3) | 2802.1 (1334.8 to 5882.6) | 842.5 (107.7 to 6592.3) | 3373.8 (1763.5 to 6454.6) | 1479.9 (852.2 to 4927.5) |
| Week 82 (N:13,5,16,18,3,7,4,4,2,3) | 6831.1 (3436.2 to 13579.9) | 5104.3 (540.8 to 48180.8) | 12261.1 (6635.8 to 22655.2) | 5771.4 (587.2 to 4172.5) |
| Week 104 (N:12,5,14,17,2,5,5,2,2,3) | 2951.6 (1259.3 to 6918.3) | 1061 (77.8 to 14476) | 6644.4 (2583.6 to 17088.1) | 1565.2 (3264.4 to 10203.5) |

| End point values | QS-21 / ACC 10 µg+QS-21 | PBS / ACC 10 µg+QS-21 | ACC 30 µg+QS-21/ACC 30 µg+QS-21 | ACC 30 µg / ACC 30 µg+QS-21 |
|---|-------------------------|-----------------------|---------------------------------|-----------------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 9 | 27 | 6 |
| Units: U/ml | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Screening Lead-in (N:21,6,41,24,5,9,27,6,16,4) | 50 (-99999 to 99999) | 50 (-99999 to 99999) | 50 (-99999 to 99999) | 50 (-99999 to 99999) |

| | | | | |
|---|--------------------------|---------------------------|-----------------------------|---------------------------|
| Screening Extension (N:21,6,41,24,5,9,27,6,16,4) | 50 (-99999 to 99999) | 50 (-99999 to 99999) | 1718.3 (1101.2 to 2681.3) | 424.2 (70.9 to 2539.4) |
| Week 4 (N:21,6,41,24,5,9,27,5,16,4) | 50 (-99999 to 99999) | 60.6 (38.9 to 94.4) | 8436.2 (5569.8 to 12778) | 4223 (185 to 96408.3) |
| Week 12 (N:21,6,41,23,4,9,27,5,16,4) | 50 (-99999 to 99999) | 62 (37.8 to 101.7) | 3604.3 (2009.6 to 6464.5) | 761.6 (33.2 to 17472.9) |
| Week 24 (N:21,6,39,24,4,9,27,5,15,3) | 50 (-99999 to 99999) | 57.5 (41.7 to 79.2) | 2146.4 (1309 to 3519.7) | 541.1 (31.3 to 9362.1) |
| Week 30 (N:18,6,38,20,4,6,24,5,14,3) | 552.2 (37.8 to 8075.8) | 317 (27.5 to 3654.9) | 12939.5 (8634.4 to 19391.2) | 1374.9 (54.4 to 34722.9) |
| Week 36 (N:18,6,36,20,4,9,25,5,14,3) | 282.9 (43.5 to 1838.7) | 428 (83.8 to 2186.8) | 6228.9 (3794.3 to 10225.7) | 706.7 (33.6 to 14852.3) |
| Week 50 (N:17,6,37,20,4,8,20,5,13,3) | 169.6 (35.8 to 804.5) | 333.6 (63 to 1767) | 2439 (1369.5 to 4343.8) | 527.7 (33.4 to 8348.8) |
| Week 56 (N:17,6,32,19,4,8,12,4,5,3) | 1720 (108.1 to 27356.9) | 3451 (478.9 to 24871.3) | 5241.2 (2459.3 to 11170.1) | 2216.1 (38 to 129086.9) |
| Week 66 (N:17,6,30,19,4,7,8,5,3,3) | 891 (32.6 to 24385.5) | 1989.2 (152.1 to 26014.2) | 4341.1 (1677.8 to 11232.1) | 1315.8 (117.1 to 14780.6) |
| Week 76 (N:14,5,23,19,4,7,5,5,3,3) | 628.5 (26.6 to 1478.7) | 1235.3 (116.5 to 13096.6) | 2030.7 (576.9 to 7147.4) | 875 (94.7 to 8083.3) |
| Week 82 (N:13,5,16,18,3,7,4,4,2,3) | 2768.5 (79 to 97040.9) | 4779.6 (706.4 to 32339.3) | 1902 (35 to 103340.7) | 3736.1 (594.2 to 23491.3) |
| Week 104 (N:12,5,14,17,2,5,5,2,2,3) | 1128.4 (0.1 to 25253974) | 832.4 (56.5 to 12268.2) | 1447.6 (548.5 to 3820.9) | 3654.5 (11.3 to 1181935) |

| End point values | QS-21 / ACC 30 µg+QS-21 | PBS / ACC 30 µg+QS-21 | | |
|---|----------------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 16 | 4 | | |
| Units: U/ml | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Screening Lead-in (N:21,6,41,24,5,9,27,6,16,4) | 58.8 (41.6 to 83.3) | 50 (-99999 to 99999) | | |
| Screening Extension (N:21,6,41,24,5,9,27,6,16,4) | 59.5 (41 to 86.3) | 50 (-99999 to 99999) | | |
| Week 4 (N:21,6,41,24,5,9,27,5,16,4) | 144.7 (67.9 to 308) | 100.1 (11 to 912.6) | | |
| Week 12 (N:21,6,41,23,4,9,27,5,16,4) | 89.3 (43.7 to 182.5) | 87.9 (14.6 to 529.8) | | |
| Week 24 (N:21,6,39,24,4,9,27,5,15,3) | 78.9 (42.6 to 146.1) | 50 (-99999 to 99999) | | |
| Week 30 (N:18,6,38,20,4,6,24,5,14,3) | 1889.4 (570.8 to 6254.5) | 4360.1 (30.3 to 627361.8) | | |
| Week 36 (N:18,6,36,20,4,9,25,5,14,3) | 1018.5 (297.8 to 3483.6) | 1164.2 (23.4 to 57811.5) | | |
| Week 50 (N:17,6,37,20,4,8,20,5,13,3) | 651.3 (189.9 to 2233.5) | 401.4 (4.5 to 35461.1) | | |
| Week 56 (N:17,6,32,19,4,8,12,4,5,3) | 578.3 (26.6 to 12559.5) | 8033.5 (584.5 to 110404.7) | | |
| Week 66 (N:17,6,30,19,4,7,8,5,3,3) | 968.4 (43 to 21784.1) | 5403.5 (171.1 to 170698.5) | | |

| | | | | |
|-------------------------------------|-------------------------|----------------------------|--|--|
| Week 76 (N:14,5,23,19,4,7,5,5,3,3) | 494.1 (1.2 to 198416.2) | 2042.8 (107.4 to 38841.8) | | |
| Week 82 (N:13,5,16,18,3,7,4,4,2,3) | 1617.1 (3 to 868223.9) | 9922.5 (2059.8 to 47798.6) | | |
| Week 104 (N:12,5,14,17,2,5,5,2,2,3) | 321.9 (0 to 12636639) | 1340.5 (421.5 to 4263.3) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 24 months, starting from Day 1, inclusive 18 months of dosing and 6 months of follow-up after the last dose.

Adverse event reporting additional description:

Treatment emergent SAEs and non-SAEs are presented. Same event may appear as both an AE and SAE. However, what is presented are distinct events. An event may be categorized as serious in 1 participant and as nonserious in another participant, or 1 participant may have experienced both a serious and nonserious event during the study.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------------------------|
| Reporting group title | ACC 3 µg+QS-21 / ACC 3 µg+QS-21 |
|-----------------------|---------------------------------|

Reporting group description:

Participants received 3 µg of ACC-001 and 50 µg of QS-21 in the lead-in study and in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|-----------------------|------------------------|
| Reporting group title | QS-21 / ACC 3 µg+QS-21 |
|-----------------------|------------------------|

Reporting group description:

Participants received 50 µg of QS-21 in the lead-in study and 3 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|-----------------------|--------------------------|
| Reporting group title | Active / ACC 10 µg+QS-21 |
|-----------------------|--------------------------|

Reporting group description:

Participants received 10 µg of ACC-001 and 50 µg of QS-21 or 10 µg of ACC-001 alone in the lead-in study and 10 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|-----------------------|--------------------------|
| Reporting group title | Control / ACC 10µg+QS-21 |
|-----------------------|--------------------------|

Reporting group description:

Participants received 50 µg of QS-21 or PBS in the lead-in study and 10 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|-----------------------|--------------------------|
| Reporting group title | Active / ACC 30 µg+QS-21 |
|-----------------------|--------------------------|

Reporting group description:

Participants received 30 µg of ACC-001 and 50 µg of QS-21 or 30 µg of ACC-001 alone in the lead-in study and 30 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| | |
|-----------------------|---------------------------|
| Reporting group title | Control / ACC 30 µg+QS-21 |
|-----------------------|---------------------------|

Reporting group description:

Participants received 50 µg of QS-21 or PBS in the lead-in study and 30 µg of ACC-001 and 50 µg of QS-21 in the extension study. Test article was given by intramuscular injection into the deltoid muscle at 0, 6, 12, and 18 months.

| Serious adverse events | ACC 3 µg+QS-21 / ACC 3 µg+QS-21 | QS-21 / ACC 3 µg+QS-21 | Active / ACC 10 µg+QS-21 |
|--|------------------------------------|---------------------------|-----------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 6 / 21 (28.57%) | 0 / 6 (0.00%) | 16 / 65 (24.62%) |
| number of deaths (all causes) | 2 | 0 | 1 |

| | | | |
|---|----------------|---------------|----------------|
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Gallbladder cancer metastatic | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (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 |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Raynaud's phenomenon | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (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 |
| Pelvic mass | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (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 |
| Psychiatric disorders | | | |
| Abnormal behaviour | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (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 |
| Agitated depression | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (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 |
| Agitation | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Suicidal ideation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (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 |

| | | | |
|---|----------------|---------------|----------------|
| Investigations | | | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (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 |
| Fall | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Forearm fracture | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (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 |
| Hand fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (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 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (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 |
| Lower limb fracture | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (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 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|---------------|----------------|
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (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 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (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 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradyarrhythmia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cyanosis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mitral valve prolapse | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular tachycardia | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebral haemosiderin deposition | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dementia Alzheimer's type | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (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 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Partial seizures | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (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 |
| Syncope | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vasogenic cerebral oedema | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Biliary colic | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Drug eruption | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Petechiae | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin exfoliation | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin fissures | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin haemorrhage | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Calculus ureteric | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (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 |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| 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 | | | |

| | | | |
|---|----------------|---------------|----------------|
| Dehydration | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Control / ACC 10µg+QS-21 | Active / ACC 30 µg+QS-21 | Control / ACC 30 µg+QS-21 |
|---|-----------------------------|-----------------------------|------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 4 / 33 (12.12%) | 4 / 20 (20.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Gallbladder cancer metastatic | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 33 (3.03%) | 0 / 20 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral vascular disorder | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Raynaud's phenomenon | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Device dislocation | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 33 (3.03%) | 0 / 20 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic mass | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 33 (3.03%) | 0 / 20 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Psychiatric disorders | | | |
| Abnormal behaviour | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 33 (3.03%) | 0 / 20 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Agitated depression | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Agitation | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Investigations | | | |
| Liver function test abnormal | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 | | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Fall | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Forearm fracture | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Hand fracture | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Bradyarrhythmia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Cyanosis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Mitral valve prolapse | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Nervous system disorders | | | |
| Cerebral haemosiderin deposition | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Dementia Alzheimer's type | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Epilepsy | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Partial seizures | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Syncope | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 2 / 33 (6.06%) | 1 / 20 (5.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Vasogenic cerebral oedema | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Gastrointestinal disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Ileus | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Hepatobiliary disorders | | | |
| Biliary colic | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Drug eruption | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Petechiae | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Skin exfoliation | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Skin fissures | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Skin haemorrhage | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Renal and urinary disorders | | | |
| Calculus ureteric | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 33 (3.03%) | 0 / 20 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (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 %

| Non-serious adverse events | ACC 3 µg+QS-21 / ACC 3 µg+QS-21 | QS-21 / ACC 3 µg+QS-21 | Active / ACC 10 µg+QS-21 |
|---|------------------------------------|---------------------------|-----------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 19 / 21 (90.48%) | 6 / 6 (100.00%) | 55 / 65 (84.62%) |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences (all) | 1 | 0 | 3 |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|---|----------------------|---------------------|---------------------|
| Hypertension subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 0 / 6 (0.00%) 0 | 3 / 65 (4.62%) 3 |
| Hypotension subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 5 / 65 (7.69%) 5 |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 3 / 21 (14.29%) 3 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Face oedema subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Fatigue subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 1 / 6 (16.67%) 1 | 4 / 65 (6.15%) 7 |
| Induration subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 1 / 65 (1.54%) 1 |
| Inflammation subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Injection site bruising subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 0 / 6 (0.00%) 0 | 1 / 65 (1.54%) 2 |
| Injection site erythema subjects affected / exposed occurrences (all) | 4 / 21 (19.05%) 8 | 0 / 6 (0.00%) 0 | 5 / 65 (7.69%) 5 |
| Injection site haemorrhage subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Injection site hypersensitivity subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Injection site induration | | | |

| | | | |
|---|----------------------|---------------------|------------------------|
| subjects affected / exposed occurrences (all) | 3 / 21 (14.29%) 4 | 0 / 6 (0.00%) 0 | 1 / 65 (1.54%) 1 |
| Injection site inflammation subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 2 / 65 (3.08%) 3 |
| Injection site pain subjects affected / exposed occurrences (all) | 4 / 21 (19.05%) 7 | 0 / 6 (0.00%) 0 | 11 / 65 (16.92%) 15 |
| Injection site pruritus subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 4 / 6 (66.67%) 4 | 0 / 65 (0.00%) 0 |
| Injection site swelling subjects affected / exposed occurrences (all) | 3 / 21 (14.29%) 3 | 0 / 6 (0.00%) 0 | 5 / 65 (7.69%) 6 |
| Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Reproductive system and breast disorders Testicular pain subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 3 | 1 / 6 (16.67%) 1 | 3 / 65 (4.62%) 3 |
| Hiccups subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Psychiatric disorders Abnormal behaviour subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| Aggression | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 6 (16.67%) | 2 / 65 (3.08%) |
| occurrences (all) | 1 | 1 | 5 |
| Agitation | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 4 / 6 (66.67%) | 5 / 65 (7.69%) |
| occurrences (all) | 5 | 4 | 7 |
| Anxiety | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 0 / 6 (0.00%) | 4 / 65 (6.15%) |
| occurrences (all) | 2 | 0 | 5 |
| Confusional state | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 4 / 65 (6.15%) |
| occurrences (all) | 1 | 0 | 4 |
| Delirium | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Delusional perception | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Depression | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 0 / 6 (0.00%) | 3 / 65 (4.62%) |
| occurrences (all) | 3 | 0 | 3 |
| Irritability | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 6 (16.67%) | 1 / 65 (1.54%) |
| occurrences (all) | 0 | 1 | 1 |
| Nightmare | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 6 (16.67%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Investigations | | | |
| Bartonella test positive | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Urine output decreased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 6 (16.67%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vitamin B1 decreased | | | |

| | | | |
|--|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Weight decreased | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences (all) | 0 | 0 | 1 |
| Injury, poisoning and procedural complications | | | |
| Ankle fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Contusion | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 1 / 6 (16.67%) | 2 / 65 (3.08%) |
| occurrences (all) | 4 | 1 | 2 |
| Corneal abrasion | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Eye contusion | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Fall | | | |
| subjects affected / exposed | 4 / 21 (19.05%) | 1 / 6 (16.67%) | 7 / 65 (10.77%) |
| occurrences (all) | 6 | 1 | 8 |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Laceration | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 3 / 65 (4.62%) |
| occurrences (all) | 0 | 0 | 3 |
| Limb injury | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Periorbital contusion | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 6 (16.67%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |

| | | | |
|---|---------------------|---------------------|---------------------|
| Bradycardia subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 1 / 65 (1.54%) 1 |
| Nervous system disorders | | | |
| Balance disorder subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Cognitive disorder subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 1 / 6 (16.67%) 1 | 0 / 65 (0.00%) 0 |
| Dementia Alzheimer's type subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 6 (16.67%) 1 | 1 / 65 (1.54%) 1 |
| Dizziness subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 0 / 6 (0.00%) 0 | 5 / 65 (7.69%) 6 |
| Headache subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 0 / 6 (0.00%) 0 | 6 / 65 (9.23%) 9 |
| Hyperreflexia subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 6 (16.67%) 1 | 0 / 65 (0.00%) 0 |
| Hypoaesthesia subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Lethargy subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Myoclonus subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 1 / 6 (16.67%) 1 | 2 / 65 (3.08%) 2 |
| Syncope subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 0 / 6 (0.00%) 0 | 2 / 65 (3.08%) 2 |
| Tremor | | | |

| | | | |
|---|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 6 (16.67%) 1 | 0 / 65 (0.00%) 0 |
| Ear and labyrinth disorders Hearing impaired subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Eye disorders Cataract subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Glaucoma subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Heterophoria subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Retinal degeneration subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 2 / 65 (3.08%) 2 |
| Dental caries subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Diarrhoea subjects affected / exposed occurrences (all) | 4 / 21 (19.05%) 5 | 1 / 6 (16.67%) 1 | 3 / 65 (4.62%) 3 |
| Faeces soft subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 6 (16.67%) 1 | 0 / 65 (0.00%) 0 |
| Inguinal hernia | | | |

| | | | |
|---|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 6 (16.67%) 1 | 0 / 65 (0.00%) 0 |
| Nausea subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 2 | 0 / 6 (0.00%) 0 | 3 / 65 (4.62%) 3 |
| Periodontal disease subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Vomiting subjects affected / exposed occurrences (all) | 3 / 21 (14.29%) 4 | 0 / 6 (0.00%) 0 | 1 / 65 (1.54%) 1 |
| Skin and subcutaneous tissue disorders | | | |
| Ecchymosis subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Erythema subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 2 / 65 (3.08%) 2 |
| Pruritus subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 0 / 6 (0.00%) 0 | 3 / 65 (4.62%) 4 |
| Rash subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 | 0 / 6 (0.00%) 0 | 4 / 65 (6.15%) 5 |
| Rosacea subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Skin lesion subjects affected / exposed occurrences (all) | 2 / 21 (9.52%) 2 | 0 / 6 (0.00%) 0 | 1 / 65 (1.54%) 1 |
| Renal and urinary disorders | | | |
| Haematuria subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 0 / 65 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| Arthralgia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 4 / 65 (6.15%) |
| occurrences (all) | 0 | 0 | 6 |
| Back pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 4 / 65 (6.15%) |
| occurrences (all) | 0 | 0 | 5 |
| Muscle spasms | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 6 (16.67%) | 4 / 65 (6.15%) |
| occurrences (all) | 0 | 1 | 4 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences (all) | 1 | 0 | 1 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 4 / 65 (6.15%) |
| occurrences (all) | 0 | 0 | 4 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 3 / 65 (4.62%) |
| occurrences (all) | 1 | 0 | 3 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 21 (14.29%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences (all) | 3 | 0 | 1 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 2 / 6 (33.33%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 6 (16.67%) | 2 / 65 (3.08%) |
| occurrences (all) | 2 | 1 | 2 |
| Infected bites | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 6 (16.67%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Localised infection | | | |

| | | | |
|------------------------------------|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 6 (16.67%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lyme disease | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 21 (9.52%) | 1 / 6 (16.67%) | 6 / 65 (9.23%) |
| occurrences (all) | 4 | 1 | 9 |
| Onychomycosis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 1 / 6 (16.67%) | 0 / 65 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 1 / 6 (16.67%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 2 / 65 (3.08%) |
| occurrences (all) | 0 | 0 | 3 |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 1 / 65 (1.54%) |
| occurrences (all) | 4 | 0 | 1 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 0 / 6 (0.00%) | 3 / 65 (4.62%) |
| occurrences (all) | 1 | 0 | 3 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | 4 / 6 (66.67%) | 9 / 65 (13.85%) |
| occurrences (all) | 2 | 4 | 10 |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 6 (0.00%) | 0 / 65 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Metabolism and nutrition disorders | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Diabetes mellitus subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 0 / 6 (0.00%) 0 | 1 / 65 (1.54%) 1 |
| Glucose tolerance impaired subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 6 (16.67%) 1 | 0 / 65 (0.00%) 0 |
| Vitamin D deficiency subjects affected / exposed occurrences (all) | 0 / 21 (0.00%) 0 | 1 / 6 (16.67%) 1 | 3 / 65 (4.62%) 3 |

| Non-serious adverse events | Control / ACC 10µg+QS-21 | Active / ACC 30 µg+QS-21 | Control / ACC 30 µg+QS-21 |
|---|-----------------------------|-----------------------------|------------------------------|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 13 / 14 (92.86%) | 23 / 33 (69.70%) | 17 / 20 (85.00%) |
| Vascular disorders | | | |
| Haematoma subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Haemorrhage subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Hypertension subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 2 / 33 (6.06%) 2 | 0 / 20 (0.00%) 0 |
| Hypotension subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Face oedema subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Fatigue subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 33 (3.03%) 1 | 0 / 20 (0.00%) 0 |

| | | | |
|---------------------------------|-----------------|-----------------|-----------------|
| Induration | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Inflammation | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injection site bruising | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 2 / 33 (6.06%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 2 | 1 |
| Injection site erythema | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 5 / 33 (15.15%) | 4 / 20 (20.00%) |
| occurrences (all) | 1 | 9 | 6 |
| Injection site haemorrhage | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 33 (0.00%) | 3 / 20 (15.00%) |
| occurrences (all) | 1 | 0 | 4 |
| Injection site hypersensitivity | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Injection site induration | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injection site inflammation | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 33 (3.03%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Injection site pain | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 5 / 33 (15.15%) | 6 / 20 (30.00%) |
| occurrences (all) | 2 | 9 | 8 |
| Injection site pruritus | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Injection site swelling | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 4 / 33 (12.12%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 7 | 1 |
| Immune system disorders | | | |
| Seasonal allergy | | | |

| | | | |
|---|--|--|--|
| subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Reproductive system and breast disorders Testicular pain subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Hiccups subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 0 / 14 (0.00%) 0 1 / 14 (7.14%) 1 | 1 / 33 (3.03%) 1 0 / 33 (0.00%) 0 0 / 33 (0.00%) 0 | 0 / 20 (0.00%) 0 1 / 20 (5.00%) 1 0 / 20 (0.00%) 0 |
| Psychiatric disorders Abnormal behaviour subjects affected / exposed occurrences (all) Aggression subjects affected / exposed occurrences (all) Agitation subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all) Confusional state subjects affected / exposed occurrences (all) Delirium subjects affected / exposed occurrences (all) Delusional perception | 1 / 14 (7.14%) 1 0 / 14 (0.00%) 0 2 / 14 (14.29%) 2 1 / 14 (7.14%) 1 0 / 14 (0.00%) 0 0 / 14 (0.00%) 0 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 0 / 33 (0.00%) 0 3 / 33 (9.09%) 3 1 / 33 (3.03%) 3 0 / 33 (0.00%) 0 0 / 33 (0.00%) 0 | 0 / 20 (0.00%) 0 1 / 20 (5.00%) 1 1 / 20 (5.00%) 1 0 / 20 (0.00%) 0 0 / 20 (0.00%) 0 1 / 20 (5.00%) 1 |

| | | | |
|--|----------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 33 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Depression subjects affected / exposed occurrences (all) | 3 / 14 (21.43%) 3 | 2 / 33 (6.06%) 2 | 0 / 20 (0.00%) 0 |
| Irritability subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 33 (3.03%) 1 | 0 / 20 (0.00%) 0 |
| Nightmare subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Investigations Bartonella test positive subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 33 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Urine output decreased subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Vitamin B1 decreased subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Weight decreased subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Injury, poisoning and procedural complications Ankle fracture subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Contusion subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 2 / 33 (6.06%) 2 | 1 / 20 (5.00%) 1 |
| Corneal abrasion subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 33 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Eye contusion | | | |

| | | | |
|--|----------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Fall subjects affected / exposed occurrences (all) | 2 / 14 (14.29%) 2 | 2 / 33 (6.06%) 2 | 2 / 20 (10.00%) 6 |
| Hip fracture subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Laceration subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 2 / 33 (6.06%) 2 | 1 / 20 (5.00%) 1 |
| Limb injury subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Periorbital contusion subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Cardiac disorders Bradycardia subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 0 / 33 (0.00%) 0 | 0 / 20 (0.00%) 0 |
| Nervous system disorders Balance disorder subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 | 1 / 20 (5.00%) 1 |
| Cognitive disorder subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 0 / 33 (0.00%) 0 | 2 / 20 (10.00%) 2 |
| Dementia Alzheimer's type subjects affected / exposed occurrences (all) | 0 / 14 (0.00%) 0 | 1 / 33 (3.03%) 1 | 0 / 20 (0.00%) 0 |
| Dizziness subjects affected / exposed occurrences (all) | 2 / 14 (14.29%) 2 | 2 / 33 (6.06%) 2 | 2 / 20 (10.00%) 2 |
| Headache | | | |

| | | | |
|--------------------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 14 (7.14%) | 3 / 33 (9.09%) | 1 / 20 (5.00%) |
| occurrences (all) | 1 | 4 | 1 |
| Hyperreflexia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Lethargy | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Myoclonus | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tremor | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Hearing impaired | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Glaucoma | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Heterophoria | | | |

| | | | |
|--|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Retinal degeneration | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 2 / 33 (6.06%) | 2 / 20 (10.00%) |
| occurrences (all) | 0 | 2 | 2 |
| Dental caries | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 33 (3.03%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 2 / 33 (6.06%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Faeces soft | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 3 / 20 (15.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Periodontal disease | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 33 (3.03%) | 1 / 20 (5.00%) |
| occurrences (all) | 1 | 1 | 4 |
| Skin and subcutaneous tissue disorders | | | |
| Ecchymosis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Erythema | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 33 (3.03%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Rash | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rosacea | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 33 (3.03%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Skin lesion | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 1 / 33 (3.03%) | 1 / 20 (5.00%) |
| occurrences (all) | 2 | 1 | 1 |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 33 (3.03%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 33 (3.03%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Back pain | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 33 (3.03%) | 2 / 20 (10.00%) |
| occurrences (all) | 2 | 1 | 2 |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 1 / 33 (3.03%) | 1 / 20 (5.00%) |
| occurrences (all) | 1 | 1 | 1 |
| Neck pain | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pain in extremity | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 14 (7.14%) 1 | 1 / 33 (3.03%) 1 | 0 / 20 (0.00%) 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Conjunctivitis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal infection | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Infected bites | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Localised infection | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Lyme disease | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 33 (3.03%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Onychomycosis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 1 / 33 (3.03%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 1 | 1 |

| | | | |
|------------------------------------|-----------------|----------------|----------------|
| Sinusitis | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 14 (14.29%) | 1 / 33 (3.03%) | 0 / 20 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 2 / 33 (6.06%) | 1 / 20 (5.00%) |
| occurrences (all) | 1 | 2 | 3 |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Wound infection | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 1 / 20 (5.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 1 / 14 (7.14%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Glucose tolerance impaired | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 14 (0.00%) | 0 / 33 (0.00%) | 0 / 20 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 04 February 2010 | The following major changes were made in protocol amendment 1: - Study design was revised to clarify the study population, inclusion/exclusion criteria, concomitant medications, and procedures. - Protocol inconsistencies, omissions and errors were corrected. |
| 30 June 2010 | The following major changes were made in protocol amendment 2: - Study design was revised to clarify the study population, inclusion/exclusion criteria, concomitant medications, and procedures. - Protocol inconsistencies, omissions and errors were corrected. |
| 13 January 2012 | Protocol amendment 3 was made to update: - Exclusion criteria, inclusion of suicidality assessment, addition of direct and indirect bilirubin testing, and to update information and instructions pertaining to retrieval subjects, CSF sample collection, AEs/SAEs, discontinuation of investigational product due to injection site reactions, and reporting of safety issues. |
| 14 June 2012 | Protocol amendment 4 was made to update: - Adverse events, adverse events of special interest, concomitant treatments, and to add cerebral hemorrhage as an adverse drug reaction. |
| 17 December 2013 | The following major changes were made in protocol amendment 5: - CSF assays for anti-A-beta antibodies and IgG subtype analysis were listed as exploratory objectives and it was clarified that the analysis will not be conducted. - Specific protocol section was revised to clarify the inconsistency with the Investigator Brochure regarding the adverse events of special circumstance. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|--------------|--|--------------|
| 12 July 2013 | This study was prematurely terminated. In July 2013 the Alliance made a decision that ACC-001 would not be further developed in mild to moderate AD. Consequently, on 12 July 2013, dosing in the long-term extension studies was terminated and all remaining subjects were followed for safety for up to 6 months following their last administration of investigational product in accordance with the study protocols. | - |

Notes:

Limitations and caveats

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

The following endpoints are not presented as these were not analyzed: GMTs of Anti-A-beta IgM and IgG Subtypes (where an IgG total response was measurable) using ELISA at Weeks 0, 4, 12, 24, 30, 36, 50, 56, 66, 76, 82, and 104.

Notes: