



## Clinical trial results:

**A randomized, double blind placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and preliminary pharmacodynamics of single and multiple ascending doses of QBW251 in healthy subjects and multiple doses in cystic fibrosis patients.**

**Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.**

## Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2011-005085-37   |
| Trial protocol           | GB DE IE BE FR   |
| Global end of trial date | 30 November 2015 |

## Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 12 July 2018 |
| First version publication date | 12 July 2018 |

## Trial information

### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CQBW251X2101 |
|-----------------------|--------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02190604 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

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

Notes:

## Paediatric regulatory details

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

|                                |  |
|--------------------------------|--|
| 1901/2006 apply to this trial? |  |
|--------------------------------|--|

Notes:

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### Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 30 November 2015 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 30 November 2015 |
| Was the trial ended prematurely?                     | Yes              |

Notes:

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### General information about the trial

Main objective of the trial:

To assess the safety and tolerability of multiple ascending multiple oral doses in CF patients and to evaluate the preliminary efficacy of multiple doses of QBW251 on change from baseline in lung clearance index (LCI) in cystic fibrosis (CF) patients at Day 15.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 31 July 2012 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

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### Population of trial subjects

#### Subjects enrolled per country

|                                      |                     |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 113 |
| Country: Number of subjects enrolled | Belgium: 3          |
| Country: Number of subjects enrolled | France: 12          |
| Country: Number of subjects enrolled | Germany: 4          |
| Country: Number of subjects enrolled | Ireland: 3          |
| Country: Number of subjects enrolled | Romania: 1          |
| Country: Number of subjects enrolled | United States: 17   |
| Worldwide total number of subjects   | 153                 |
| EEA total number of subjects         | 136                 |

Notes:

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#### 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)                      | 153 |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

In parts 1 and 2, participants (Healthy Volunteers) were randomized 3:1 to receive QBW251X or placebo. In part 3, participants (cystic fibrosis (CF) patients) were randomized 3:1 to receive QBW251X or placebo.

### Period 1

|                              |                                   |
|------------------------------|-----------------------------------|
| Period 1 title               | Part 1 and 2 (Healthy Volunteers) |
| Is this the baseline period? | Yes                               |
| Allocation method            | Randomised - controlled           |
| Blinding used                | Double blind                      |
| Roles blinded                | Subject, Investigator, Carer      |

### Arms

|                              |                         |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes                     |
| <b>Arm title</b>             | Part 1 Cohort 1: QBW251 |

Arm description:

Single dose of QBW251 10 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | QBW251       |
| Investigational medicinal product code | QBW251       |
| Other name                             | QBW251       |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

QBW251 10 mg,

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Part 1 Cohort 2: QBW251 |
|------------------|-------------------------|

Arm description:

Single dose of QBW251 25 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | QBW251       |
| Investigational medicinal product code | QBW251       |
| Other name                             | QBW251       |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

QBW251 25mg orally

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Part 1 Cohort 3: QBW251 |
|------------------|-------------------------|

Arm description:

Single dose of QBW251 75 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | QBW251       |
| Investigational medicinal product code | QBW251       |
| Other name                             | QBW251       |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

QBW251, 75mg orally

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Part 1 Cohort 4: QBW251 |
|------------------|-------------------------|

Arm description:

Single dose of QBW251 150 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | QBW251       |
| Investigational medicinal product code | QBW251       |
| Other name                             | QBW251       |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

QBW251, 150mg orally

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Part 1 Cohort 5: QBW251 |
|------------------|-------------------------|

Arm description:

Single dose of QBW251 300 mg in healthy volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | QBW251       |
| Investigational medicinal product code | QBW251       |
| Other name                             | QBW251       |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

QBW251, 300mg orally

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Part 1 Cohort 6: QBW251 |
|------------------|-------------------------|

Arm description:

Single dose of QBW251 500 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | QBW251       |
| Investigational medicinal product code | QBW251       |
| Other name                             | QBW251       |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

QBW251, 500mg orally

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Part 1 Cohort 7: QBW251 |
|------------------|-------------------------|

Arm description:

Single dose of QBW251 750 mg in Healthy Volunteers. Each treatment period was comprised of a

baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | QBW251       |
| Investigational medicinal product code | QBW251       |
| Other name                             | QBW251       |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

QBW251, 750mg orally

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Part 1 Cohort 8: QBW251 |
|------------------|-------------------------|

Arm description:

Single dose of QBW251 1000 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | QBW251       |
| Investigational medicinal product code | QBW251       |
| Other name                             | QBW251       |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

QBW251, 1000mg orally

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Part 1 Placebo |
|------------------|----------------|

Arm description:

Placebo to QBW251 in all cohorts of part 1 in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).

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

Dosage and administration details:

Placebo, orally

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Part 2 Cohort 1: QBW251 |
|------------------|-------------------------|

Arm description:

Multiple doses of QBW25 150 mg qd in Healthy Volunteers. 14-day treatment period, follow-up study visits (Days 18, 22 and 29) and one End-of-Study evaluation (Day 36).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | QBW251       |
| Investigational medicinal product code | QBW251       |
| Other name                             | QBW251       |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

QBW251, 150 mg qd

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Part 2 Cohort 2: QBW251 |
|------------------|-------------------------|

## Arm description:

Multiple doses of QBW251 400 mg qd in Healthy Volunteers. 14-day treatment period, follow-up study visits (Days 18, 22 and 29) and one End-of-Study evaluation (Day 36).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | QBW251       |
| Investigational medicinal product code | QBW251       |
| Other name                             | QBW251       |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

## Dosage and administration details:

QBW251, 450mg qd

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Part 2 Cohort 3: QBW251 |
|------------------|-------------------------|

## Arm description:

Multiple doses of QBW251 750 mg qd in Healthy Volunteers. 14-day treatment period, follow-up study visits (Days 18, 22 and 29) and one End-of-Study evaluation (Day 36).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | QBW251       |
| Investigational medicinal product code | QBW251       |
| Other name                             | QBW251       |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

## Dosage and administration details:

QBW251, 750mg qd

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Part 2 Cohort 4: QBW251 |
|------------------|-------------------------|

## Arm description:

Multiple doses of QBW251 450 mg bid in Healthy Volunteers. 14-day treatment period, follow-up study visits (Days 18, 22 and 29) and one End-of-Study evaluation (Day 36).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | QBW251       |
| Investigational medicinal product code | QBW251       |
| Other name                             | QBW251       |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

## Dosage and administration details:

QBW251, 450mg bid

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Part 2 Cohort 5: QBW251 |
|------------------|-------------------------|

## Arm description:

Multiple doses of QBW251 750 mg bid in Healthy Volunteers. 14-day treatment period, follow-up study visits (Days 18, 22 and 29) and one End-of-Study evaluation (Day 36).

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | QBW251       |
| Investigational medicinal product code | QBW251       |
| Other name                             | QBW251       |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

## Dosage and administration details:

QBW251, 750mg bid

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Part 2 Placebo |
|------------------|----------------|

## Arm description:

Placebo to QBW251 in all cohorts of part 2 in Healthy Volunteers. 14-day treatment period, follow-up study visits (Days 18, 22 and 29) and one End-of-Study evaluation (Day 36).

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|  |          |
|--|----------|
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code | Placebo  |
| Other name                             | Placebo  |
| Pharmaceutical forms                   | Capsule  |
| Routes of administration               | Oral use |

Dosage and administration details:

Placebo

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Part 1 Cohort 1:<br>QBW251 | Part 1 Cohort 2:<br>QBW251 | Part 1 Cohort 3:<br>QBW251 |
|---|----------------------------|----------------------------|----------------------------|
| Started   | 6                          | 6                          | 6                          |
| Completed   | 6                          | 6                          | 6                          |
| Not completed                                       | 0                          | 0                          | 0                          |
| Adverse event, non-fatal                            | -                          | -                          | -                          |
| Lost to follow-up                                   | -                          | -                          | -                          |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Part 1 Cohort 4:<br>QBW251 | Part 1 Cohort 5:<br>QBW251 | Part 1 Cohort 6:<br>QBW251 |
|---|----------------------------|----------------------------|----------------------------|
| Started   | 6                          | 6                          | 6                          |
| Completed   | 6                          | 6                          | 6                          |
| Not completed                                       | 0                          | 0                          | 0                          |
| Adverse event, non-fatal                            | -                          | -                          | -                          |
| Lost to follow-up                                   | -                          | -                          | -                          |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Part 1 Cohort 7:<br>QBW251 | Part 1 Cohort 8:<br>QBW251 | Part 1 Placebo |
|---|----------------------------|----------------------------|----------------|
| Started   | 6                          | 6                          | 16             |
| Completed   | 6                          | 6                          | 16             |
| Not completed                                       | 0                          | 0                          | 0              |
| Adverse event, non-fatal                            | -                          | -                          | -              |
| Lost to follow-up                                   | -                          | -                          | -              |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Part 2 Cohort 1:<br>QBW251 | Part 2 Cohort 2:<br>QBW251 | Part 2 Cohort 3:<br>QBW251 |
|---|----------------------------|----------------------------|----------------------------|
| Started   | 6                          | 6                          | 6                          |
| Completed   | 6                          | 6                          | 6                          |
| Not completed                                       | 0                          | 0                          | 0                          |
| Adverse event, non-fatal                            | -                          | -                          | -                          |
| Lost to follow-up                                   | -                          | -                          | -                          |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Part 2 Cohort 4:<br>QBW251 | Part 2 Cohort 5:<br>QBW251 | Part 2 Placebo |
|---|----------------------------|----------------------------|----------------|
| Started   | 6                          | 6                          | 10             |
| Completed   | 6                          | 5                          | 8              |
| Not completed                                       | 0                          | 1                          | 2              |

|                          |   |   |   |
|--------------------------|---|---|---|
| Adverse event, non-fatal | - | - | 2 |
| Lost to follow-up        | - | 1 | - |

Notes:

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

Justification: This is an adaptive design parts one and 2 were conducted first then part 3 conducted later . The total equals the ww number.

**Period 2**

|                              |                              |
|------------------------------|------------------------------|
| Period 2 title               | Part 3 (Patients)            |
| Is this the baseline period? | No                           |
| Allocation method            | Randomised - controlled      |
| Blinding used                | Double blind                 |
| Roles blinded                | Subject, Investigator, Carer |

**Arms**

|                              |                         |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes                     |
| <b>Arm title</b>             | Part 3 Cohort 1: QBW251 |

Arm description:

150 mg b.i.d. Multiple doses. Patients having a class III, IV, V, or VI mutation on one allele and any other CFTR mutation on the other allele in patients. treatment period (Day 1 to Day 14) with study visits on Days 1, 4, 7 and 14 with follow-up visits on Days 15, 28 and 42.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | QBW251       |
| Investigational medicinal product code | QBW251       |
| Other name                             | QBW251       |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

QBW251, 150mg bid

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Part 3 Cohort 2: QBW251 |
|------------------|-------------------------|

Arm description:

450 mg b.i.d. Multiple doses. Patients having a class III, IV, V, or VI mutation on one allele and any other CFTR mutation on the other allele in patients. treatment period (Day 1 to Day 14) with study visits on Days 1, 4, 7 and 14 with follow-up visits on Days 15, 28 and 42.

|  |              |
|--|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | QBW251       |
| Investigational medicinal product code | QBW251       |
| Other name                             | QBW251       |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

QBW251, 450mg bid

|                  |                         |
|------------------|-------------------------|
| <b>Arm title</b> | Part 3 Cohort 3: QBW251 |
|------------------|-------------------------|

Arm description:

450 mg b.i.d. Multiple doses. Patients who are homozygous for the F508del mutation in patients. treatment period (Day 1 to Day 14) with study visits on Days 1, 4, 7 and 14 with follow-up visits on Days 15, 28 and 42.

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

|  |          |
|--|----------|
| Investigational medicinal product name | QBW251   |
| Investigational medicinal product code | QBW251   |
| Other name                             | QBW251   |
| Pharmaceutical forms                   | Capsule  |
| Routes of administration               | Oral use |

Dosage and administration details:

QBW251, 450mg bid

|                  |                |
|------------------|----------------|
| <b>Arm title</b> | Part 3 Placebo |
|------------------|----------------|

Arm description:

Placebo to QBW251 in all cohorts of part 3 in patients. treatment period (Day 1 to Day 14) with study visits on Days 1, 4, 7 and 14 with follow-up visits on Days 15, 28 and 42.

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

Dosage and administration details:

Placebo

| <b>Number of subjects in period 2<sup>[2]</sup></b> | Part 3 Cohort 1:<br>QBW251 | Part 3 Cohort 2:<br>QBW251 | Part 3 Cohort 3:<br>QBW251 |
|---|----------------------------|----------------------------|----------------------------|
| Started   | 6                          | 12                         | 19                         |
| Completed   | 6                          | 12                         | 19                         |

| <b>Number of subjects in period 2<sup>[2]</sup></b> | Part 3 Placebo |
|---|----------------|
| Started   | 12             |
| Completed   | 12             |

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: group started after period one and 2 which were with healthy volunteers.

## Baseline characteristics

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### Reporting groups

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|-----------------------|-------------------------|
| Reporting group title | Part 1 Cohort 1: QBW251 |
|-----------------------|-------------------------|

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Reporting group description:

Single dose of QBW251 10 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).

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|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 1 Cohort 2: QBW251 |
|-----------------------|-------------------------|

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Reporting group description:

Single dose of QBW251 25 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).

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|-----------------------|-------------------------|
| Reporting group title | Part 1 Cohort 3: QBW251 |
|-----------------------|-------------------------|

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Reporting group description:

Single dose of QBW251 75 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).

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|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 1 Cohort 4: QBW251 |
|-----------------------|-------------------------|

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Reporting group description:

Single dose of QBW251 150 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).

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|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 1 Cohort 5: QBW251 |
|-----------------------|-------------------------|

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Reporting group description:

Single dose of QBW251 300 mg in healthy volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).

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|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 1 Cohort 6: QBW251 |
|-----------------------|-------------------------|

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Reporting group description:

Single dose of QBW251 500 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).

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|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 1 Cohort 7: QBW251 |
|-----------------------|-------------------------|

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Reporting group description:

Single dose of QBW251 750 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).

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|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 1 Cohort 8: QBW251 |
|-----------------------|-------------------------|

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Reporting group description:

Single dose of QBW251 1000 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).

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|                       |                |
|-----------------------|----------------|
| Reporting group title | Part 1 Placebo |
|-----------------------|----------------|

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Reporting group description:

Placebo to QBW251 in all cohorts of part 1 in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).

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|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 2 Cohort 1: QBW251 |
|-----------------------|-------------------------|

---

Reporting group description:

Multiple doses of QBW25 150 mg qd in Healthy Volunteers. 14-day treatment period, follow-up study visits (Days 18, 22 and 29) and one End-of-Study evaluation (Day 36).

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 2 Cohort 2: QBW251 |
|-----------------------|-------------------------|

Reporting group description:

Multiple doses of QBW251 400 mg qd in Healthy Volunteers. 14-day treatment period, follow-up study visits (Days 18, 22 and 29) and one End-of-Study evaluation (Day 36).

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 2 Cohort 3: QBW251 |
|-----------------------|-------------------------|

Reporting group description:

Multiple doses of QBW251 750 mg qd in Healthy Volunteers. 14-day treatment period, follow-up study visits (Days 18, 22 and 29) and one End-of-Study evaluation (Day 36).

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 2 Cohort 4: QBW251 |
|-----------------------|-------------------------|

Reporting group description:

Multiple doses of QBW251 450 mg bid in Healthy Volunteers. 14-day treatment period, follow-up study visits (Days 18, 22 and 29) and one End-of-Study evaluation (Day 36).

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 2 Cohort 5: QBW251 |
|-----------------------|-------------------------|

Reporting group description:

Multiple doses of QBW251 750 mg bid in Healthy Volunteers. 14-day treatment period, follow-up study visits (Days 18, 22 and 29) and one End-of-Study evaluation (Day 36).

|                       |                |
|-----------------------|----------------|
| Reporting group title | Part 2 Placebo |
|-----------------------|----------------|

Reporting group description:

Placebo to QBW251 in all cohorts of part 2 in Healthy Volunteers. 14-day treatment period, follow-up study visits (Days 18, 22 and 29) and one End-of-Study evaluation (Day 36).

| Reporting group values                                | Part 1 Cohort 1:<br>QBW251 | Part 1 Cohort 2:<br>QBW251 | Part 1 Cohort 3:<br>QBW251 |
|---|----------------------------|----------------------------|----------------------------|
| Number of subjects                                    | 6                          | 6                          | 6                          |
| Age categorical<br>Units: Subjects                    |                            |                            |                            |
| In utero  | 0                          | 0                          | 0                          |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                          | 0                          | 0                          |
| Newborns (0-27 days)                                  | 0                          | 0                          | 0                          |
| Infants and toddlers (28 days-23<br>months)           | 0                          | 0                          | 0                          |
| Children (2-11 years)                                 | 0                          | 0                          | 0                          |
| Adolescents (12-17 years)                             | 0                          | 0                          | 0                          |
| Adults (18-64 years)                                  | 6                          | 6                          | 6                          |
| From 65-84 years                                      | 0                          | 0                          | 0                          |
| 85 years and over                                     | 0                          | 0                          | 0                          |
| Age Continuous<br>Units: Years                        |                            |                            |                            |
| arithmetic mean                                       | 36.3                       | 35                         | 43.5                       |
| standard deviation                                    | ± 8.69                     | ± 14.25                    | ± 3.39                     |
| Gender, Male/Female<br>Units: Subjects                |                            |                            |                            |
| Female  | 0                          | 0                          | 0                          |
| Male  | 6                          | 6                          | 6                          |
| Age Continuous   Part 2, HV (n=40)<br>Units: Years    |                            |                            |                            |
| arithmetic mean                                       | 0.9999                     | 0.9999                     | 0.9999                     |
| standard deviation                                    | ± 0.9999                   | ± 0.9999                   | ± 0.9999                   |
| Age Continuous   Part 3, CF patients                  |                            |                            |                            |

|                    |          |          |          |
|--------------------|----------|----------|----------|
| (n=49)             |          |          |          |
| Units: Years       |          |          |          |
| arithmetic mean    | 0.9999   | 0.9999   | 0.9999   |
| standard deviation | ± 0.9999 | ± 0.9999 | ± 0.9999 |

| <b>Reporting group values</b>                         | Part 1 Cohort 4:<br>QBW251 | Part 1 Cohort 5:<br>QBW251 | Part 1 Cohort 6:<br>QBW251 |
|---|----------------------------|----------------------------|----------------------------|
| Number of subjects                                    | 6                          | 6                          | 6                          |
| Age categorical                                       |                            |                            |                            |
| Units: Subjects                                       |                            |                            |                            |
| In utero  | 0                          | 0                          | 0                          |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                          | 0                          | 0                          |
| Newborns (0-27 days)                                  | 0                          | 0                          | 0                          |
| Infants and toddlers (28 days-23<br>months)           | 0                          | 0                          | 0                          |
| Children (2-11 years)                                 | 0                          | 0                          | 0                          |
| Adolescents (12-17 years)                             | 0                          | 0                          | 0                          |
| Adults (18-64 years)                                  | 6                          | 6                          | 6                          |
| From 65-84 years                                      | 0                          | 0                          | 0                          |
| 85 years and over                                     | 0                          | 0                          | 0                          |
| Age Continuous  |                            |                            |                            |
| Units: Years  |                            |                            |                            |
| arithmetic mean                                       | 33.3                       | 32.7                       | 44.2                       |
| standard deviation                                    | ± 9.61                     | ± 5.85                     | ± 8.23                     |
| Gender, Male/Female                                   |                            |                            |                            |
| Units: Subjects                                       |                            |                            |                            |
| Female  | 0                          | 0                          | 0                          |
| Male  | 6                          | 6                          | 6                          |
| Age Continuous   Part 2, HV (n=40)                    |                            |                            |                            |
| Units: Years  |                            |                            |                            |
| arithmetic mean                                       | 0.9999                     | 0.9999                     | 0.9999                     |
| standard deviation                                    | ± 0.9999                   | ± 0.9999                   | ± 0.9999                   |
| Age Continuous   Part 3, CF patients<br>(n=49)        |                            |                            |                            |
| Units: Years  |                            |                            |                            |
| arithmetic mean                                       | 0.9999                     | 0.9999                     | 0.9999                     |
| standard deviation                                    | ± 0.9999                   | ± 0.9999                   | ± 0.9999                   |

| <b>Reporting group values</b>                         | Part 1 Cohort 7:<br>QBW251 | Part 1 Cohort 8:<br>QBW251 | Part 1 Placebo |
|---|----------------------------|----------------------------|----------------|
| Number of subjects                                    | 6                          | 6                          | 16             |
| Age categorical                                       |                            |                            |                |
| Units: Subjects                                       |                            |                            |                |
| In utero  | 0                          | 0                          | 0              |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                          | 0                          | 0              |
| Newborns (0-27 days)                                  | 0                          | 0                          | 0              |
| Infants and toddlers (28 days-23<br>months)           | 0                          | 0                          | 0              |
| Children (2-11 years)                                 | 0                          | 0                          | 0              |
| Adolescents (12-17 years)                             | 0                          | 0                          | 0              |
| Adults (18-64 years)                                  | 6                          | 6                          | 16             |
| From 65-84 years                                      | 0                          | 0                          | 0              |

|                   |   |   |   |
|-------------------|---|---|---|
| 85 years and over | 0 | 0 | 0 |
|-------------------|---|---|---|

|  |                    |                    |                    |
|--|--------------------|--------------------|--------------------|
| Age Continuous<br>Units: Years<br>arithmetic mean<br>standard deviation                              | 28.2<br>± 9.28     | 33.2<br>± 9.47     | 30.3<br>± 9.18     |
| Gender, Male/Female<br>Units: Subjects   |                    |                    |                    |
| Female   | 0                  | 0                  | 0                  |
| Male   | 6                  | 6                  | 16                 |
| Age Continuous   Part 2, HV (n=40)<br>Units: Years<br>arithmetic mean<br>standard deviation          | 0.9999<br>± 0.9999 | 0.9999<br>± 0.9999 | 0.9999<br>± 0.9999 |
| Age Continuous   Part 3, CF patients (n=49)<br>Units: Years<br>arithmetic mean<br>standard deviation | 0.9999<br>± 0.9999 | 0.9999<br>± 0.9999 | 0.9999<br>± 0.9999 |

| <b>Reporting group values</b>   | Part 2 Cohort 1:<br>QBW251 | Part 2 Cohort 2:<br>QBW251 | Part 2 Cohort 3:<br>QBW251 |
|---|----------------------------|----------------------------|----------------------------|
| Number of subjects  | 6                          | 6                          | 6                          |
| Age categorical<br>Units: Subjects  |                            |                            |                            |
| In utero  | 0                          | 0                          | 0                          |
| Preterm newborn infants (gestational age < 37 wks)  | 0                          | 0                          | 0                          |
| Newborns (0-27 days)  | 0                          | 0                          | 0                          |
| Infants and toddlers (28 days-23 months)  | 0                          | 0                          | 0                          |
| Children (2-11 years)   | 0                          | 0                          | 0                          |
| Adolescents (12-17 years)   | 0                          | 0                          | 0                          |
| Adults (18-64 years)  | 6                          | 6                          | 6                          |
| From 65-84 years  | 0                          | 0                          | 0                          |
| 85 years and over   | 0                          | 0                          | 0                          |
| Age Continuous<br>Units: Years<br>arithmetic mean<br>standard deviation                     | 0.9999<br>± 0.9999         | 0.9999<br>± 0.9999         | 0.9999<br>± 0.9999         |
| Gender, Male/Female<br>Units: Subjects  |                            |                            |                            |
| Female  | 0                          | 0                          | 0                          |
| Male  | 6                          | 6                          | 6                          |
| Age Continuous   Part 2, HV (n=40)<br>Units: Years<br>arithmetic mean<br>standard deviation | 30.3<br>± 5.13             | 30.5<br>± 5.89             | 29.2<br>± 11.62            |
| Age Continuous   Part 3, CF patients (n=49)<br>Units: Years<br>arithmetic mean              | 0.9999                     | 0.9999                     | 0.9999                     |

|                    |          |          |          |
|--------------------|----------|----------|----------|
| standard deviation | ± 0.9999 | ± 0.9999 | ± 0.9999 |
|--------------------|----------|----------|----------|

| <b>Reporting group values</b>                                  | Part 2 Cohort 4:<br>QBW251 | Part 2 Cohort 5:<br>QBW251 | Part 2 Placebo |
|--|----------------------------|----------------------------|----------------|
| Number of subjects   | 6                          | 6                          | 10             |
| Age categorical<br>Units: Subjects                             |                            |                            |                |
| In utero   | 0                          | 0                          | 0              |
| Preterm newborn infants<br>(gestational age < 37 wks)          | 0                          | 0                          | 0              |
| Newborns (0-27 days)   | 0                          | 0                          | 0              |
| Infants and toddlers (28 days-23<br>months)                    | 0                          | 0                          | 0              |
| Children (2-11 years)  | 0                          | 0                          | 0              |
| Adolescents (12-17 years)                                      | 0                          | 0                          | 0              |
| Adults (18-64 years)   | 6                          | 6                          | 10             |
| From 65-84 years   | 0                          | 0                          | 0              |
| 85 years and over  | 0                          | 0                          | 0              |
| Age Continuous<br>Units: Years                                 |                            |                            |                |
| arithmetic mean  | 0.9999                     | 0.9999                     | 0.9999         |
| standard deviation   | ± 0.9999                   | ± 0.9999                   | ± 0.9999       |
| Gender, Male/Female<br>Units: Subjects                         |                            |                            |                |
| Female   | 0                          | 0                          | 0              |
| Male   | 6                          | 6                          | 10             |
| Age Continuous   Part 2, HV (n=40)<br>Units: Years             |                            |                            |                |
| arithmetic mean  | 31.7                       | 27.8                       | 29             |
| standard deviation   | ± 13.22                    | ± 5                        | ± 6.22         |
| Age Continuous   Part 3, CF patients<br>(n=49)<br>Units: Years |                            |                            |                |
| arithmetic mean  | 0.9999                     | 0.9999                     | 0.9999         |
| standard deviation   | ± 0.9999                   | ± 0.9999                   | ± 0.9999       |

| <b>Reporting group values</b>                         | Total |  |  |
|---|-------|--|--|
| Number of subjects                                    | 104   |  |  |
| Age categorical<br>Units: Subjects                    |       |  |  |
| In utero  | 0     |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0     |  |  |
| Newborns (0-27 days)                                  | 0     |  |  |
| Infants and toddlers (28 days-23<br>months)           | 0     |  |  |
| Children (2-11 years)                                 | 0     |  |  |
| Adolescents (12-17 years)                             | 0     |  |  |
| Adults (18-64 years)                                  | 104   |  |  |
| From 65-84 years                                      | 0     |  |  |
| 85 years and over                                     | 0     |  |  |

|  |     |  |  |
|--|-----|--|--|
| Age Continuous<br>Units: Years<br>arithmetic mean<br>standard deviation                              | -   |  |  |
| Gender, Male/Female<br>Units: Subjects   |     |  |  |
| Female   | 0   |  |  |
| Male   | 104 |  |  |
| Age Continuous   Part 2, HV (n=40)<br>Units: Years<br>arithmetic mean<br>standard deviation          | -   |  |  |
| Age Continuous   Part 3, CF patients (n=49)<br>Units: Years<br>arithmetic mean<br>standard deviation | -   |  |  |

## End points

### End points reporting groups

|   |                         |
|---|-------------------------|
| Reporting group title   | Part 1 Cohort 1: QBW251 |
| Reporting group description:<br>Single dose of QBW251 10 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).                |                         |
| Reporting group title   | Part 1 Cohort 2: QBW251 |
| Reporting group description:<br>Single dose of QBW251 25 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).                |                         |
| Reporting group title   | Part 1 Cohort 3: QBW251 |
| Reporting group description:<br>Single dose of QBW251 75 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).                |                         |
| Reporting group title   | Part 1 Cohort 4: QBW251 |
| Reporting group description:<br>Single dose of QBW251 150 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).               |                         |
| Reporting group title   | Part 1 Cohort 5: QBW251 |
| Reporting group description:<br>Single dose of QBW251 300 mg in healthy volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).               |                         |
| Reporting group title   | Part 1 Cohort 6: QBW251 |
| Reporting group description:<br>Single dose of QBW251 500 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).               |                         |
| Reporting group title   | Part 1 Cohort 7: QBW251 |
| Reporting group description:<br>Single dose of QBW251 750 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).               |                         |
| Reporting group title   | Part 1 Cohort 8: QBW251 |
| Reporting group description:<br>Single dose of QBW251 1000 mg in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15).              |                         |
| Reporting group title   | Part 1 Placebo          |
| Reporting group description:<br>Placebo to QBW251 in all cohorts of part 1 in Healthy Volunteers. Each treatment period was comprised of a baseline period (Day -1), an inpatient dosing period (Days 1 to 3), three follow-up visits (Days 4, 5, and 8), and one end-of-treatment-period evaluation performed 14 days after the dose of study drug (Day 15). |                         |
| Reporting group title   | Part 2 Cohort 1: QBW251 |

Reporting group description:

Multiple doses of QBW25 150 mg qd in Healthy Volunteers. 14-day treatment period, follow-up study visits (Days 18, 22 and 29) and one End-of-Study evaluation (Day 36).

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 2 Cohort 2: QBW251 |
|-----------------------|-------------------------|

Reporting group description:

Multiple doses of QBW251 400 mg qd in Healthy Volunteers. 14-day treatment period, follow-up study visits (Days 18, 22 and 29) and one End-of-Study evaluation (Day 36).

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 2 Cohort 3: QBW251 |
|-----------------------|-------------------------|

Reporting group description:

Multiple doses of QBW251 750 mg qd in Healthy Volunteers. 14-day treatment period, follow-up study visits (Days 18, 22 and 29) and one End-of-Study evaluation (Day 36).

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 2 Cohort 4: QBW251 |
|-----------------------|-------------------------|

Reporting group description:

Multiple doses of QBW251 450 mg bid in Healthy Volunteers. 14-day treatment period, follow-up study visits (Days 18, 22 and 29) and one End-of-Study evaluation (Day 36).

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 2 Cohort 5: QBW251 |
|-----------------------|-------------------------|

Reporting group description:

Multiple doses of QBW251 750 mg bid in Healthy Volunteers. 14-day treatment period, follow-up study visits (Days 18, 22 and 29) and one End-of-Study evaluation (Day 36).

|                       |                |
|-----------------------|----------------|
| Reporting group title | Part 2 Placebo |
|-----------------------|----------------|

Reporting group description:

Placebo to QBW251 in all cohorts of part 2 in Healthy Volunteers. 14-day treatment period, follow-up study visits (Days 18, 22 and 29) and one End-of-Study evaluation (Day 36).

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 3 Cohort 1: QBW251 |
|-----------------------|-------------------------|

Reporting group description:

150 mg b.i.d. Multiple doses. Patients having a class III, IV, V, or VI mutation on one allele and any other CFTR mutation on the other allele in patients. treatment period (Day 1 to Day 14) with study visits on Days 1, 4, 7 and 14 with follow-up visits on Days 15, 28 and 42.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 3 Cohort 2: QBW251 |
|-----------------------|-------------------------|

Reporting group description:

450 mg b.i.d. Multiple doses. Patients having a class III, IV, V, or VI mutation on one allele and any other CFTR mutation on the other allele in patients. treatment period (Day 1 to Day 14) with study visits on Days 1, 4, 7 and 14 with follow-up visits on Days 15, 28 and 42.

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 3 Cohort 3: QBW251 |
|-----------------------|-------------------------|

Reporting group description:

450 mg b.i.d. Multiple doses. Patients who are homozygous for the F508del mutation in patients. treatment period (Day 1 to Day 14) with study visits on Days 1, 4, 7 and 14 with follow-up visits on Days 15, 28 and 42.

|                       |                |
|-----------------------|----------------|
| Reporting group title | Part 3 Placebo |
|-----------------------|----------------|

Reporting group description:

Placebo to QBW251 in all cohorts of part 3 in patients. treatment period (Day 1 to Day 14) with study visits on Days 1, 4, 7 and 14 with follow-up visits on Days 15, 28 and 42.

|                            |                     |
|----------------------------|---------------------|
| Subject analysis set title | Part 1 cohort 6 FED |
|----------------------------|---------------------|

|                           |               |
|---------------------------|---------------|
| Subject analysis set type | Full analysis |
|---------------------------|---------------|

Subject analysis set description:

part 1 cohort 6 had testing done in fasting and fed stat....this data represents the Fed state

---

**Primary: Part 1 and 2: Number of participants (Healthy Volunteers) with reported adverse events receiving QBW251**

---

|                 |  |
|-----------------|--|
| End point title | Part 1 and 2: Number of participants (Healthy Volunteers) with reported adverse events receiving QBW251 <sup>[1]</sup> |
|-----------------|--|

End point description:

All adverse events (in healthy volunteers) reported. There were no reporting of serious adverse events or death in part 1 and 2. No statistical analysis was planned for this primary outcome

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

End point timeframe:

Day 1 to Day 36

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: All end points are verified

| <b>End point values</b>     | Part 1 Cohort 1: QBW251 | Part 1 Cohort 2: QBW251 | Part 1 Cohort 3: QBW251 | Part 1 Cohort 4: QBW251 |
|-----------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type          | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed | 6                       | 6                       | 6                       | 6                       |
| Units: Participants         | 1                       | 0                       | 0                       | 0                       |

| <b>End point values</b>     | Part 1 Cohort 5: QBW251 | Part 1 Cohort 6: QBW251 | Part 1 Cohort 7: QBW251 | Part 1 Cohort 8: QBW251 |
|-----------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type          | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed | 6                       | 6                       | 6                       | 6                       |
| Units: Participants         | 0                       | 0                       | 0                       | 0                       |

| <b>End point values</b>     | Part 1 Placebo  | Part 2 Cohort 1: QBW251 | Part 2 Cohort 2: QBW251 | Part 2 Cohort 3: QBW251 |
|-----------------------------|-----------------|-------------------------|-------------------------|-------------------------|
| Subject group type          | Reporting group | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed | 16              | 6                       | 6                       | 6                       |
| Units: Participants         | 2               | 0                       | 1                       | 0                       |

| <b>End point values</b>     | Part 2 Cohort 4: QBW251 | Part 2 Cohort 5: QBW251 | Part 2 Placebo  | Part 1 cohort 6 FED  |
|-----------------------------|-------------------------|-------------------------|-----------------|----------------------|
| Subject group type          | Reporting group         | Reporting group         | Reporting group | Subject analysis set |
| Number of subjects analysed | 6                       | 6                       | 10              | 5                    |
| Units: Participants         | 0                       | 1                       | 1               | 0                    |

## Statistical analyses

No statistical analyses for this end point

### Primary: Part 3: Change in Lung Clearance Index (LCI) from baseline to day 15

|                 |   |
|-----------------|---|
| End point title | Part 3: Change in Lung Clearance Index (LCI) from baseline to day 15 <sup>[2]</sup> |
|-----------------|---|

End point description:

Change in Lung Clearance Index (LCI) will be conducted according to international standards in cystic fibrosis patients. Lung clearance index (LCI) is a measure of ventilation inhomogeneity that is derived from a multiple-breath washout test, A reduction in mean change from baseline for LCI2.5 indicates improvement. No statistical analysis was planned for this primary outcome

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

---

End point timeframe:

Baseline and Day 15

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Notes:

[2] - 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: All end points are verified

---

### Statistical analyses

---

No statistical analyses for this end point

---

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#### **Primary: Part 3: Number of participants (Patients) with reported adverse events receiving QBW251**

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|                 |  |
|-----------------|--|
| End point title | Part 3: Number of participants (Patients) with reported adverse events receiving QBW251 <sup>[3]</sup> |
|-----------------|--|

---

End point description:

All adverse events and serious adverse events (in patients) reported. There were no reporting of death in part 3. No statistical analysis was planned for this primary outcome

---

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

---

End point timeframe:

Day 1 to Day 56

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Notes:

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

Justification: All end points are verified

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### Statistical analyses

---

No statistical analyses for this end point

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#### **Secondary: Part 3: Change in Forced Expiratory Volume in 1 second (FEV1) at day 15**

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|                 |   |
|-----------------|---|
| End point title | Part 3: Change in Forced Expiratory Volume in 1 second (FEV1) at day 15 |
|-----------------|---|

---

End point description:

Forced Expiratory Volume in 1 second (FEV1) will be measured via spirometer according to international standards. Forced Expiratory Volume in 1 second (FEV1) is the amount of air which can be forcibly exhaled from the lungs in the first second of a forced exhalation

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

---

End point timeframe:

Baseline and Day 15

---

## Statistical analyses

---

No statistical analyses for this end point

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### Secondary: Part 3: Change in Cystic Fibrosis Questionnaire-Revised reported outcomes

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|                 |   |
|-----------------|---|
| End point title | Part 3: Change in Cystic Fibrosis Questionnaire-Revised reported outcomes |
|-----------------|---|

---

End point description:

Change in Cystic Fibrosis Questionnaire data will be obtained from patient reported outcomes (CFQ-R PRO). Respiratory Domain, cores range from 0 to 100, with higher scores indicating better health, a change of 4 is considered clinically relevant

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

---

End point timeframe:

Baseline and Day 14

---

## Statistical analyses

---

No statistical analyses for this end point

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### Secondary: Part 1: AUC0-t in healthy volunteers

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|                 |   |
|-----------------|---|
| End point title | Part 1: AUC0-t in healthy volunteers <sup>[4]</sup> |
|-----------------|---|

---

End point description:

Pharmacokinetics of QBW251 in plasma: area under the plasma concentration versus time curve from time zero to time of last measurable concentration (AUC0-t). In part one of the study a single dose was administered and samples were collected up to 5 days. As a result the AUC0-t goes from Day 1 to Day 5 (for some lower doses QBW251 concentrations were not measured up to Day 5 as the concentrations were low due to the low dose administered)

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

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End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose at Day 1; 24, 48, 72 and 96 hr post dose (i.e. Days 2-5)

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Notes:

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

| <b>End point values</b>              | Part 1 Cohort 1: QBW251 | Part 1 Cohort 2: QBW251 | Part 1 Cohort 3: QBW251 | Part 1 Cohort 4: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: hr*ng/mL                      |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 52.5 (± 28.1)           | 73.7 (± 51.8)           | 692 (± 389)             | 1650 (± 907)            |

| <b>End point values</b>              | Part 1 Cohort 5: QBW251 | Part 1 Cohort 6: QBW251 | Part 1 Cohort 7: QBW251 | Part 1 Cohort 8: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: hr*ng/mL                      |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 5470 (± 1070)           | 9450 (± 1740)           | 20200 (± 11500)         | 35900 (± 9100)          |

| <b>End point values</b>              | Part 1 Placebo    |  |  |  |
|--------------------------------------|-------------------|--|--|--|
| Subject group type                   | Reporting group   |  |  |  |
| Number of subjects analysed          | 16                |  |  |  |
| Units: hr*ng/mL                      |                   |  |  |  |
| arithmetic mean (standard deviation) | 0.9999 (± 0.9999) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 1: Maximum concentration (Cmax) in healthy volunteers

|                 |   |
|-----------------|---|
| End point title | Part 1: Maximum concentration (Cmax) in healthy volunteers <sup>[5]</sup> |
|-----------------|---|

End point description:

Pharmacokinetics of QBW251 in plasma: observed maximum plasma concentration following administration of QBW251. In this analysis Cmax will be reported using blood samples taken on Days 1-5 are from healthy volunteers

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

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose at Day 1; 24, 48, 72 and 96 hr post dose (i.e. Days 1 - 5)

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.  
Justification: All end points are verified

| <b>End point values</b>              | Part 1 Cohort 1: QBW251 | Part 1 Cohort 2: QBW251 | Part 1 Cohort 3: QBW251 | Part 1 Cohort 4: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: ug/L                          |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 21.1 (± 11.9)           | 24.7 (± 15.9)           | 186 (± 82.3)            | 459 (± 267)             |

| <b>End point values</b>              | Part 1 Cohort 5: QBW251 | Part 1 Cohort 6: QBW251 | Part 1 Cohort 7: QBW251 | Part 1 Cohort 8: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: ug/L                          |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 1110 (± 330)            | 1910 (± 413)            | 2680 (± 1000)           | 4540 (± 930)            |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part 1: Time to maximum concentration (Tmax) in healthy volunteers

|                 |   |
|-----------------|---|
| End point title | Part 1: Time to maximum concentration (Tmax) in healthy volunteers <sup>[6]</sup> |
|-----------------|---|

End point description:

Pharmacokinetics of QBW251 in plasma: time to reach the maximum concentration after administration of QBW251. In this analysis Tmax will be reported using blood samples taken on Days 1 - 5 from healthy volunteers. In this part of the study a single dose was administered and samples were collected up to 5 days. As a result the Tmax is one value as the concentration-time curve goes to Day 5 (for some lower doses QBW251 concentrations were not measured up to Day 5 as the concentrations were low due to the low dose administered).

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

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose at Day 1; 24, 48, 72 and 96 hr post dose (i.e. Days 1 - 5)

Notes:

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

Justification: All end points are verified

| <b>End point values</b>              | Part 1 Cohort 1: QBW251 | Part 1 Cohort 2: QBW251 | Part 1 Cohort 3: QBW251 | Part 1 Cohort 4: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: hr                            |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 0.756 (± 0.268)         | 1.25 (± 0.612)          | 1.33 (± 0.516)          | 1.5 (± 0.548)           |

| <b>End point values</b> | Part 1 Cohort 5: QBW251 | Part 1 Cohort 6: QBW251 | Part 1 Cohort 7: QBW251 | Part 1 Cohort 8: QBW251 |
|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
|-------------------------|-------------------------|-------------------------|-------------------------|-------------------------|

|                                      |                 |                 |                 |                 |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed          | 6               | 6               | 6               | 6               |
| Units: hr                            |                 |                 |                 |                 |
| arithmetic mean (standard deviation) | 1.5 (± 0.837)   | 2.17 (± 1.17)   | 2.52 (± 0.85)   | 1.83 (± 0.753)  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part 1: T1/2 in healthy volunteers

End point title | Part 1: T1/2 in healthy volunteers<sup>[7]</sup>

End point description:

Pharmacokinetics of QBW251 in plasma: terminal elimination half-life. In this analysis T1/2 will be reported using blood samples taken on Days 1 - 5 from healthy volunteers. In part one of the study a single dose was administered and samples were collected up to 5 days. As a result the T1/2 goes from Day 1 to Day 5 (for some lower doses QBW251 concentrations were not measured up to Day 5 as the concentrations were low due to the low dose administered).

End point type | Secondary

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose at Day 1; 24, 48, 72 and 96 hr post dose (i.e. Days 1 - 5)

Notes:

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

Justification: All end points are verified

| End point values                     | Part 1 Cohort 1: QBW251 | Part 1 Cohort 2: QBW251 | Part 1 Cohort 3: QBW251 | Part 1 Cohort 4: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: hr                            |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 0.9999 (± 0.9999)       | 0.9999 (± 0.9999)       | 10.3 (± 4.24)           | 10.1 (± 3.35)           |

| End point values                     | Part 1 Cohort 5: QBW251 | Part 1 Cohort 6: QBW251 | Part 1 Cohort 7: QBW251 | Part 1 Cohort 8: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: hr                            |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 12 (± 2.26)             | 12.7 (± 1.99)           | 12.8 (± 3.85)           | 10.7 (± 2.19)           |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part 1: AUCinf in healthy volunteers

End point title | Part 1: AUCinf in healthy volunteers<sup>[8]</sup>

End point description:

Pharmacokinetics of QBW251 in plasma: area under the plasma concentration time curve from time zero to infinity. In this analysis AUCinf will be reported using blood samples taken on Days 1 - 5 from healthy volunteers. In part one of the study a single dose was administered and samples were collected up to 5 days. As a result the AUCinf goes from Day 1 to Day 5 (for some lower doses QBW251 concentrations were not measured up to Day 5 as the concentrations were low due to the low dose administered)

End point type Secondary

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose at Day 1; 24, 48, 72 and 96 hr post dose (i.e. Days 1 - 5)

Notes:

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

Justification: All end points are verified

| End point values                     | Part 1 Cohort 1: QBW251 | Part 1 Cohort 2: QBW251 | Part 1 Cohort 3: QBW251 | Part 1 Cohort 4: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: hr*ng/mL                      |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 0.9999 (± 0.9999)       | 0.9999 (± 0.9999)       | 731 (± 387)             | 1680 (± 903)            |

| End point values                     | Part 1 Cohort 5: QBW251 | Part 1 Cohort 6: QBW251 | Part 1 Cohort 7: QBW251 | Part 1 Cohort 8: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: hr*ng/mL                      |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 5510 (± 1080)           | 9480 (± 1740)           | 20300 (± 11500)         | 36000 (± 9120)          |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part 1: CL/F in healthy volunteers

End point title Part 1: CL/F in healthy volunteers<sup>[9]</sup>

End point description:

Pharmacokinetics of QBW251 in plasma: apparent systemic clearance from plasma following extravascular administration. In this analysis CL/F will be reported using blood samples taken on Days 1 - 5 from healthy volunteers. In part one of the study a single dose was administered and samples were collected up to 5 days. As a result the CL/F goes from Day 1 to Day 5 (for some lower doses QBW251 concentrations were not measured up to Day 5 as the concentrations were low due to the low dose administered)

End point type Secondary

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose at Day 1; 24, 48, 72 and 96 hr post dose (i.e. Days 1 - 5)

Notes:

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

Justification: All end points are verified

| <b>End point values</b>              | Part 1 Cohort 1: QBW251 | Part 1 Cohort 2: QBW251 | Part 1 Cohort 3: QBW251 | Part 1 Cohort 4: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: L/hr                          |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 0.9999 ( $\pm$ 0.9999)  | 0.9999 ( $\pm$ 0.9999)  | 123 ( $\pm$ 49)         | 114 ( $\pm$ 63.9)       |

| <b>End point values</b>              | Part 1 Cohort 5: QBW251 | Part 1 Cohort 6: QBW251 | Part 1 Cohort 7: QBW251 | Part 1 Cohort 8: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: L/hr                          |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 56.2 ( $\pm$ 11)        | 54.5 ( $\pm$ 11.9)      | 45.9 ( $\pm$ 19.9)      | 29.7 ( $\pm$ 9)         |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Part 1: Vz/F in healthy volunteers

|                 |  |
|-----------------|--|
| End point title | Part 1: Vz/F in healthy volunteers <sup>[10]</sup> |
|-----------------|--|

End point description:

Pharmacokinetics of QBW251 in plasma: apparent volume of distribution during the terminal elimination phase following extravascular administration. In this analysis Vz/F will be reported using blood samples taken on Days 1 - 5 from healthy volunteers.

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

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose at Day 1; 24, 48, 72 and 96 hr post dose (i.e. Days 1 - 5)

Notes:

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

Justification: All end points are verified

| <b>End point values</b>              | Part 1 Cohort 1: QBW251 | Part 1 Cohort 2: QBW251 | Part 1 Cohort 3: QBW251 | Part 1 Cohort 4: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: Liters                        |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 0.9999 ( $\pm$ 0.9999)  | 0.9999 ( $\pm$ 0.9999)  | 1700 ( $\pm$ 772)       | 1490 ( $\pm$ 622)       |

| <b>End point values</b>     | Part 1 Cohort 5: QBW251 | Part 1 Cohort 6: QBW251 | Part 1 Cohort 7: QBW251 | Part 1 Cohort 8: QBW251 |
|-----------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type          | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed | 6                       | 6                       | 6                       | 6                       |

|                                      |             |             |             |             |
|--------------------------------------|-------------|-------------|-------------|-------------|
| Units: Liters                        |             |             |             |             |
| arithmetic mean (standard deviation) | 957 (± 151) | 995 (± 235) | 827 (± 375) | 447 (± 112) |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part 2: Ae0-t in healthy volunteers

|                 |   |
|-----------------|---|
| End point title | Part 2: Ae0-t in healthy volunteers <sup>[11]</sup> |
|-----------------|---|

End point description:

Pharmacokinetics of QBW251 in urine: amount of drug excreted in urine from time zero until last measurable concentration. In this analysis Ae0-t will be reported using urine samples taken on Day 1 from healthy volunteers.

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

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose at Day 1; 24, 48, 72 and 96 hr post dose Day 1

Notes:

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

Justification: All end points are verified

| End point values                     | Part 2 Cohort 1: QBW251 | Part 2 Cohort 2: QBW251 | Part 2 Cohort 3: QBW251 | Part 2 Cohort 4: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 5                       |
| Units: L/hr                          |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 2.36 (± 1.84)           | 2.2 (± 1.26)            | 1.21 (± 0.697)          | 0.419 (± 0.271)         |

| End point values                     | Part 2 Cohort 5: QBW251 | Part 2 Placebo    |  |  |
|--------------------------------------|-------------------------|-------------------|--|--|
| Subject group type                   | Reporting group         | Reporting group   |  |  |
| Number of subjects analysed          | 5                       | 10                |  |  |
| Units: L/hr                          |                         |                   |  |  |
| arithmetic mean (standard deviation) | 0.14 (± 0.0936)         | 0.9999 (± 0.9999) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part 2: CLr in healthy volunteers

|                 |   |
|-----------------|---|
| End point title | Part 2: CLr in healthy volunteers <sup>[12]</sup> |
|-----------------|---|

End point description:

Pharmacokinetics of QBW251 in urine: renal clearance following drug administration. In this analysis CLr will be reported using urine samples taken on Day 1 from healthy volunteers.

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

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose at Day 1; 24, 48, 72 and 96 hr post dose Day 1; Day 14 was calculated as urine was only collected up to 12 hours on Day 1 thus CLr cannot be calculated.

Notes:

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

Justification: All end points are verified

| End point values                     | Part 2 Cohort 1: QBW251 | Part 2 Cohort 2: QBW251 | Part 2 Cohort 3: QBW251 | Part 2 Cohort 4: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: L/hr                          |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 2.36 (± 1.84)           | 2.2 (± 1.26)            | 1.21 (± 0.697)          | 0.419 (± 0.271)         |

| End point values                     | Part 2 Cohort 5: QBW251 |  |  |  |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type                   | Reporting group         |  |  |  |
| Number of subjects analysed          | 6                       |  |  |  |
| Units: L/hr                          |                         |  |  |  |
| arithmetic mean (standard deviation) | 0.14 (± 0.0936)         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: AUCtau in healthy volunteers

|                 |  |
|-----------------|--|
| End point title | Part 2: AUCtau in healthy volunteers <sup>[13]</sup> |
|-----------------|--|

End point description:

Pharmacokinetics of QBW251 in plasma after multiple doses: the area under the plasma concentration-time curve from time zero to end of the dosing interval tau. In this analysis AUCtau will be reported. Samples taken on Days 1 and 14 from healthy volunteers

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

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose at Day 1; 24, 48, 72 and 96 hr post dose Day 1 and 14; ( If B ID dosing, 12 hours samples will be pre-dosed)

Notes:

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

Justification: All end points are verified

| <b>End point values</b>              | Part 2 Cohort 1: QBW251 | Part 2 Cohort 2: QBW251 | Part 2 Cohort 3: QBW251 | Part 2 Cohort 4: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: hr*ng/mL                      |                         |                         |                         |                         |
| arithmetic mean (standard deviation) |                         |                         |                         |                         |
| Day1                                 | 1800 (± 794)            | 6170 (± 1250)           | 16100 (± 8170)          | 7160 (± 1960)           |
| Day 14                               | 2060 (± 708)            | 7620 (± 1470)           | 28300 (± 5570)          | 12100 (± 4930)          |

| <b>End point values</b>              | Part 2 Cohort 5: QBW251 |  |  |  |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type                   | Reporting group         |  |  |  |
| Number of subjects analysed          | 6                       |  |  |  |
| Units: hr*ng/mL                      |                         |  |  |  |
| arithmetic mean (standard deviation) |                         |  |  |  |
| Day1                                 | 18800 (± 6360)          |  |  |  |
| Day 14                               | 80300 (± 56300)         |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Maximum concentration (Cmax) in healthy volunteers

|                 |   |
|-----------------|---|
| End point title | Part 2: Maximum concentration (Cmax) in healthy |
|-----------------|---|

End point description:

Pharmacokinetics of QBW251 in plasma after multiple doses: observed maximum plasma concentration following QBW251 at steady state. In this analysis Cmax will be reported using blood samples taken on Days 1 and 14 from healthy volunteers.

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

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4 , 8 hr post-dose at Day 1; 24, 48, 72 and 96 hr post dose Day 1 and 14; ( If B ID dosing, 12 hours samples will be pre-dosed)

Notes:

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

Justification: All end points are verified

| <b>End point values</b>              | Part 2 Cohort 1: QBW251 | Part 2 Cohort 2: QBW251 | Part 2 Cohort 3: QBW251 | Part 2 Cohort 4: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: ug/L                          |                         |                         |                         |                         |
| arithmetic mean (standard deviation) |                         |                         |                         |                         |
| Day 1                                | 541 (± 338)             | 1650 (± 343)            | 2790 (± 1040)           | 1650 (± 188)            |
| Day 14                               | 430 (± 145)             | 1500 (± 442)            | 3840 (± 868)            | 2190 (± 769)            |

|                                      |                         |  |  |  |
|--------------------------------------|-------------------------|--|--|--|
| <b>End point values</b>              | Part 2 Cohort 5: QBW251 |  |  |  |
| Subject group type                   | Reporting group         |  |  |  |
| Number of subjects analysed          | 6                       |  |  |  |
| Units: ug/L                          |                         |  |  |  |
| arithmetic mean (standard deviation) |                         |  |  |  |
| Day 1                                | 3720 (± 1530)           |  |  |  |
| Day 14                               | 9420 (± 4330)           |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: Time to maximum concentration (Tmax) in healthy volunteers

|                 |  |
|-----------------|--|
| End point title | Part 2: Time to maximum concentration (Tmax) in healthy volunteers <sup>[15]</sup> |
|-----------------|--|

End point description:

Pharmacokinetics of QBW251 in plasma after multiple doses: time to reach the maximum concentration after administration of QBW251. In this analysis Tmax will be reported using blood samples taken on Days 1 and 14 from healthy volunteers.

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

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose at Day 1; 24, 48, 72 and 96 hr post dose Day 1 and 14; ( If B ID dosing, 12 hours samples will be pre-dosed)

Notes:

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

Justification: All end points are verified

|                                      |                         |                         |                         |                         |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| <b>End point values</b>              | Part 2 Cohort 1: QBW251 | Part 2 Cohort 2: QBW251 | Part 2 Cohort 3: QBW251 | Part 2 Cohort 4: QBW251 |
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: hr                            |                         |                         |                         |                         |
| arithmetic mean (standard deviation) |                         |                         |                         |                         |
| Day 1                                | 1.67 (± 0.816)          | 1.17 (± 0.408)          | 2.33 (± 1.21)           | 2.68 (± 0.813)          |
| Day 2                                | 2.17 (± 1.17)           | 2.17 (± 0.408)          | 2.33 (± 1.03)           | 3.25 (± 1.41)           |

|                                      |                         |  |  |  |
|--------------------------------------|-------------------------|--|--|--|
| <b>End point values</b>              | Part 2 Cohort 5: QBW251 |  |  |  |
| Subject group type                   | Reporting group         |  |  |  |
| Number of subjects analysed          | 6                       |  |  |  |
| Units: hr                            |                         |  |  |  |
| arithmetic mean (standard deviation) |                         |  |  |  |
| Day 1                                | 3.67 (± 0.516)          |  |  |  |

|       |                    |  |  |  |
|-------|--------------------|--|--|--|
| Day 2 | 3.8 ( $\pm$ 0.447) |  |  |  |
|-------|--------------------|--|--|--|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Part 2: AUC0-t

|                 |                                |
|-----------------|--------------------------------|
| End point title | Part 2: AUC0-t <sup>[16]</sup> |
|-----------------|--------------------------------|

End point description:

Pharmacokinetics of QBW251 in plasma: area under the plasma concentration versus time curve from time zero to time of last measurable concentration. In this analysis AUC0-t will be reported using blood samples taken on Day 14 are from healthy volunteers.

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

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose at Day 1; 24, 48, 72 and 96 hr post dose Day 14; ( If B ID dosing, 12 hours samples will be pre-dosed)

Notes:

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

Justification: All end points are verified

| End point values                     | Part 2 Cohort 1: QBW251 | Part 2 Cohort 2: QBW251 | Part 2 Cohort 3: QBW251 | Part 2 Cohort 4: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: hr*ng/mL                      |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 2060 ( $\pm$ 708)       | 7620 ( $\pm$ 1470)      | 28300 ( $\pm$ 5570)     | 12100 ( $\pm$ 4930)     |

| End point values                     | Part 2 Cohort 5: QBW251 | Part 2 Placebo         |  |  |
|--------------------------------------|-------------------------|------------------------|--|--|
| Subject group type                   | Reporting group         | Reporting group        |  |  |
| Number of subjects analysed          | 5                       | 10                     |  |  |
| Units: hr*ng/mL                      |                         |                        |  |  |
| arithmetic mean (standard deviation) | 80300 ( $\pm$ 56300)    | 0.9999 ( $\pm$ 0.9999) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Part 2: Cav in healthy volunteers

|                 |   |
|-----------------|---|
| End point title | Part 2: Cav in healthy volunteers <sup>[17]</sup> |
|-----------------|---|

End point description:

The average drug concentration in plasma during multiple dosing. In this analysis Cav will be reported using blood samples taken on Days 1 and 14 are from healthy volunteers.

End point type Secondary

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose at Day 1; 24, 48, 72 and 96 hr post dose Day 1 and 14; ( If B ID dosing, 12 hours samples will be pre-dosed)

Notes:

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

Justification: All end points are verified

| End point values                     | Part 2 Cohort 1: QBW251 | Part 2 Cohort 2: QBW251 | Part 2 Cohort 3: QBW251 | Part 2 Cohort 4: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: ug/L                          |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 85.8 (± 29.5)           | 318 (± 61.1)            | 1180 (± 232)            | 0.9999 (± 0.9999)       |

| End point values                     | Part 2 Cohort 5: QBW251 |  |  |  |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type                   | Reporting group         |  |  |  |
| Number of subjects analysed          | 6                       |  |  |  |
| Units: ug/L                          |                         |  |  |  |
| arithmetic mean (standard deviation) | 0.9999 (± 0.9999)       |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Part 2: CL/F in healthy volunteers

End point title Part 2: CL/F in healthy volunteers<sup>[18]</sup>

End point description:

apparent systemic clearance from plasma following extravascular administration. In this analysis CL/F will be reported using blood samples taken on Day 14 from healthy volunteers.

End point type Secondary

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose at Day 1; 24, 48, 72 and 96 hr post dose Day 14; ( If B ID dosing, 12 hours samples will be pre-dosed)

Notes:

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

Justification: All end points are verified

| <b>End point values</b>              | Part 2 Cohort 1: QBW251 | Part 2 Cohort 2: QBW251 | Part 2 Cohort 3: QBW251 | Part 2 Cohort 4: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: L/hr                          |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 80.8 (± 29.7)           | 54 (± 9.4)              | 27.5 (± 5.98)           | 0.9999 (± 0.9999)       |

| <b>End point values</b>              | Part 2 Cohort 5: QBW251 |  |  |  |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type                   | Reporting group         |  |  |  |
| Number of subjects analysed          | 6                       |  |  |  |
| Units: L/hr                          |                         |  |  |  |
| arithmetic mean (standard deviation) | 0.9999 (± 0.9999)       |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Part 2: Vz/F in healthy volunteers

|                 |  |
|-----------------|--|
| End point title | Part 2: Vz/F in healthy volunteers <sup>[19]</sup> |
|-----------------|--|

End point description:

Apparent volume of distribution during the terminal elimination phase following extravascular administration. In this analysis Vz/F will be reported using blood samples taken on Day 14 from healthy volunteers.

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

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose at Day 1; 24, 48, 72 and 96 hr post dose Day 14; ( If B ID dosing, 12 hours samples will be pre-dosed)

Notes:

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

Justification: All end points are verified

| <b>End point values</b>              | Part 2 Cohort 1: QBW251 | Part 2 Cohort 2: QBW251 | Part 2 Cohort 3: QBW251 | Part 2 Cohort 4: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: Liters                        |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 1330 (± 550)            | 1120 (± 395)            | 608 (± 255)             | 0.9999 (± 0.9999)       |

| <b>End point values</b>     | Part 2 Cohort 5: QBW251 |  |  |  |
|-----------------------------|-------------------------|--|--|--|
| Subject group type          | Reporting group         |  |  |  |
| Number of subjects analysed | 6                       |  |  |  |

|                                      |                        |  |  |  |
|--------------------------------------|------------------------|--|--|--|
| Units: Liters                        |                        |  |  |  |
| arithmetic mean (standard deviation) | 0.9999 ( $\pm$ 0.9999) |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part 2: Racc in healthy volunteers

|                 |  |
|-----------------|--|
| End point title | Part 2: Racc in healthy volunteers <sup>[20]</sup> |
|-----------------|--|

End point description:

Accumulation ratio (Racc). In this analysis Racc will be reported using blood samples taken on Days 1 - 14 from healthy volunteers.

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

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose at Day 1; 24, 48, 72 and 96 hr post dose Day 1 - 14; ( If B ID dosing, 12 hours samples will be pre-dosed)

Notes:

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

Justification: All end points are verified

| End point values                     | Part 2 Cohort 1: QBW251 | Part 2 Cohort 2: QBW251 | Part 2 Cohort 3: QBW251 | Part 2 Cohort 4: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: Ratio                         |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 1.27 ( $\pm$ 0.425)     | 1.25 ( $\pm$ 0.199)     | 2.08 ( $\pm$ 0.913)     | 1.66 ( $\pm$ 0.386)     |

| End point values                     | Part 2 Cohort 5: QBW251 |  |  |  |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type                   | Reporting group         |  |  |  |
| Number of subjects analysed          | 6                       |  |  |  |
| Units: Ratio                         |                         |  |  |  |
| arithmetic mean (standard deviation) | 3.88 ( $\pm$ 2.07)      |  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Part 2: T1/2 in healthy volunteers

|                 |  |
|-----------------|--|
| End point title | Part 2: T1/2 in healthy volunteers <sup>[21]</sup> |
|-----------------|--|

End point description:

terminal elimination half-life (T1/2). In this analysis T1/2 will be reported using blood samples taken on Day 14 from healthy volunteers.

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

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose at Day 1; 24, 48, 72 and 96 hr post dose Day 14;  
( If B ID dosing, 12 hours samples will be pre-dosed)

Notes:

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

Justification: All end points are verified

| End point values                     | Part 2 Cohort 1: QBW251 | Part 2 Cohort 2: QBW251 | Part 2 Cohort 3: QBW251 | Part 2 Cohort 4: QBW251 |
|--------------------------------------|-------------------------|-------------------------|-------------------------|-------------------------|
| Subject group type                   | Reporting group         | Reporting group         | Reporting group         | Reporting group         |
| Number of subjects analysed          | 6                       | 6                       | 6                       | 6                       |
| Units: hr                            |                         |                         |                         |                         |
| arithmetic mean (standard deviation) | 11.3 (± 1.44)           | 14.1 (± 3.8)            | 15.1 (± 4.4)            | 0.9999 (± 0.9999)       |

| End point values                     | Part 2 Cohort 5: QBW251 |  |  |  |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type                   | Reporting group         |  |  |  |
| Number of subjects analysed          | 6                       |  |  |  |
| Units: hr                            |                         |  |  |  |
| arithmetic mean (standard deviation) | 0.9999 (± 0.9999)       |  |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Part 3: Area Under the Curve From Time Zero to Last Quantifiable Concentration (AUClast) of QBW251 in CF patients

|                 |   |
|-----------------|---|
| End point title | Part 3: Area Under the Curve From Time Zero to Last Quantifiable Concentration (AUClast) of QBW251 in CF patients |
|-----------------|---|

End point description:

Area under the plasma concentration time-curve from zero to the last measured concentration (AUClast)

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

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose in Day 1, Day 14

## Statistical analyses

No statistical analyses for this end point

---

### Secondary: Part 3: Plasma Concentration at the Last Quantifiable Time Point (Clast) of QBW251 in CF patients

|                 |   |
|-----------------|---|
| End point title | Part 3: Plasma Concentration at the Last Quantifiable Time Point (Clast) of QBW251 in CF patients |
|-----------------|---|

End point description:

Blood samples were collected at timepoints prespecified in the study protocol. Tlast of QBW251 was the last time point when blood sample collected was quantifiable

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

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose in Day 1, Day2

---

## Statistical analyses

No statistical analyses for this end point

---

### Secondary: Part 3: Maximum concentration (Cmax) in CF patients

|                 |   |
|-----------------|---|
| End point title | Part 3: Maximum concentration (Cmax) in CF patients |
|-----------------|---|

End point description:

Observed maximum plasma concentration following administration of QBW251. In this analysis Cmax will be reported using blood samples taken on Day 1 and day 14 from patients

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

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose in Day 1, Day 14

---

## Statistical analyses

No statistical analyses for this end point

---

### Secondary: Part 3: Tlast in CF patients

|                 |                              |
|-----------------|------------------------------|
| End point title | Part 3: Tlast in CF patients |
|-----------------|------------------------------|

---

End point description:

Blood samples were collected at timepoints prespecified in the study protocol. Tlast of QBW251 was the last time point when blood sample collected was quantifiable day 1 and day 14

---

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

---

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose in Day 1, Day 14

---

### Statistical analyses

---

No statistical analyses for this end point

---

### Secondary: Part 3: Time to maximum concentration (Tmax)

---

---

|                 |  |
|-----------------|--|
| End point title | Part 3: Time to maximum concentration (Tmax) |
|-----------------|--|

---

End point description:

Pharmacokinetics of QBW251 in plasma after multiple doses: time to reach the maximum concentration after administration of QBW251. In this analysis Tmax will be reported using blood samples taken on Days 1 and 14 in patients

---

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

---

End point timeframe:

Pre-dose (0 hr), 0.25, 0.5, 1, 2, 3, 4, 8 hr post-dose in Day 1, Day 14

---

### Statistical analyses

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 18.0   |

### Reporting groups

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Part 1 QBW251 150 mg |
|-----------------------|----------------------|

Reporting group description:

Part 1 QBW251 150 mg

|                       |                |
|-----------------------|----------------|
| Reporting group title | Part 1 Placebo |
|-----------------------|----------------|

Reporting group description:

Part 1 Placebo

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Part 1 QBW251 25 mg |
|-----------------------|---------------------|

Reporting group description:

Part 1 QBW251 25 mg

|                       |                     |
|-----------------------|---------------------|
| Reporting group title | Part 1 QBW251 10 mg |
|-----------------------|---------------------|

Reporting group description:

Part 1 QBW251 10 mg

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Part 1 QBW251 750 mg |
|-----------------------|----------------------|

Reporting group description:

Part 1 QBW251 750 mg

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Part 1 QBW251 1000 mg |
|-----------------------|-----------------------|

Reporting group description:

Part 1 QBW251 1000 mg

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Part 1 QBW251 500 mg |
|-----------------------|----------------------|

Reporting group description:

Part 1 QBW251 500 mg

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Part 1 QBW251 500 mg (fed) |
|-----------------------|----------------------------|

Reporting group description:

Part 1 QBW251 500 mg (fed)

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Part 1 QBW251 300 mg |
|-----------------------|----------------------|

Reporting group description:

Part 1 QBW251 300 mg

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Part 2 QBW251 150 mg |
|-----------------------|----------------------|

Reporting group description:

Part 2 QBW251 150 mg

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Part 2 QBW251 400 mg |
|-----------------------|----------------------|

Reporting group description:

Part 2 QBW251 400 mg

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Part 2 QBW251 750 mg |
|-----------------------|----------------------|

Reporting group description:

Part 2 QBW251 750 mg

|                       |                |
|-----------------------|----------------|
| Reporting group title | Part 2 Placebo |
|-----------------------|----------------|

Reporting group description:

Part 2 Placebo

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | Part 3 Placebo C1/C2/C3 |
|-----------------------|-------------------------|

Reporting group description:

Part 3 Placebo C1/C2/C3

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Part 3 QBW251 150 mg b.i.d. C1 |
|-----------------------|--------------------------------|

Reporting group description:

Part 3 QBW251 150 mg b.i.d. C1

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Part 3 QBW251 450 mg b.i.d. C2 |
|-----------------------|--------------------------------|

Reporting group description:

Part 3 QBW251 450 mg b.i.d. C2

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Part 2 QBW251 450 mg bid |
|-----------------------|--------------------------|

Reporting group description:

Part 2 QBW251 450 mg bid

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Part 2 QBW251 750 mg bid |
|-----------------------|--------------------------|

Reporting group description:

Part 2 QBW251 750 mg bid

|                       |                                |
|-----------------------|--------------------------------|
| Reporting group title | Part 3 QBW251 450 mg b.i.d. C3 |
|-----------------------|--------------------------------|

Reporting group description:

Part 3 QBW251 450 mg b.i.d. C3

| <b>Serious adverse events</b>                       | Part 1 QBW251 150 mg | Part 1 Placebo | Part 1 QBW251 25 mg |
|---|----------------------|----------------|---------------------|
| Total subjects affected by serious adverse events   |                      |                |                     |
| subjects affected / exposed                         | 0 / 6 (0.00%)        | 0 / 16 (0.00%) | 0 / 6 (0.00%)       |
| number of deaths (all causes)                       | 0                    | 0              | 0                   |
| number of deaths resulting from adverse events      | 0                    | 0              | 0                   |
| Infections and infestations                         |                      |                |                     |
| Infective pulmonary exacerbation of cystic fibrosis |                      |                |                     |
| subjects affected / exposed                         | 0 / 6 (0.00%)        | 0 / 16 (0.00%) | 0 / 6 (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               |
| Sinusitis   |                      |                |                     |
| subjects affected / exposed                         | 0 / 6 (0.00%)        | 0 / 16 (0.00%) | 0 / 6 (0.00%)       |
| occurrences causally related to treatment / all     | 0 / 0                | 0 / 0          | 0 / 0               |
| deaths causally related to treatment / all          | 0 / 0                | 0 / 0          | 0 / 0               |

| <b>Serious adverse events</b>                     | Part 1 QBW251 10 mg | Part 1 QBW251 750 mg | Part 1 QBW251 1000 mg |
|---|---------------------|----------------------|-----------------------|
| Total subjects affected by serious adverse events |                     |                      |                       |
| subjects affected / exposed                       | 0 / 6 (0.00%)       | 0 / 6 (0.00%)        | 0 / 6 (0.00%)         |
| number of deaths (all causes)                     | 0                   | 0                    | 0                     |
| number of deaths resulting from                   | 0                   | 0                    | 0                     |

| adverse events                                      |               |               |               |
|---|---------------|---------------|---------------|
| Infections and infestations                         |               |               |               |
| Infective pulmonary exacerbation of cystic fibrosis |               |               |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (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         |
| Sinusitis   |               |               |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all     | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all          | 0 / 0         | 0 / 0         | 0 / 0         |

| <b>Serious adverse events</b>                       | Part 1 QBW251 500 mg | Part 1 QBW251 500 mg (fed) | Part 1 QBW251 300 mg |
|---|----------------------|----------------------------|----------------------|
| Total subjects affected by serious adverse events   |                      |                            |                      |
| subjects affected / exposed                         | 0 / 6 (0.00%)        | 0 / 5 (0.00%)              | 0 / 6 (0.00%)        |
| number of deaths (all causes)                       | 0                    | 0                          | 0                    |
| number of deaths resulting from adverse events      | 0                    | 0                          | 0                    |
| Infections and infestations                         |                      |                            |                      |
| Infective pulmonary exacerbation of cystic fibrosis |                      |                            |                      |
| subjects affected / exposed                         | 0 / 6 (0.00%)        | 0 / 5 (0.00%)              | 0 / 6 (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                |
| Sinusitis   |                      |                            |                      |
| subjects affected / exposed                         | 0 / 6 (0.00%)        | 0 / 5 (0.00%)              | 0 / 6 (0.00%)        |
| occurrences causally related to treatment / all     | 0 / 0                | 0 / 0                      | 0 / 0                |
| deaths causally related to treatment / all          | 0 / 0                | 0 / 0                      | 0 / 0                |

| <b>Serious adverse events</b>                       | Part 2 QBW251 150 mg | Part 2 QBW251 400 mg | Part 2 QBW251 750 mg |
|---|----------------------|----------------------|----------------------|
| Total subjects affected by serious adverse events   |                      |                      |                      |
| subjects affected / exposed                         | 0 / 6 (0.00%)        | 0 / 6 (0.00%)        | 0 / 6 (0.00%)        |
| number of deaths (all causes)                       | 0                    | 0                    | 0                    |
| number of deaths resulting from adverse events      | 0                    | 0                    | 0                    |
| Infections and infestations                         |                      |                      |                      |
| Infective pulmonary exacerbation of cystic fibrosis |                      |                      |                      |

|   |               |               |               |
|---|---------------|---------------|---------------|
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (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         |
| Sinusitis                                       |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0         | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0         | 0 / 0         | 0 / 0         |

| <b>Serious adverse events</b>                       | Part 2 Placebo | Part 3 Placebo C1/C2/C3 | Part 3 QBW251 150 mg b.i.d. C1 |
|---|----------------|-------------------------|--------------------------------|
| Total subjects affected by serious adverse events   |                |                         |                                |
| subjects affected / exposed                         | 0 / 10 (0.00%) | 0 / 12 (0.00%)          | 1 / 6 (16.67%)                 |
| number of deaths (all causes)                       | 0              | 0                       | 0                              |
| number of deaths resulting from adverse events      | 0              | 0                       | 0                              |
| Infections and infestations                         |                |                         |                                |
| Infective pulmonary exacerbation of cystic fibrosis |                |                         |                                |
| subjects affected / exposed                         | 0 / 10 (0.00%) | 0 / 12 (0.00%)          | 0 / 6 (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                          |
| Sinusitis   |                |                         |                                |
| subjects affected / exposed                         | 0 / 10 (0.00%) | 0 / 12 (0.00%)          | 1 / 6 (16.67%)                 |
| occurrences causally related to treatment / all     | 0 / 0          | 0 / 0                   | 0 / 1                          |
| deaths causally related to treatment / all          | 0 / 0          | 0 / 0                   | 0 / 0                          |

| <b>Serious adverse events</b>                       | Part 3 QBW251 450 mg b.i.d. C2 | Part 2 QBW251 450 mg bid | Part 2 QBW251 750 mg bid |
|---|--------------------------------|--------------------------|--------------------------|
| Total subjects affected by serious adverse events   |                                |                          |                          |
| subjects affected / exposed                         | 1 / 12 (8.33%)                 | 0 / 6 (0.00%)            | 0 / 6 (0.00%)            |
| number of deaths (all causes)                       | 0                              | 0                        | 0                        |
| number of deaths resulting from adverse events      | 0                              | 0                        | 0                        |
| Infections and infestations                         |                                |                          |                          |
| Infective pulmonary exacerbation of cystic fibrosis |                                |                          |                          |
| subjects affected / exposed                         | 1 / 12 (8.33%)                 | 0 / 6 (0.00%)            | 0 / 6 (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                    |
| Sinusitis   |                                |                          |                          |

|   |                |               |               |
|---|----------------|---------------|---------------|
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0         | 0 / 0         |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         | 0 / 0         |

| <b>Serious adverse events</b>                       | Part 3 QBW251 450 mg b.i.d. C3 |  |  |
|---|--------------------------------|--|--|
| Total subjects affected by serious adverse events   |                                |  |  |
| subjects affected / exposed                         | 1 / 19 (5.26%)                 |  |  |
| number of deaths (all causes)                       | 0                              |  |  |
| number of deaths resulting from adverse events      | 0                              |  |  |
| Infections and infestations                         |                                |  |  |
| Infective pulmonary exacerbation of cystic fibrosis |                                |  |  |
| subjects affected / exposed                         | 1 / 19 (5.26%)                 |  |  |
| occurrences causally related to treatment / all     | 0 / 1                          |  |  |
| deaths causally related to treatment / all          | 0 / 0                          |  |  |
| Sinusitis   |                                |  |  |
| subjects affected / exposed                         | 0 / 19 (0.00%)                 |  |  |
| occurrences causally related to treatment / all     | 0 / 0                          |  |  |
| deaths causally related to treatment / all          | 0 / 0                          |  |  |

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

| <b>Non-serious adverse events</b>                     | Part 1 QBW251 150 mg | Part 1 Placebo  | Part 1 QBW251 25 mg |
|---|----------------------|-----------------|---------------------|
| Total subjects affected by non-serious adverse events |                      |                 |                     |
| subjects affected / exposed                           | 1 / 6 (16.67%)       | 8 / 16 (50.00%) | 2 / 6 (33.33%)      |
| Vascular disorders                                    |                      |                 |                     |
| Hot flush   |                      |                 |                     |
| subjects affected / exposed                           | 0 / 6 (0.00%)        | 0 / 16 (0.00%)  | 0 / 6 (0.00%)       |
| occurrences (all)                                     | 0                    | 0               | 0                   |
| General disorders and administration site conditions  |                      |                 |                     |
| Asthenia  |                      |                 |                     |
| subjects affected / exposed                           | 0 / 6 (0.00%)        | 0 / 16 (0.00%)  | 0 / 6 (0.00%)       |
| occurrences (all)                                     | 0                    | 0               | 0                   |
| Chest discomfort                                      |                      |                 |                     |
| subjects affected / exposed                           | 0 / 6 (0.00%)        | 0 / 16 (0.00%)  | 0 / 6 (0.00%)       |
| occurrences (all)                                     | 0                    | 0               | 0                   |

|   |               |                |               |
|---|---------------|----------------|---------------|
| Chest pain                                      |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0              | 0             |
| Fatigue   |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0              | 0             |
| Influenza like illness                          |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0              | 0             |
| Pain  |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0              | 0             |
| Peripheral swelling                             |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0              | 0             |
| Pyrexia   |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0              | 0             |
| Sensation of foreign body                       |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0              | 0             |
| Thirst  |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0              | 0             |
| Vessel puncture site bruise                     |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0              | 0             |
| Respiratory, thoracic and mediastinal disorders |               |                |               |
| Bronchial obstruction                           |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0              | 0             |
| Cough   |               |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0              | 0             |
| Dyspnoea  |               |                |               |

|                             |               |                |               |
|-----------------------------|---------------|----------------|---------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Epistaxis                   |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Haemoptysis                 |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Nasal congestion            |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Nasal discomfort            |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Oropharyngeal pain          |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Painful respiration         |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Productive cough            |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Pulmonary congestion        |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Rhinorrhoea                 |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Sinus congestion            |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Sneezing                    |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Sputum increased            |               |                |               |

|  |                    |                     |                    |
|--|--------------------|---------------------|--------------------|
| subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Throat irritation<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Tonsillar disorder<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Psychiatric disorders  |                    |                     |                    |
| Agitation<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Depression<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Stress<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Investigations   |                    |                     |                    |
| Adenovirus test positive<br>subjects affected / exposed<br>occurrences (all)             | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Blood potassium decreased<br>subjects affected / exposed<br>occurrences (all)            | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Breath sounds abnormal<br>subjects affected / exposed<br>occurrences (all)               | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Coronavirus test positive  |                    |                     |                    |

|  |                    |                     |                    |
|--|--------------------|---------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Injury, poisoning and procedural complications   |                    |                     |                    |
| Arthropod bite                                   |                    |                     |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)      | 0 / 16 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Ligament sprain                                  |                    |                     |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)      | 0 / 16 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Skin wound                                       |                    |                     |                    |
| subjects affected / exposed                      | 1 / 6 (16.67%)     | 0 / 16 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 1                  | 0                   | 0                  |
| Congenital, familial and genetic disorders       |                    |                     |                    |
| Ichthyosis                                       |                    |                     |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)      | 0 / 16 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Cardiac disorders                                |                    |                     |                    |
| Palpitations                                     |                    |                     |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)      | 0 / 16 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Nervous system disorders                         |                    |                     |                    |
| Balance disorder                                 |                    |                     |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)      | 0 / 16 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |
| Dizziness  |                    |                     |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)      | 3 / 16 (18.75%)     | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                  | 3                   | 0                  |
| Headache   |                    |                     |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)      | 2 / 16 (12.50%)     | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                  | 2                   | 0                  |
| Hyperaesthesia                                   |                    |                     |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)      | 1 / 16 (6.25%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                  | 1                   | 0                  |
| Presyncope                                       |                    |                     |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)      | 0 / 16 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                  | 0                   | 0                  |

|                             |               |                |                |
|-----------------------------|---------------|----------------|----------------|
| Sciatica                    |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Syncope                     |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Tremor                      |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Ear and labyrinth disorders |               |                |                |
| Ear discomfort              |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Ear pain                    |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Tinnitus                    |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Gastrointestinal disorders  |               |                |                |
| Abdominal discomfort        |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Abdominal distension        |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)           | 0             | 0              | 1              |
| Abdominal pain              |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Abdominal pain lower        |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Aphthous stomatitis         |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Diarrhoea                   |               |                |                |

|   |               |                |                |
|---|---------------|----------------|----------------|
| subjects affected / exposed                   | 0 / 6 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 1              | 0              |
| Faeces discoloured                            |               |                |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0              | 0              |
| Flatulence                                    |               |                |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0              | 0              |
| Gastrooesophageal reflux disease              |               |                |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)                             | 0             | 0              | 1              |
| Gingival disorder                             |               |                |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0              | 0              |
| Nausea  |               |                |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0              | 0              |
| Saliva altered                                |               |                |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0              | 0              |
| Salivary gland pain                           |               |                |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0              | 0              |
| Vomiting                                      |               |                |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0              | 0              |
| <b>Skin and subcutaneous tissue disorders</b> |               |                |                |
| Erythema                                      |               |                |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0              | 0              |
| Heat rash                                     |               |                |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0              | 0              |
| Night sweats                                  |               |                |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0              | 0              |

|  |                    |                     |                     |
|--|--------------------|---------------------|---------------------|
| Photosensitivity reaction<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Pruritus generalised<br>subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0 | 1 / 16 (6.25%)<br>1 | 0 / 6 (0.00%)<br>0  |
| Rash<br>subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Rash erythematous<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Rash pruritic<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Renal and urinary disorders<br>Chromaturia<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Glycosuria<br>subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Proteinuria<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 16 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 |
| Joint swelling   |                    |                     |                     |

|   |               |                |                |
|---|---------------|----------------|----------------|
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                       | 0             | 0              | 0              |
| Muscle spasms                           |               |                |                |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                       | 0             | 0              | 0              |
| Musculoskeletal chest pain              |               |                |                |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                       | 0             | 0              | 0              |
| Musculoskeletal pain                    |               |                |                |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                       | 0             | 0              | 0              |
| Musculoskeletal stiffness               |               |                |                |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                       | 0             | 0              | 0              |
| Neck pain                               |               |                |                |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                       | 0             | 0              | 0              |
| Pain in extremity                       |               |                |                |
| subjects affected / exposed             | 0 / 6 (0.00%) | 1 / 16 (6.25%) | 1 / 6 (16.67%) |
| occurrences (all)                       | 0             | 1              | 1              |
| Infections and infestations             |               |                |                |
| Bronchitis                              |               |                |                |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                       | 0             | 0              | 0              |
| Bronchopulmonary aspergillosis allergic |               |                |                |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                       | 0             | 0              | 0              |
| Folliculitis                            |               |                |                |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                       | 0             | 0              | 0              |
| Fungal infection                        |               |                |                |
| subjects affected / exposed             | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                       | 0             | 0              | 0              |
| Gastroenteritis                         |               |                |                |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| Infective pulmonary exacerbation of cystic fibrosis |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| Nasopharyngitis                                     |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 1 / 16 (6.25%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 1              | 0             |
| Oral herpes   |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| Pharyngitis   |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| Sinusitis   |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| Upper respiratory tract infection                   |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| Viral upper respiratory tract infection             |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| <b>Metabolism and nutrition disorders</b>           |               |                |               |
| Decreased appetite                                  |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| Hypoglycaemia                                       |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| Vitamin d deficiency                                |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 16 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |

| <b>Non-serious adverse events</b>      | Part 1 QBW251 10 mg | Part 1 QBW251 750 mg | Part 1 QBW251 1000 mg |
|--|---------------------|----------------------|-----------------------|
| Total subjects affected by non-serious |                     |                      |                       |

|  |                |                |                |
|--|----------------|----------------|----------------|
| adverse events                                       |                |                |                |
| subjects affected / exposed                          | 3 / 6 (50.00%) | 1 / 6 (16.67%) | 4 / 6 (66.67%) |
| Vascular disorders                                   |                |                |                |
| Hot flush  |                |                |                |
| subjects affected / exposed                          | 1 / 6 (16.67%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                                    | 1              | 0              | 0              |
| General disorders and administration site conditions |                |                |                |
| Asthenia   |                |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                                    | 0              | 0              | 0              |
| Chest discomfort                                     |                |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                                    | 0              | 0              | 0              |
| Chest pain   |                |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                                    | 0              | 0              | 0              |
| Fatigue  |                |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                                    | 0              | 0              | 0              |
| Influenza like illness                               |                |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                                    | 0              | 0              | 0              |
| Pain   |                |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                                    | 0              | 0              | 0              |
| Peripheral swelling                                  |                |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                                    | 0              | 0              | 0              |
| Pyrexia  |                |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                                    | 0              | 0              | 0              |
| Sensation of foreign body                            |                |                |                |
| subjects affected / exposed                          | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                                    | 0              | 0              | 0              |
| Thirst   |                |                |                |

|  |               |               |               |
|--|---------------|---------------|---------------|
| subjects affected / exposed                            | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                      | 0             | 0             | 0             |
| Vessel puncture site bruise                            |               |               |               |
| subjects affected / exposed                            | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                      | 0             | 0             | 0             |
| <b>Respiratory, thoracic and mediastinal disorders</b> |               |               |               |
| Bronchial obstruction                                  |               |               |               |
| subjects affected / exposed                            | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                      | 0             | 0             | 0             |
| Cough  |               |               |               |
| subjects affected / exposed                            | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                      | 0             | 0             | 0             |
| Dyspnoea   |               |               |               |
| subjects affected / exposed                            | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                      | 0             | 0             | 0             |
| Epistaxis  |               |               |               |
| subjects affected / exposed                            | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                      | 0             | 0             | 0             |
| Haemoptysis  |               |               |               |
| subjects affected / exposed                            | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                      | 0             | 0             | 0             |
| Nasal congestion                                       |               |               |               |
| subjects affected / exposed                            | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                      | 0             | 0             | 0             |
| Nasal discomfort                                       |               |               |               |
| subjects affected / exposed                            | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                      | 0             | 0             | 0             |
| Oropharyngeal pain                                     |               |               |               |
| subjects affected / exposed                            | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                      | 0             | 0             | 0             |
| Painful respiration                                    |               |               |               |
| subjects affected / exposed                            | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                      | 0             | 0             | 0             |
| Productive cough                                       |               |               |               |

|                             |               |               |               |
|-----------------------------|---------------|---------------|---------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Pulmonary congestion        |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Rhinorrhoea                 |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Sinus congestion            |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Sneezing                    |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Sputum increased            |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Throat irritation           |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Tonsillar disorder          |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Psychiatric disorders       |               |               |               |
| Agitation                   |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Depression                  |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Insomnia                    |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Stress                      |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |

|  |               |               |               |
|--|---------------|---------------|---------------|
| Investigations                                 |               |               |               |
| Adenovirus test positive                       |               |               |               |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0             | 0             | 0             |
| Blood alkaline phosphatase increased           |               |               |               |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0             | 0             | 0             |
| Blood potassium decreased                      |               |               |               |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0             | 0             | 0             |
| Breath sounds abnormal                         |               |               |               |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0             | 0             | 0             |
| Coronavirus test positive                      |               |               |               |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0             | 0             | 0             |
| Injury, poisoning and procedural complications |               |               |               |
| Arthropod bite                                 |               |               |               |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0             | 0             | 0             |
| Ligament sprain                                |               |               |               |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0             | 0             | 0             |
| Skin wound                                     |               |               |               |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0             | 0             | 0             |
| Congenital, familial and genetic disorders     |               |               |               |
| Ichthyosis                                     |               |               |               |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0             | 0             | 0             |
| Cardiac disorders                              |               |               |               |
| Palpitations                                   |               |               |               |
| subjects affected / exposed                    | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0             | 0             | 0             |
| Nervous system disorders                       |               |               |               |

|                             |                |               |                |
|-----------------------------|----------------|---------------|----------------|
| Balance disorder            |                |               |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Dizziness                   |                |               |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all)           | 0              | 0             | 2              |
| Headache                    |                |               |                |
| subjects affected / exposed | 2 / 6 (33.33%) | 0 / 6 (0.00%) | 2 / 6 (33.33%) |
| occurrences (all)           | 2              | 0             | 2              |
| Hyperaesthesia              |                |               |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Presyncope                  |                |               |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Sciatica                    |                |               |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Syncope                     |                |               |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Tremor                      |                |               |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Ear and labyrinth disorders |                |               |                |
| Ear discomfort              |                |               |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Ear pain                    |                |               |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)           | 0              | 0             | 2              |
| Tinnitus                    |                |               |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0             | 0              |
| Gastrointestinal disorders  |                |               |                |

|                                  |               |               |               |
|----------------------------------|---------------|---------------|---------------|
| Abdominal discomfort             |               |               |               |
| subjects affected / exposed      | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0             | 0             | 0             |
| Abdominal distension             |               |               |               |
| subjects affected / exposed      | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0             | 0             | 0             |
| Abdominal pain                   |               |               |               |
| subjects affected / exposed      | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0             | 0             | 0             |
| Abdominal pain lower             |               |               |               |
| subjects affected / exposed      | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0             | 0             | 0             |
| Aphthous stomatitis              |               |               |               |
| subjects affected / exposed      | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0             | 0             | 0             |
| Diarrhoea                        |               |               |               |
| subjects affected / exposed      | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0             | 0             | 0             |
| Faeces discoloured               |               |               |               |
| subjects affected / exposed      | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0             | 0             | 0             |
| Flatulence                       |               |               |               |
| subjects affected / exposed      | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0             | 0             | 0             |
| Gastrooesophageal reflux disease |               |               |               |
| subjects affected / exposed      | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0             | 0             | 0             |
| Gingival disorder                |               |               |               |
| subjects affected / exposed      | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0             | 0             | 0             |
| Nausea                           |               |               |               |
| subjects affected / exposed      | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0             | 0             | 0             |
| Saliva altered                   |               |               |               |
| subjects affected / exposed      | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                | 0             | 0             | 0             |

|   |                |               |                |
|---|----------------|---------------|----------------|
| Salivary gland pain                           |                |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0             | 0              |
| Vomiting                                      |                |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0             | 0              |
| <b>Skin and subcutaneous tissue disorders</b> |                |               |                |
| Erythema                                      |                |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0             | 0              |
| Heat rash                                     |                |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0             | 0              |
| Night sweats                                  |                |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0             | 0              |
| Photosensitivity reaction                     |                |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0             | 0              |
| Pruritus                                      |                |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0             | 0              |
| Pruritus generalised                          |                |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0             | 0              |
| Rash  |                |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0             | 0              |
| Rash erythematous                             |                |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%)  | 0 / 6 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0             | 0              |
| Rash pruritic                                 |                |               |                |
| subjects affected / exposed                   | 1 / 6 (16.67%) | 0 / 6 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)                             | 1              | 0             | 1              |
| Urticaria                                     |                |               |                |

|  |                     |                    |                    |
|--|---------------------|--------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 1 / 6 (16.67%)<br>1 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Renal and urinary disorders                      |                     |                    |                    |
| Chromaturia                                      |                     |                    |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)       | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Glycosuria                                       |                     |                    |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)       | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Proteinuria                                      |                     |                    |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)       | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Musculoskeletal and connective tissue disorders  |                     |                    |                    |
| Back pain  |                     |                    |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)       | 1 / 6 (16.67%)     | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                   | 1                  | 0                  |
| Joint swelling                                   |                     |                    |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)       | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Muscle spasms                                    |                     |                    |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)       | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Musculoskeletal chest pain                       |                     |                    |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)       | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Musculoskeletal pain                             |                     |                    |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)       | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Musculoskeletal stiffness                        |                     |                    |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)       | 0 / 6 (0.00%)      | 1 / 6 (16.67%)     |
| occurrences (all)                                | 0                   | 0                  | 1                  |
| Neck pain  |                     |                    |                    |
| subjects affected / exposed                      | 0 / 6 (0.00%)       | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                | 0                   | 0                  | 0                  |
| Pain in extremity                                |                     |                    |                    |

|  |               |                |                |
|--|---------------|----------------|----------------|
| subjects affected / exposed                                | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)  | 0             | 0              | 0              |
| <b>Infections and infestations</b>                         |               |                |                |
| <b>Bronchitis</b>  |               |                |                |
| subjects affected / exposed                                | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)  | 0             | 0              | 0              |
| <b>Bronchopulmonary aspergillosis allergic</b>             |               |                |                |
| subjects affected / exposed                                | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)  | 0             | 0              | 0              |
| <b>Folliculitis</b>  |               |                |                |
| subjects affected / exposed                                | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%)  |
| occurrences (all)  | 0             | 1              | 0              |
| <b>Fungal infection</b>                                    |               |                |                |
| subjects affected / exposed                                | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)  | 0             | 0              | 0              |
| <b>Gastroenteritis</b>                                     |               |                |                |
| subjects affected / exposed                                | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)  | 0             | 0              | 0              |
| <b>Infective pulmonary exacerbation of cystic fibrosis</b> |               |                |                |
| subjects affected / exposed                                | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)  | 0             | 0              | 0              |
| <b>Nasopharyngitis</b>                                     |               |                |                |
| subjects affected / exposed                                | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)  | 0             | 0              | 1              |
| <b>Oral herpes</b>   |               |                |                |
| subjects affected / exposed                                | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)  | 0             | 0              | 1              |
| <b>Pharyngitis</b>   |               |                |                |
| subjects affected / exposed                                | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)  | 0             | 0              | 0              |
| <b>Sinusitis</b>   |               |                |                |
| subjects affected / exposed                                | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)  | 0             | 0              | 0              |
| <b>Upper respiratory tract infection</b>                   |               |                |                |

|   |                    |                    |                    |
|---|--------------------|--------------------|--------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| <b>Metabolism and nutrition disorders</b>   |                    |                    |                    |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Hypoglycaemia<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Vitamin d deficiency<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |

| <b>Non-serious adverse events</b>   | Part 1 QBW251 500<br>mg | Part 1 QBW251 500<br>mg (fed) | Part 1 QBW251 300<br>mg |
|---|-------------------------|-------------------------------|-------------------------|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed | 2 / 6 (33.33%)          | 1 / 5 (20.00%)                | 2 / 6 (33.33%)          |
| <b>Vascular disorders</b>   |                         |                               |                         |
| Hot flush<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 6 (0.00%)<br>0      | 0 / 5 (0.00%)<br>0            | 0 / 6 (0.00%)<br>0      |
| <b>General disorders and administration<br/>site conditions</b>                         |                         |                               |                         |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 6 (0.00%)<br>0      | 0 / 5 (0.00%)<br>0            | 0 / 6 (0.00%)<br>0      |
| Chest discomfort<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 6 (0.00%)<br>0      | 0 / 5 (0.00%)<br>0            | 0 / 6 (0.00%)<br>0      |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 6 (0.00%)<br>0      | 0 / 5 (0.00%)<br>0            | 0 / 6 (0.00%)<br>0      |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 6 (0.00%)<br>0      | 0 / 5 (0.00%)<br>0            | 0 / 6 (0.00%)<br>0      |

|   |               |               |               |
|---|---------------|---------------|---------------|
| Influenza like illness                          |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Pain  |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Peripheral swelling                             |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Pyrexia   |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Sensation of foreign body                       |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Thirst  |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Vessel puncture site bruise                     |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Respiratory, thoracic and mediastinal disorders |               |               |               |
| Bronchial obstruction                           |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Cough   |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Dyspnoea  |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Epistaxis                                       |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Haemoptysis                                     |               |               |               |

|                             |               |               |               |
|-----------------------------|---------------|---------------|---------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Nasal congestion            |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Nasal discomfort            |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Oropharyngeal pain          |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Painful respiration         |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Productive cough            |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Pulmonary congestion        |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Rhinorrhoea                 |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Sinus congestion            |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Sneezing                    |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Sputum increased            |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Throat irritation           |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Tonsillar disorder          |               |               |               |

|  |                    |                    |                    |
|--|--------------------|--------------------|--------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Psychiatric disorders                            |                    |                    |                    |
| Agitation  |                    |                    |                    |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Depression                                       |                    |                    |                    |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Insomnia   |                    |                    |                    |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Stress   |                    |                    |                    |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Investigations                                   |                    |                    |                    |
| Adenovirus test positive                         |                    |                    |                    |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Blood alkaline phosphatase increased             |                    |                    |                    |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Blood potassium decreased                        |                    |                    |                    |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Breath sounds abnormal                           |                    |                    |                    |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Coronavirus test positive                        |                    |                    |                    |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Injury, poisoning and procedural complications   |                    |                    |                    |
| Arthropod bite                                   |                    |                    |                    |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Ligament sprain                                  |                    |                    |                    |

|  |                     |                    |                     |
|--|---------------------|--------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Skin wound<br>subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Congenital, familial and genetic disorders<br>Ichthyosis<br>subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Cardiac disorders<br>Palpitations<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 6 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Nervous system disorders<br>Balance disorder<br>subjects affected / exposed<br>occurrences (all)             | 0 / 6 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 2 / 6 (33.33%)<br>2 | 0 / 5 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 |
| Hyperaesthesia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Presyncope<br>subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Sciatica<br>subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Syncope<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6 (0.00%)<br>0  | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Tremor   |                     |                    |                     |

|  |                    |                    |                     |
|--|--------------------|--------------------|---------------------|
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Ear and labyrinth disorders                      |                    |                    |                     |
| Ear discomfort                                   |                    |                    |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Ear pain   |                    |                    |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Tinnitus   |                    |                    |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Gastrointestinal disorders                       |                    |                    |                     |
| Abdominal discomfort                             |                    |                    |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Abdominal distension                             |                    |                    |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Abdominal pain                                   |                    |                    |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Abdominal pain lower                             |                    |                    |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Aphthous stomatitis                              |                    |                    |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Diarrhoea  |                    |                    |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 |
| Faeces discoloured                               |                    |                    |                     |
| subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Flatulence                                       |                    |                    |                     |

|   |               |               |                |
|---|---------------|---------------|----------------|
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0             | 0              |
| Gastroesophageal reflux disease               |               |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0             | 0              |
| Gingival disorder                             |               |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0             | 0              |
| Nausea  |               |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0             | 0              |
| Saliva altered                                |               |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0             | 0              |
| Salivary gland pain                           |               |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0             | 0              |
| Vomiting                                      |               |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)                             | 0             | 0             | 1              |
| <b>Skin and subcutaneous tissue disorders</b> |               |               |                |
| Erythema                                      |               |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0             | 0              |
| Heat rash                                     |               |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0             | 0              |
| Night sweats                                  |               |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0             | 0              |
| Photosensitivity reaction                     |               |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0             | 0              |
| Pruritus                                      |               |               |                |
| subjects affected / exposed                   | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0             | 0             | 0              |

|   |               |               |               |
|---|---------------|---------------|---------------|
| Pruritus generalised                            |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Rash  |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Rash erythematous                               |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Rash pruritic                                   |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Urticaria                                       |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Renal and urinary disorders                     |               |               |               |
| Chromaturia                                     |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Glycosuria                                      |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Proteinuria                                     |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Musculoskeletal and connective tissue disorders |               |               |               |
| Back pain                                       |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Joint swelling                                  |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Muscle spasms                                   |               |               |               |
| subjects affected / exposed                     | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0             | 0             | 0             |
| Musculoskeletal chest pain                      |               |               |               |

|   |               |               |               |
|---|---------------|---------------|---------------|
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0             | 0             |
| Musculoskeletal pain                                |               |               |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0             | 0             |
| Musculoskeletal stiffness                           |               |               |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0             | 0             |
| Neck pain   |               |               |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0             | 0             |
| Pain in extremity                                   |               |               |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0             | 0             |
| Infections and infestations                         |               |               |               |
| Bronchitis  |               |               |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0             | 0             |
| Bronchopulmonary aspergillosis allergic             |               |               |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0             | 0             |
| Folliculitis  |               |               |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0             | 0             |
| Fungal infection                                    |               |               |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0             | 0             |
| Gastroenteritis                                     |               |               |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0             | 0             |
| Infective pulmonary exacerbation of cystic fibrosis |               |               |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 5 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0             | 0             |
| Nasopharyngitis                                     |               |               |               |

|  |                    |                     |                    |
|--|--------------------|---------------------|--------------------|
| subjects affected / exposed<br>occurrences (all)   | 0 / 6 (0.00%)<br>0 | 1 / 5 (20.00%)<br>1 | 0 / 6 (0.00%)<br>0 |
| Oral herpes<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Sinusitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Metabolism and nutrition disorders<br>Decreased appetite<br>subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Hypoglycaemia<br>subjects affected / exposed<br>occurrences (all)  | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Vitamin d deficiency<br>subjects affected / exposed<br>occurrences (all)                                     | 0 / 6 (0.00%)<br>0 | 0 / 5 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |

| <b>Non-serious adverse events</b>   | Part 2 QBW251 150<br>mg | Part 2 QBW251 400<br>mg | Part 2 QBW251 750<br>mg |
|---|-------------------------|-------------------------|-------------------------|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed | 3 / 6 (50.00%)          | 6 / 6 (100.00%)         | 3 / 6 (50.00%)          |
| Vascular disorders<br>Hot flush<br>subjects affected / exposed<br>occurrences (all)     | 0 / 6 (0.00%)<br>0      | 0 / 6 (0.00%)<br>0      | 0 / 6 (0.00%)<br>0      |
| General disorders and administration<br>site conditions                                 |                         |                         |                         |

|   |                |                |               |
|---|----------------|----------------|---------------|
| Asthenia  |                |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0             |
| Chest discomfort                                |                |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0             |
| Chest pain                                      |                |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 1              | 0             |
| Fatigue   |                |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0             |
| Influenza like illness                          |                |                |               |
| subjects affected / exposed                     | 1 / 6 (16.67%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 1              | 0              | 0             |
| Pain  |                |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0             |
| Peripheral swelling                             |                |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0             |
| Pyrexia   |                |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0             |
| Sensation of foreign body                       |                |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0             |
| Thirst  |                |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0             |
| Vessel puncture site bruise                     |                |                |               |
| subjects affected / exposed                     | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0              | 0             |
| Respiratory, thoracic and mediastinal disorders |                |                |               |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| Bronchial obstruction       |                |                |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Cough                       |                |                |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 6 (16.67%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 2              | 0              |
| Dyspnoea                    |                |                |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 6 (16.67%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0              |
| Epistaxis                   |                |                |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)           | 0              | 0              | 1              |
| Haemoptysis                 |                |                |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Nasal congestion            |                |                |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 6 (16.67%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0              |
| Nasal discomfort            |                |                |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 1 / 6 (16.67%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 1              | 0              |
| Oropharyngeal pain          |                |                |                |
| subjects affected / exposed | 1 / 6 (16.67%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 1              | 0              | 0              |
| Painful respiration         |                |                |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Productive cough            |                |                |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Pulmonary congestion        |                |                |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |
| Rhinorrhoea                 |                |                |                |
| subjects affected / exposed | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0              | 0              |

|  |                    |                    |                     |
|--|--------------------|--------------------|---------------------|
| Sinus congestion<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Sneezing<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Sputum increased<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Throat irritation<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 |
| Tonsillar disorder<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Psychiatric disorders  |                    |                    |                     |
| Agitation<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Depression<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Stress<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Investigations   |                    |                    |                     |
| Adenovirus test positive<br>subjects affected / exposed<br>occurrences (all)             | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Blood potassium decreased  |                    |                    |                     |

|   |                    |                     |                    |
|---|--------------------|---------------------|--------------------|
| subjects affected / exposed<br>occurrences (all)                              | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Breath sounds abnormal<br>subjects affected / exposed<br>occurrences (all)    | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Coronavirus test positive<br>subjects affected / exposed<br>occurrences (all) | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Injury, poisoning and procedural complications                                |                    |                     |                    |
| Arthropod bite<br>subjects affected / exposed<br>occurrences (all)            | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)           | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Skin wound<br>subjects affected / exposed<br>occurrences (all)                | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Congenital, familial and genetic disorders                                    |                    |                     |                    |
| Ichthyosis<br>subjects affected / exposed<br>occurrences (all)                | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Cardiac disorders   |                    |                     |                    |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)              | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Nervous system disorders  |                    |                     |                    |
| Balance disorder<br>subjects affected / exposed<br>occurrences (all)          | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Headache<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 6 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 | 0 / 6 (0.00%)<br>0 |

|                             |               |                |                |
|-----------------------------|---------------|----------------|----------------|
| Hyperaesthesia              |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Presyncope                  |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 1              | 0              |
| Sciatica                    |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Syncope                     |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Tremor                      |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Ear and labyrinth disorders |               |                |                |
| Ear discomfort              |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Ear pain                    |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Tinnitus                    |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Gastrointestinal disorders  |               |                |                |
| Abdominal discomfort        |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Abdominal distension        |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0             | 0              | 0              |
| Abdominal pain              |               |                |                |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)           | 0             | 0              | 1              |
| Abdominal pain lower        |               |                |                |

|  |                |                |               |
|--|----------------|----------------|---------------|
| subjects affected / exposed            | 0 / 6 (0.00%)  | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all)                      | 0              | 1              | 0             |
| Aphthous stomatitis                    |                |                |               |
| subjects affected / exposed            | 1 / 6 (16.67%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                      | 1              | 0              | 0             |
| Diarrhoea                              |                |                |               |
| subjects affected / exposed            | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0             |
| Faeces discoloured                     |                |                |               |
| subjects affected / exposed            | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0             |
| Flatulence                             |                |                |               |
| subjects affected / exposed            | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0             |
| Gastrooesophageal reflux disease       |                |                |               |
| subjects affected / exposed            | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0             |
| Gingival disorder                      |                |                |               |
| subjects affected / exposed            | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0             |
| Nausea                                 |                |                |               |
| subjects affected / exposed            | 0 / 6 (0.00%)  | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all)                      | 0              | 1              | 0             |
| Saliva altered                         |                |                |               |
| subjects affected / exposed            | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0             |
| Salivary gland pain                    |                |                |               |
| subjects affected / exposed            | 1 / 6 (16.67%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                      | 1              | 0              | 0             |
| Vomiting                               |                |                |               |
| subjects affected / exposed            | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0             |
| Skin and subcutaneous tissue disorders |                |                |               |
| Erythema                               |                |                |               |
| subjects affected / exposed            | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                      | 0              | 0              | 0             |

|                             |               |                |               |
|-----------------------------|---------------|----------------|---------------|
| Heat rash                   |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Night sweats                |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Photosensitivity reaction   |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Pruritus                    |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Pruritus generalised        |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Rash                        |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Rash erythematous           |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Rash pruritic               |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 1              | 0             |
| Urticaria                   |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Renal and urinary disorders |               |                |               |
| Chromaturia                 |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Glycosuria                  |               |                |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0              | 0             |
| Proteinuria                 |               |                |               |

|  |                    |                    |                    |
|--|--------------------|--------------------|--------------------|
| subjects affected / exposed<br>occurrences (all)       | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| <b>Musculoskeletal and connective tissue disorders</b> |                    |                    |                    |
| Back pain  |                    |                    |                    |
| subjects affected / exposed                            | 0 / 6 (0.00%)      | 1 / 6 (16.67%)     | 0 / 6 (0.00%)      |
| occurrences (all)                                      | 0                  | 1                  | 0                  |
| Joint swelling   |                    |                    |                    |
| subjects affected / exposed                            | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                      | 0                  | 0                  | 0                  |
| Muscle spasms  |                    |                    |                    |
| subjects affected / exposed                            | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                      | 0                  | 0                  | 0                  |
| Musculoskeletal chest pain                             |                    |                    |                    |
| subjects affected / exposed                            | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                      | 0                  | 0                  | 0                  |
| Musculoskeletal pain                                   |                    |                    |                    |
| subjects affected / exposed                            | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                      | 0                  | 0                  | 0                  |
| Musculoskeletal stiffness                              |                    |                    |                    |
| subjects affected / exposed                            | 0 / 6 (0.00%)      | 1 / 6 (16.67%)     | 0 / 6 (0.00%)      |
| occurrences (all)                                      | 0                  | 1                  | 0                  |
| Neck pain  |                    |                    |                    |
| subjects affected / exposed                            | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                      | 0                  | 0                  | 0                  |
| Pain in extremity                                      |                    |                    |                    |
| subjects affected / exposed                            | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                      | 0                  | 0                  | 0                  |
| <b>Infections and infestations</b>                     |                    |                    |                    |
| Bronchitis   |                    |                    |                    |
| subjects affected / exposed                            | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                      | 0                  | 0                  | 0                  |
| Bronchopulmonary aspergillosis allergic                |                    |                    |                    |
| subjects affected / exposed                            | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      | 0 / 6 (0.00%)      |
| occurrences (all)                                      | 0                  | 0                  | 0                  |
| Folliculitis   |                    |                    |                    |

|   |               |                |               |
|---|---------------|----------------|---------------|
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| Fungal infection                                    |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| Gastroenteritis                                     |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| Infective pulmonary exacerbation of cystic fibrosis |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| Nasopharyngitis                                     |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 1              | 0             |
| Oral herpes   |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| Pharyngitis   |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| Sinusitis   |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| Upper respiratory tract infection                   |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| Viral upper respiratory tract infection             |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| Metabolism and nutrition disorders                  |               |                |               |
| Decreased appetite                                  |               |                |               |
| subjects affected / exposed                         | 0 / 6 (0.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0             | 0              | 0             |
| Hypoglycaemia                                       |               |                |               |

|                             |               |               |               |
|-----------------------------|---------------|---------------|---------------|
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |
| Vitamin d deficiency        |               |               |               |
| subjects affected / exposed | 0 / 6 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)           | 0             | 0             | 0             |

| <b>Non-serious adverse events</b>                     | Part 2 Placebo  | Part 3 Placebo<br>C1/C2/C3 | Part 3 QBW251 150<br>mg b.i.d. C1 |
|---|-----------------|----------------------------|-----------------------------------|
| Total subjects affected by non-serious adverse events |                 |                            |                                   |
| subjects affected / exposed                           | 7 / 10 (70.00%) | 8 / 12 (66.67%)            | 5 / 6 (83.33%)                    |
| Vascular disorders                                    |                 |                            |                                   |
| Hot flush   |                 |                            |                                   |
| subjects affected / exposed                           | 0 / 10 (0.00%)  | 0 / 12 (0.00%)             | 0 / 6 (0.00%)                     |
| occurrences (all)                                     | 0               | 0                          | 0                                 |
| General disorders and administration site conditions  |                 |                            |                                   |
| Asthenia  |                 |                            |                                   |
| subjects affected / exposed                           | 0 / 10 (0.00%)  | 0 / 12 (0.00%)             | 0 / 6 (0.00%)                     |
| occurrences (all)                                     | 0               | 0                          | 0                                 |
| Chest discomfort                                      |                 |                            |                                   |
| subjects affected / exposed                           | 0 / 10 (0.00%)  | 2 / 12 (16.67%)            | 0 / 6 (0.00%)                     |
| occurrences (all)                                     | 0               | 2                          | 0                                 |
| Chest pain  |                 |                            |                                   |
| subjects affected / exposed                           | 0 / 10 (0.00%)  | 0 / 12 (0.00%)             | 0 / 6 (0.00%)                     |
| occurrences (all)                                     | 0               | 0                          | 0                                 |
| Fatigue   |                 |                            |                                   |
| subjects affected / exposed                           | 0 / 10 (0.00%)  | 0 / 12 (0.00%)             | 0 / 6 (0.00%)                     |
| occurrences (all)                                     | 0               | 0                          | 0                                 |
| Influenza like illness                                |                 |                            |                                   |
| subjects affected / exposed                           | 0 / 10 (0.00%)  | 0 / 12 (0.00%)             | 0 / 6 (0.00%)                     |
| occurrences (all)                                     | 0               | 0                          | 0                                 |
| Pain  |                 |                            |                                   |
| subjects affected / exposed                           | 0 / 10 (0.00%)  | 0 / 12 (0.00%)             | 0 / 6 (0.00%)                     |
| occurrences (all)                                     | 0               | 0                          | 0                                 |
| Peripheral swelling                                   |                 |                            |                                   |
| subjects affected / exposed                           | 0 / 10 (0.00%)  | 0 / 12 (0.00%)             | 0 / 6 (0.00%)                     |
| occurrences (all)                                     | 0               | 0                          | 0                                 |
| Pyrexia   |                 |                            |                                   |

|   |                      |                      |                     |
|---|----------------------|----------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Sensation of foreign body<br>subjects affected / exposed<br>occurrences (all)   | 0 / 10 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1  | 0 / 6 (0.00%)<br>0  |
| Thirst<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Vessel puncture site bruise<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Respiratory, thoracic and mediastinal disorders                                 |                      |                      |                     |
| Bronchial obstruction<br>subjects affected / exposed<br>occurrences (all)       | 0 / 10 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1  | 0 / 6 (0.00%)<br>0  |
| Cough<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 10 (0.00%)<br>0  | 2 / 12 (16.67%)<br>2 | 1 / 6 (16.67%)<br>1 |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Epistaxis<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 10 (10.00%)<br>1 | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Haemoptysis<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 10 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1  | 0 / 6 (0.00%)<br>0  |
| Nasal congestion<br>subjects affected / exposed<br>occurrences (all)            | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Nasal discomfort<br>subjects affected / exposed<br>occurrences (all)            | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Oropharyngeal pain  |                      |                      |                     |

|                             |                |                 |                |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Painful respiration         |                |                 |                |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Productive cough            |                |                 |                |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 12 (8.33%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Pulmonary congestion        |                |                 |                |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Rhinorrhoea                 |                |                 |                |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Sinus congestion            |                |                 |                |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 12 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)           | 0              | 0               | 1              |
| Sneezing                    |                |                 |                |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Sputum increased            |                |                 |                |
| subjects affected / exposed | 0 / 10 (0.00%) | 2 / 12 (16.67%) | 3 / 6 (50.00%) |
| occurrences (all)           | 0              | 2               | 3              |
| Throat irritation           |                |                 |                |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 12 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)           | 0              | 0               | 1              |
| Tonsillar disorder          |                |                 |                |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 12 (8.33%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 1               | 0              |
| Psychiatric disorders       |                |                 |                |
| Agitation                   |                |                 |                |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |
| Depression                  |                |                 |                |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)           | 0              | 0               | 0              |

|  |                     |                     |                     |
|--|---------------------|---------------------|---------------------|
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 10 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1 | 1 / 6 (16.67%)<br>1 |
| Stress<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 10 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Investigations   |                     |                     |                     |
| Adenovirus test positive<br>subjects affected / exposed<br>occurrences (all)             | 0 / 10 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Blood potassium decreased<br>subjects affected / exposed<br>occurrences (all)            | 0 / 10 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Breath sounds abnormal<br>subjects affected / exposed<br>occurrences (all)               | 0 / 10 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Coronavirus test positive<br>subjects affected / exposed<br>occurrences (all)            | 0 / 10 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Injury, poisoning and procedural complications   |                     |                     |                     |
| Arthropod bite<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 10 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 10 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1 | 0 / 6 (0.00%)<br>0  |
| Skin wound<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 10 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Congenital, familial and genetic disorders   |                     |                     |                     |
| Ichthyosis<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 10 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1 | 0 / 6 (0.00%)<br>0  |

|                             |                 |                |                |
|-----------------------------|-----------------|----------------|----------------|
| Cardiac disorders           |                 |                |                |
| Palpitations                |                 |                |                |
| subjects affected / exposed | 0 / 10 (0.00%)  | 1 / 12 (8.33%) | 1 / 6 (16.67%) |
| occurrences (all)           | 0               | 1              | 1              |
| Nervous system disorders    |                 |                |                |
| Balance disorder            |                 |                |                |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 1               | 0              | 0              |
| Dizziness                   |                 |                |                |
| subjects affected / exposed | 2 / 10 (20.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 2               | 0              | 0              |
| Headache                    |                 |                |                |
| subjects affected / exposed | 4 / 10 (40.00%) | 0 / 12 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)           | 4               | 0              | 1              |
| Hyperaesthesia              |                 |                |                |
| subjects affected / exposed | 0 / 10 (0.00%)  | 0 / 12 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0               | 0              | 0              |
| Presyncope                  |                 |                |                |
| subjects affected / exposed | 0 / 10 (0.00%)  | 0 / 12 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0               | 0              | 0              |
| Sciatica                    |                 |                |                |
| subjects affected / exposed | 0 / 10 (0.00%)  | 0 / 12 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0               | 0              | 0              |
| Syncope                     |                 |                |                |
| subjects affected / exposed | 0 / 10 (0.00%)  | 0 / 12 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)           | 0               | 0              | 1              |
| Tremor                      |                 |                |                |
| subjects affected / exposed | 0 / 10 (0.00%)  | 0 / 12 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0               | 0              | 0              |
| Ear and labyrinth disorders |                 |                |                |
| Ear discomfort              |                 |                |                |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 1               | 0              | 0              |
| Ear pain                    |                 |                |                |
| subjects affected / exposed | 0 / 10 (0.00%)  | 0 / 12 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)           | 0               | 0              | 0              |
| Tinnitus                    |                 |                |                |

|  |                      |                     |                     |
|--|----------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                     | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 |
| <b>Gastrointestinal disorders</b>  |                      |                     |                     |
| Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all)             | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all)             | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 10 (10.00%)<br>1 | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Abdominal pain lower<br>subjects affected / exposed<br>occurrences (all)             | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Aphthous stomatitis<br>subjects affected / exposed<br>occurrences (all)              | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 10 (10.00%)<br>1 | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Faeces discoloured<br>subjects affected / exposed<br>occurrences (all)               | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Flatulence<br>subjects affected / exposed<br>occurrences (all)                       | 2 / 10 (20.00%)<br>2 | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Gingival disorder<br>subjects affected / exposed<br>occurrences (all)                | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 |

|   |                |                |                |
|---|----------------|----------------|----------------|
| Saliva altered                                |                |                |                |
| subjects affected / exposed                   | 0 / 10 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0              | 0              |
| Salivary gland pain                           |                |                |                |
| subjects affected / exposed                   | 0 / 10 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0              | 0              |
| Vomiting                                      |                |                |                |
| subjects affected / exposed                   | 0 / 10 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0              | 0              |
| <b>Skin and subcutaneous tissue disorders</b> |                |                |                |
| Erythema                                      |                |                |                |
| subjects affected / exposed                   | 0 / 10 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0              | 0              |
| Heat rash                                     |                |                |                |
| subjects affected / exposed                   | 0 / 10 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0              | 0              |
| Night sweats                                  |                |                |                |
| subjects affected / exposed                   | 0 / 10 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0              | 0              |
| Photosensitivity reaction                     |                |                |                |
| subjects affected / exposed                   | 0 / 10 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0              | 0              |
| Pruritus                                      |                |                |                |
| subjects affected / exposed                   | 0 / 10 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0              | 0              |
| Pruritus generalised                          |                |                |                |
| subjects affected / exposed                   | 0 / 10 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0              | 0              |
| Rash  |                |                |                |
| subjects affected / exposed                   | 0 / 10 (0.00%) | 0 / 12 (0.00%) | 0 / 6 (0.00%)  |
| occurrences (all)                             | 0              | 0              | 0              |
| Rash erythematous                             |                |                |                |
| subjects affected / exposed                   | 0 / 10 (0.00%) | 0 / 12 (0.00%) | 1 / 6 (16.67%) |
| occurrences (all)                             | 0              | 0              | 1              |
| Rash pruritic                                 |                |                |                |

|  |                      |                     |                    |
|--|----------------------|---------------------|--------------------|
| subjects affected / exposed<br>occurrences (all)   | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Urticaria<br>subjects affected / exposed<br>occurrences (all)  | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Renal and urinary disorders<br>Chromaturia<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Glycosuria<br>subjects affected / exposed<br>occurrences (all)   | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Proteinuria<br>subjects affected / exposed<br>occurrences (all)  | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Musculoskeletal and connective tissue disorders<br>Back pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Joint swelling<br>subjects affected / exposed<br>occurrences (all)   | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)  | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all)                                   | 0 / 10 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1 | 0 / 6 (0.00%)<br>0 |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)   | 1 / 10 (10.00%)<br>2 | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Musculoskeletal stiffness<br>subjects affected / exposed<br>occurrences (all)                                    | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Neck pain  |                      |                     |                    |

|   |                      |                      |                     |
|---|----------------------|----------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                      | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0  | 1 / 12 (8.33%)<br>1  | 0 / 6 (0.00%)<br>0  |
| <b>Infections and infestations</b>                                    |                      |                      |                     |
| <b>Bronchitis</b>   |                      |                      |                     |
| subjects affected / exposed<br>occurrences (all)                      | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| <b>Bronchopulmonary aspergillosis<br/>allergic</b>                    |                      |                      |                     |
| subjects affected / exposed<br>occurrences (all)                      | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| <b>Folliculitis</b>   |                      |                      |                     |
| subjects affected / exposed<br>occurrences (all)                      | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| <b>Fungal infection</b>   |                      |                      |                     |
| subjects affected / exposed<br>occurrences (all)                      | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| <b>Gastroenteritis</b>  |                      |                      |                     |
| subjects affected / exposed<br>occurrences (all)                      | 1 / 10 (10.00%)<br>1 | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| <b>Infective pulmonary exacerbation of<br/>cystic fibrosis</b>        |                      |                      |                     |
| subjects affected / exposed<br>occurrences (all)                      | 0 / 10 (0.00%)<br>0  | 3 / 12 (25.00%)<br>3 | 1 / 6 (16.67%)<br>1 |
| <b>Nasopharyngitis</b>  |                      |                      |                     |
| subjects affected / exposed<br>occurrences (all)                      | 1 / 10 (10.00%)<br>1 | 1 / 12 (8.33%)<br>1  | 0 / 6 (0.00%)<br>0  |
| <b>Oral herpes</b>  |                      |                      |                     |
| subjects affected / exposed<br>occurrences (all)                      | 0 / 10 (0.00%)<br>0  | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| <b>Pharyngitis</b>  |                      |                      |                     |
| subjects affected / exposed<br>occurrences (all)                      | 1 / 10 (10.00%)<br>1 | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| <b>Sinusitis</b>  |                      |                      |                     |

|   |                     |                     |                     |
|---|---------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 10 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all)       | 0 / 10 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 0 / 10 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| <b>Metabolism and nutrition disorders</b>   |                     |                     |                     |
| Decreased appetite<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 10 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Hypoglycaemia<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 10 (0.00%)<br>0 | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  |
| Vitamin d deficiency<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 10 (0.00%)<br>0 | 1 / 12 (8.33%)<br>1 | 0 / 6 (0.00%)<br>0  |

| <b>Non-serious adverse events</b>   | Part 3 QBW251 450<br>mg b.i.d. C2 | Part 2 QBW251 450<br>mg bid | Part 2 QBW251 750<br>mg bid |
|---|-----------------------------------|-----------------------------|-----------------------------|
| Total subjects affected by non-serious<br>adverse events<br>subjects affected / exposed | 8 / 12 (66.67%)                   | 6 / 6 (100.00%)             | 4 / 6 (66.67%)              |
| <b>Vascular disorders</b>   |                                   |                             |                             |
| Hot flush<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 12 (0.00%)<br>0               | 0 / 6 (0.00%)<br>0          | 0 / 6 (0.00%)<br>0          |
| <b>General disorders and administration<br/>site conditions</b>                         |                                   |                             |                             |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)                            | 1 / 12 (8.33%)<br>1               | 0 / 6 (0.00%)<br>0          | 0 / 6 (0.00%)<br>0          |
| Chest discomfort<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 12 (0.00%)<br>0               | 0 / 6 (0.00%)<br>0          | 0 / 6 (0.00%)<br>0          |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 12 (0.00%)<br>0               | 0 / 6 (0.00%)<br>0          | 0 / 6 (0.00%)<br>0          |

|   |                 |                |               |
|---|-----------------|----------------|---------------|
| Fatigue   |                 |                |               |
| subjects affected / exposed                     | 3 / 12 (25.00%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 3               | 0              | 0             |
| Influenza like illness                          |                 |                |               |
| subjects affected / exposed                     | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0               | 0              | 0             |
| Pain  |                 |                |               |
| subjects affected / exposed                     | 1 / 12 (8.33%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 1               | 0              | 0             |
| Peripheral swelling                             |                 |                |               |
| subjects affected / exposed                     | 1 / 12 (8.33%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 1               | 0              | 0             |
| Pyrexia   |                 |                |               |
| subjects affected / exposed                     | 1 / 12 (8.33%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 1               | 0              | 0             |
| Sensation of foreign body                       |                 |                |               |
| subjects affected / exposed                     | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0               | 0              | 0             |
| Thirst  |                 |                |               |
| subjects affected / exposed                     | 0 / 12 (0.00%)  | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0               | 1              | 0             |
| Vessel puncture site bruise                     |                 |                |               |
| subjects affected / exposed                     | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0               | 0              | 0             |
| Respiratory, thoracic and mediastinal disorders |                 |                |               |
| Bronchial obstruction                           |                 |                |               |
| subjects affected / exposed                     | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0               | 0              | 0             |
| Cough   |                 |                |               |
| subjects affected / exposed                     | 1 / 12 (8.33%)  | 4 / 6 (66.67%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 1               | 4              | 0             |
| Dyspnoea  |                 |                |               |
| subjects affected / exposed                     | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)                               | 0               | 0              | 0             |
| Epistaxis                                       |                 |                |               |

|                             |                 |                |               |
|-----------------------------|-----------------|----------------|---------------|
| subjects affected / exposed | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0               | 0              | 0             |
| <b>Haemoptysis</b>          |                 |                |               |
| subjects affected / exposed | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0               | 0              | 0             |
| <b>Nasal congestion</b>     |                 |                |               |
| subjects affected / exposed | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0               | 0              | 0             |
| <b>Nasal discomfort</b>     |                 |                |               |
| subjects affected / exposed | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0               | 0              | 0             |
| <b>Oropharyngeal pain</b>   |                 |                |               |
| subjects affected / exposed | 1 / 12 (8.33%)  | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all)           | 1               | 1              | 0             |
| <b>Painful respiration</b>  |                 |                |               |
| subjects affected / exposed | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0               | 0              | 0             |
| <b>Productive cough</b>     |                 |                |               |
| subjects affected / exposed | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0               | 0              | 0             |
| <b>Pulmonary congestion</b> |                 |                |               |
| subjects affected / exposed | 2 / 12 (16.67%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 2               | 0              | 0             |
| <b>Rhinorrhoea</b>          |                 |                |               |
| subjects affected / exposed | 1 / 12 (8.33%)  | 1 / 6 (16.67%) | 0 / 6 (0.00%) |
| occurrences (all)           | 1               | 1              | 0             |
| <b>Sinus congestion</b>     |                 |                |               |
| subjects affected / exposed | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0               | 0              | 0             |
| <b>Sneezing</b>             |                 |                |               |
| subjects affected / exposed | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0               | 0              | 0             |
| <b>Sputum increased</b>     |                 |                |               |
| subjects affected / exposed | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%) |
| occurrences (all)           | 0               | 0              | 0             |
| <b>Throat irritation</b>    |                 |                |               |

|  |                     |                    |                    |
|--|---------------------|--------------------|--------------------|
| subjects affected / exposed<br>occurrences (all)   | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Tonsillar disorder<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Psychiatric disorders  |                     |                    |                    |
| Agitation<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Depression<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Stress<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Investigations   |                     |                    |                    |
| Adenovirus test positive<br>subjects affected / exposed<br>occurrences (all)             | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Blood potassium decreased<br>subjects affected / exposed<br>occurrences (all)            | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Breath sounds abnormal<br>subjects affected / exposed<br>occurrences (all)               | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Coronavirus test positive<br>subjects affected / exposed<br>occurrences (all)            | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0 |
| Injury, poisoning and procedural complications   |                     |                    |                    |

|  |                      |                     |                     |
|--|----------------------|---------------------|---------------------|
| Arthropod bite<br>subjects affected / exposed<br>occurrences (all)   | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Skin wound<br>subjects affected / exposed<br>occurrences (all)   | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Congenital, familial and genetic disorders<br>Ichthyosis<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Cardiac disorders<br>Palpitations<br>subjects affected / exposed<br>occurrences (all)                        | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Nervous system disorders<br>Balance disorder<br>subjects affected / exposed<br>occurrences (all)             | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Dizziness<br>subjects affected / exposed<br>occurrences (all)  | 2 / 12 (16.67%)<br>3 | 1 / 6 (16.67%)<br>1 | 0 / 6 (0.00%)<br>0  |
| Headache<br>subjects affected / exposed<br>occurrences (all)   | 3 / 12 (25.00%)<br>4 | 1 / 6 (16.67%)<br>1 | 2 / 6 (33.33%)<br>2 |
| Hyperaesthesia<br>subjects affected / exposed<br>occurrences (all)   | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Presyncope<br>subjects affected / exposed<br>occurrences (all)   | 0 / 12 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |
| Sciatica<br>subjects affected / exposed<br>occurrences (all)   | 1 / 12 (8.33%)<br>1  | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0  |

|  |                     |                     |                    |
|--|---------------------|---------------------|--------------------|
| Syncope<br>subjects affected / exposed<br>occurrences (all)              | 0 / 12 (0.00%)<br>0 | 1 / 6 (16.67%)<br>1 | 0 / 6 (0.00%)<br>0 |
| Tremor<br>subjects affected / exposed<br>occurrences (all)               | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Ear and labyrinth disorders  |                     |                     |                    |
| Ear discomfort<br>subjects affected / exposed<br>occurrences (all)       | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Ear pain<br>subjects affected / exposed<br>occurrences (all)             | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)             | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Gastrointestinal disorders   |                     |                     |                    |
| Abdominal discomfort<br>subjects affected / exposed<br>occurrences (all) | 1 / 12 (8.33%)<br>1 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Abdominal distension<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)       | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Abdominal pain lower<br>subjects affected / exposed<br>occurrences (all) | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Aphthous stomatitis<br>subjects affected / exposed<br>occurrences (all)  | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)            | 0 / 12 (0.00%)<br>0 | 0 / 6 (0.00%)<br>0  | 0 / 6 (0.00%)<br>0 |
| Faeces discoloured   |                     |                     |                    |

|  |                 |                |                |
|--|-----------------|----------------|----------------|
| subjects affected / exposed            | 1 / 12 (8.33%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                      | 1               | 0              | 0              |
| Flatulence                             |                 |                |                |
| subjects affected / exposed            | 1 / 12 (8.33%)  | 4 / 6 (66.67%) | 0 / 6 (0.00%)  |
| occurrences (all)                      | 1               | 4              | 0              |
| Gastroesophageal reflux disease        |                 |                |                |
| subjects affected / exposed            | 1 / 12 (8.33%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                      | 1               | 0              | 0              |
| Gingival disorder                      |                 |                |                |
| subjects affected / exposed            | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                      | 0               | 0              | 0              |
| Nausea                                 |                 |                |                |
| subjects affected / exposed            | 4 / 12 (33.33%) | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                      | 4               | 0              | 0              |
| Saliva altered                         |                 |                |                |
| subjects affected / exposed            | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)                      | 0               | 0              | 1              |
| Salivary gland pain                    |                 |                |                |
| subjects affected / exposed            | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                      | 0               | 0              | 0              |
| Vomiting                               |                 |                |                |
| subjects affected / exposed            | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                      | 0               | 0              | 0              |
| Skin and subcutaneous tissue disorders |                 |                |                |
| Erythema                               |                 |                |                |
| subjects affected / exposed            | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                      | 0               | 0              | 0              |
| Heat rash                              |                 |                |                |
| subjects affected / exposed            | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 1 / 6 (16.67%) |
| occurrences (all)                      | 0               | 0              | 1              |
| Night sweats                           |                 |                |                |
| subjects affected / exposed            | 1 / 12 (8.33%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                      | 1               | 0              | 0              |
| Photosensitivity reaction              |                 |                |                |
| subjects affected / exposed            | 0 / 12 (0.00%)  | 0 / 6 (0.00%)  | 0 / 6 (0.00%)  |
| occurrences (all)                      | 0               | 0              | 0              |

|   |                |               |               |
|---|----------------|---------------|---------------|
| Pruritus  |                |               |               |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0             | 0             |
| Pruritus generalised                            |                |               |               |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0             | 0             |
| Rash  |                |               |               |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0             | 0             |
| Rash erythematous                               |                |               |               |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0             | 0             |
| Rash pruritic                                   |                |               |               |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0             | 0             |
| Urticaria                                       |                |               |               |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0             | 0             |
| Renal and urinary disorders                     |                |               |               |
| Chromaturia                                     |                |               |               |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0             | 0             |
| Glycosuria                                      |                |               |               |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0             | 0             |
| Proteinuria                                     |                |               |               |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0             | 0             |
| Musculoskeletal and connective tissue disorders |                |               |               |
| Back pain                                       |                |               |               |
| subjects affected / exposed                     | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 0              | 0             | 0             |
| Joint swelling                                  |                |               |               |
| subjects affected / exposed                     | 1 / 12 (8.33%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                               | 1              | 0             | 0             |
| Muscle spasms                                   |                |               |               |

|   |                |               |               |
|---|----------------|---------------|---------------|
| subjects affected / exposed                         | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0              | 0             | 0             |
| Musculoskeletal chest pain                          |                |               |               |
| subjects affected / exposed                         | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0              | 0             | 0             |
| Musculoskeletal pain                                |                |               |               |
| subjects affected / exposed                         | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0              | 0             | 0             |
| Musculoskeletal stiffness                           |                |               |               |
| subjects affected / exposed                         | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0              | 0             | 0             |
| Neck pain   |                |               |               |
| subjects affected / exposed                         | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0              | 0             | 0             |
| Pain in extremity                                   |                |               |               |
| subjects affected / exposed                         | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0              | 0             | 0             |
| Infections and infestations                         |                |               |               |
| Bronchitis  |                |               |               |
| subjects affected / exposed                         | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0              | 0             | 0             |
| Bronchopulmonary aspergillosis allergic             |                |               |               |
| subjects affected / exposed                         | 1 / 12 (8.33%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 1              | 0             | 0             |
| Folliculitis  |                |               |               |
| subjects affected / exposed                         | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0              | 0             | 0             |
| Fungal infection                                    |                |               |               |
| subjects affected / exposed                         | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0              | 0             | 0             |
| Gastroenteritis                                     |                |               |               |
| subjects affected / exposed                         | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                                   | 0              | 0             | 0             |
| Infective pulmonary exacerbation of cystic fibrosis |                |               |               |

|  |                |               |               |
|--|----------------|---------------|---------------|
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| <b>Nasopharyngitis</b>                         |                |               |               |
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| <b>Oral herpes</b>                             |                |               |               |
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| <b>Pharyngitis</b>                             |                |               |               |
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| <b>Sinusitis</b>                               |                |               |               |
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| <b>Upper respiratory tract infection</b>       |                |               |               |
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| <b>Viral upper respiratory tract infection</b> |                |               |               |
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| <b>Metabolism and nutrition disorders</b>      |                |               |               |
| <b>Decreased appetite</b>                      |                |               |               |
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| <b>Hypoglycaemia</b>                           |                |               |               |
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |
| <b>Vitamin d deficiency</b>                    |                |               |               |
| subjects affected / exposed                    | 0 / 12 (0.00%) | 0 / 6 (0.00%) | 0 / 6 (0.00%) |
| occurrences (all)                              | 0              | 0             | 0             |

|  |                                   |  |  |
|--|-----------------------------------|--|--|
| <b>Non-serious adverse events</b>                        | Part 3 QBW251 450<br>mg b.i.d. C3 |  |  |
| Total subjects affected by non-serious<br>adverse events |                                   |  |  |
| subjects affected / exposed                              | 18 / 19 (94.74%)                  |  |  |
| Vascular disorders                                       |                                   |  |  |

|  |                 |  |  |
|--|-----------------|--|--|
| Hot flush  |                 |  |  |
| subjects affected / exposed                          | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                                    | 0               |  |  |
| General disorders and administration site conditions |                 |  |  |
| Asthenia   |                 |  |  |
| subjects affected / exposed                          | 1 / 19 (5.26%)  |  |  |
| occurrences (all)                                    | 1               |  |  |
| Chest discomfort                                     |                 |  |  |
| subjects affected / exposed                          | 1 / 19 (5.26%)  |  |  |
| occurrences (all)                                    | 1               |  |  |
| Chest pain   |                 |  |  |
| subjects affected / exposed                          | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                                    | 0               |  |  |
| Fatigue  |                 |  |  |
| subjects affected / exposed                          | 2 / 19 (10.53%) |  |  |
| occurrences (all)                                    | 2               |  |  |
| Influenza like illness                               |                 |  |  |
| subjects affected / exposed                          | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                                    | 0               |  |  |
| Pain   |                 |  |  |
| subjects affected / exposed                          | 1 / 19 (5.26%)  |  |  |
| occurrences (all)                                    | 2               |  |  |
| Peripheral swelling                                  |                 |  |  |
| subjects affected / exposed                          | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                                    | 0               |  |  |
| Pyrexia  |                 |  |  |
| subjects affected / exposed                          | 1 / 19 (5.26%)  |  |  |
| occurrences (all)                                    | 1               |  |  |
| Sensation of foreign body                            |                 |  |  |
| subjects affected / exposed                          | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                                    | 0               |  |  |
| Thirst   |                 |  |  |
| subjects affected / exposed                          | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                                    | 0               |  |  |
| Vessel puncture site bruise                          |                 |  |  |

|  |                     |  |  |
|--|---------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 19 (5.26%)<br>1 |  |  |
| Respiratory, thoracic and mediastinal disorders  |                     |  |  |
| Bronchial obstruction                            |                     |  |  |
| subjects affected / exposed                      | 0 / 19 (0.00%)      |  |  |
| occurrences (all)                                | 0                   |  |  |
| Cough  |                     |  |  |
| subjects affected / exposed                      | 4 / 19 (21.05%)     |  |  |
| occurrences (all)                                | 5                   |  |  |
| Dyspnoea   |                     |  |  |
| subjects affected / exposed                      | 0 / 19 (0.00%)      |  |  |
| occurrences (all)                                | 0                   |  |  |
| Epistaxis  |                     |  |  |
| subjects affected / exposed                      | 0 / 19 (0.00%)      |  |  |
| occurrences (all)                                | 0                   |  |  |
| Haemoptysis                                      |                     |  |  |
| subjects affected / exposed                      | 2 / 19 (10.53%)     |  |  |
| occurrences (all)                                | 3                   |  |  |
| Nasal congestion                                 |                     |  |  |
| subjects affected / exposed                      | 2 / 19 (10.53%)     |  |  |
| occurrences (all)                                | 2                   |  |  |
| Nasal discomfort                                 |                     |  |  |
| subjects affected / exposed                      | 0 / 19 (0.00%)      |  |  |
| occurrences (all)                                | 0                   |  |  |
| Oropharyngeal pain                               |                     |  |  |
| subjects affected / exposed                      | 0 / 19 (0.00%)      |  |  |
| occurrences (all)                                | 0                   |  |  |
| Painful respiration                              |                     |  |  |
| subjects affected / exposed                      | 1 / 19 (5.26%)      |  |  |
| occurrences (all)                                | 1                   |  |  |
| Productive cough                                 |                     |  |  |
| subjects affected / exposed                      | 0 / 19 (0.00%)      |  |  |
| occurrences (all)                                | 0                   |  |  |
| Pulmonary congestion                             |                     |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                       | 1 / 19 (5.26%)<br>1  |  |  |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)        | 2 / 19 (10.53%)<br>2 |  |  |
| Sinus congestion<br>subjects affected / exposed<br>occurrences (all)   | 1 / 19 (5.26%)<br>1  |  |  |
| Sneezing<br>subjects affected / exposed<br>occurrences (all)           | 1 / 19 (5.26%)<br>1  |  |  |
| Sputum increased<br>subjects affected / exposed<br>occurrences (all)   | 5 / 19 (26.32%)<br>5 |  |  |
| Throat irritation<br>subjects affected / exposed<br>occurrences (all)  | 0 / 19 (0.00%)<br>0  |  |  |
| Tonsillar disorder<br>subjects affected / exposed<br>occurrences (all) | 0 / 19 (0.00%)<br>0  |  |  |
| Psychiatric disorders  |                      |  |  |
| Agitation<br>subjects affected / exposed<br>occurrences (all)          | 1 / 19 (5.26%)<br>1  |  |  |
| Depression<br>subjects affected / exposed<br>occurrences (all)         | 1 / 19 (5.26%)<br>1  |  |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)           | 0 / 19 (0.00%)<br>0  |  |  |
| Stress<br>subjects affected / exposed<br>occurrences (all)             | 1 / 19 (5.26%)<br>1  |  |  |
| Investigations<br>Adenovirus test positive                             |                      |  |  |

|  |                     |  |  |
|--|---------------------|--|--|
| subjects affected / exposed<br>occurrences (all)   | 1 / 19 (5.26%)<br>1 |  |  |
| Blood alkaline phosphatase increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 19 (5.26%)<br>1 |  |  |
| Blood potassium decreased<br>subjects affected / exposed<br>occurrences (all)            | 1 / 19 (5.26%)<br>1 |  |  |
| Breath sounds abnormal<br>subjects affected / exposed<br>occurrences (all)               | 1 / 19 (5.26%)<br>1 |  |  |
| Coronavirus test positive<br>subjects affected / exposed<br>occurrences (all)            | 1 / 19 (5.26%)<br>1 |  |  |
| Injury, poisoning and procedural complications   |                     |  |  |
| Arthropod bite<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 19 (5.26%)<br>1 |  |  |
| Ligament sprain<br>subjects affected / exposed<br>occurrences (all)                      | 0 / 19 (0.00%)<br>0 |  |  |
| Skin wound<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 19 (0.00%)<br>0 |  |  |
| Congenital, familial and genetic disorders   |                     |  |  |
| Ichthyosis<br>subjects affected / exposed<br>occurrences (all)                           | 0 / 19 (0.00%)<br>0 |  |  |
| Cardiac disorders  |                     |  |  |
| Palpitations<br>subjects affected / exposed<br>occurrences (all)                         | 0 / 19 (0.00%)<br>0 |  |  |
| Nervous system disorders   |                     |  |  |
| Balance disorder<br>subjects affected / exposed<br>occurrences (all)                     | 0 / 19 (0.00%)<br>0 |  |  |

|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| Dizziness                   |                 |  |  |
| subjects affected / exposed | 1 / 19 (5.26%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Headache                    |                 |  |  |
| subjects affected / exposed | 4 / 19 (21.05%) |  |  |
| occurrences (all)           | 6               |  |  |
| Hyperaesthesia              |                 |  |  |
| subjects affected / exposed | 0 / 19 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Presyncope                  |                 |  |  |
| subjects affected / exposed | 0 / 19 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Sciatica                    |                 |  |  |
| subjects affected / exposed | 0 / 19 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Syncope                     |                 |  |  |
| subjects affected / exposed | 1 / 19 (5.26%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Tremor                      |                 |  |  |
| subjects affected / exposed | 1 / 19 (5.26%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Ear and labyrinth disorders |                 |  |  |
| Ear discomfort              |                 |  |  |
| subjects affected / exposed | 0 / 19 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Ear pain                    |                 |  |  |
| subjects affected / exposed | 0 / 19 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Tinnitus                    |                 |  |  |
| subjects affected / exposed | 0 / 19 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |
| Gastrointestinal disorders  |                 |  |  |
| Abdominal discomfort        |                 |  |  |
| subjects affected / exposed | 1 / 19 (5.26%)  |  |  |
| occurrences (all)           | 1               |  |  |
| Abdominal distension        |                 |  |  |

|                                  |                 |  |  |
|----------------------------------|-----------------|--|--|
| subjects affected / exposed      | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                | 0               |  |  |
| Abdominal pain                   |                 |  |  |
| subjects affected / exposed      | 1 / 19 (5.26%)  |  |  |
| occurrences (all)                | 1               |  |  |
| Abdominal pain lower             |                 |  |  |
| subjects affected / exposed      | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                | 0               |  |  |
| Aphthous stomatitis              |                 |  |  |
| subjects affected / exposed      | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                | 0               |  |  |
| Diarrhoea                        |                 |  |  |
| subjects affected / exposed      | 2 / 19 (10.53%) |  |  |
| occurrences (all)                | 2               |  |  |
| Faeces discoloured               |                 |  |  |
| subjects affected / exposed      | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                | 0               |  |  |
| Flatulence                       |                 |  |  |
| subjects affected / exposed      | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                | 0               |  |  |
| Gastrooesophageal reflux disease |                 |  |  |
| subjects affected / exposed      | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                | 0               |  |  |
| Gingival disorder                |                 |  |  |
| subjects affected / exposed      | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                | 0               |  |  |
| Nausea                           |                 |  |  |
| subjects affected / exposed      | 2 / 19 (10.53%) |  |  |
| occurrences (all)                | 2               |  |  |
| Saliva altered                   |                 |  |  |
| subjects affected / exposed      | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                | 0               |  |  |
| Salivary gland pain              |                 |  |  |
| subjects affected / exposed      | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                | 0               |  |  |
| Vomiting                         |                 |  |  |

|  |                      |  |  |
|--|----------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 2 / 19 (10.53%)<br>2 |  |  |
| <b>Skin and subcutaneous tissue disorders</b>    |                      |  |  |
| <b>Erythema</b>                                  |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 19 (5.26%)<br>1  |  |  |
| <b>Heat rash</b>                                 |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 19 (0.00%)<br>0  |  |  |
| <b>Night sweats</b>                              |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 19 (0.00%)<br>0  |  |  |
| <b>Photosensitivity reaction</b>                 |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 19 (5.26%)<br>1  |  |  |
| <b>Pruritus</b>                                  |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 2 / 19 (10.53%)<br>2 |  |  |
| <b>Pruritus generalised</b>                      |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 19 (0.00%)<br>0  |  |  |
| <b>Rash</b>                                      |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 1 / 19 (5.26%)<br>1  |  |  |
| <b>Rash erythematous</b>                         |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 19 (0.00%)<br>0  |  |  |
| <b>Rash pruritic</b>                             |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 19 (0.00%)<br>0  |  |  |
| <b>Urticaria</b>                                 |                      |  |  |
| subjects affected / exposed<br>occurrences (all) | 0 / 19 (0.00%)<br>0  |  |  |
| <b>Renal and urinary disorders</b>               |                      |  |  |
| <b>Chromaturia</b>                               |                      |  |  |

|  |                     |  |  |
|--|---------------------|--|--|
| subjects affected / exposed<br>occurrences (all)                               | 1 / 19 (5.26%)<br>1 |  |  |
| Glycosuria<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 19 (5.26%)<br>1 |  |  |
| Proteinuria<br>subjects affected / exposed<br>occurrences (all)                | 1 / 19 (5.26%)<br>1 |  |  |
| Musculoskeletal and connective tissue disorders                                |                     |  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 19 (0.00%)<br>0 |  |  |
| Joint swelling<br>subjects affected / exposed<br>occurrences (all)             | 0 / 19 (0.00%)<br>0 |  |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all)              | 1 / 19 (5.26%)<br>1 |  |  |
| Musculoskeletal chest pain<br>subjects affected / exposed<br>occurrences (all) | 0 / 19 (0.00%)<br>0 |  |  |
| Musculoskeletal pain<br>subjects affected / exposed<br>occurrences (all)       | 0 / 19 (0.00%)<br>0 |  |  |
| Musculoskeletal stiffness<br>subjects affected / exposed<br>occurrences (all)  | 0 / 19 (0.00%)<br>0 |  |  |
| Neck pain<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 19 (5.26%)<br>1 |  |  |
| Pain in extremity<br>subjects affected / exposed<br>occurrences (all)          | 0 / 19 (0.00%)<br>0 |  |  |
| Infections and infestations  |                     |  |  |

|   |                 |  |  |
|---|-----------------|--|--|
| Bronchitis  |                 |  |  |
| subjects affected / exposed                         | 1 / 19 (5.26%)  |  |  |
| occurrences (all)                                   | 1               |  |  |
| Bronchopulmonary aspergillosis allergic             |                 |  |  |
| subjects affected / exposed                         | 1 / 19 (5.26%)  |  |  |
| occurrences (all)                                   | 1               |  |  |
| Folliculitis  |                 |  |  |
| subjects affected / exposed                         | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                                   | 0               |  |  |
| Fungal infection                                    |                 |  |  |
| subjects affected / exposed                         | 1 / 19 (5.26%)  |  |  |
| occurrences (all)                                   | 1               |  |  |
| Gastroenteritis                                     |                 |  |  |
| subjects affected / exposed                         | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                                   | 0               |  |  |
| Infective pulmonary exacerbation of cystic fibrosis |                 |  |  |
| subjects affected / exposed                         | 2 / 19 (10.53%) |  |  |
| occurrences (all)                                   | 2               |  |  |
| Nasopharyngitis                                     |                 |  |  |
| subjects affected / exposed                         | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                                   | 0               |  |  |
| Oral herpes   |                 |  |  |
| subjects affected / exposed                         | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                                   | 0               |  |  |
| Pharyngitis   |                 |  |  |
| subjects affected / exposed                         | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                                   | 0               |  |  |
| Sinusitis   |                 |  |  |
| subjects affected / exposed                         | 0 / 19 (0.00%)  |  |  |
| occurrences (all)                                   | 0               |  |  |
| Upper respiratory tract infection                   |                 |  |  |
| subjects affected / exposed                         | 1 / 19 (5.26%)  |  |  |
| occurrences (all)                                   | 1               |  |  |
| Viral upper respiratory tract infection             |                 |  |  |

|  |                     |  |  |
|--|---------------------|--|--|
| subjects affected / exposed<br>occurrences (all) | 1 / 19 (5.26%)<br>1 |  |  |
| Metabolism and nutrition disorders               |                     |  |  |
| Decreased appetite                               |                     |  |  |
| subjects affected / exposed                      | 1 / 19 (5.26%)      |  |  |
| occurrences (all)                                | 1                   |  |  |
| Hypoglycaemia                                    |                     |  |  |
| subjects affected / exposed                      | 1 / 19 (5.26%)      |  |  |
| occurrences (all)                                | 2                   |  |  |
| Vitamin d deficiency                             |                     |  |  |
| subjects affected / exposed                      | 0 / 19 (0.00%)      |  |  |
| occurrences (all)                                | 0                   |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 14 June 2012    | <p>The purpose of this amendment was to respond to the MHRA response received on 07-Jun-2012 regarding 'Discontinuation of study treatment and premature subject withdrawal', which states the following: Discontinuation of study treatment and subject withdrawal was at the discretion of the Investigator, under the following circumstances:</p> <ul style="list-style-type: none"><li>• An SAE that was suspected of being related to study drug</li><li>• An AE which was severe (Grade 3 or greater) and suspected of being related to study drug</li></ul> <p>MHRA stated the above was unacceptable; if either of the situation under 2 bullets occurred the subject was required to be discontinued from the study medication. Minor typographical errors have been addressed throughout the protocol</p>  |
| 10 October 2012 | <p>The purpose of this amendment was to address discrepancies in the assessment schedule with the urine and blood logs in addition to minor clarifications for Parts 1 and Parts 2.</p>   |
| 17 July 2013    | <p>The rationale for this amendment was based on the preliminary PK data from the food effect study performed in Part 1, which demonstrated an approximate 21% and 43% reduction in total (AUCinf) and maximal (Cmax) systemic exposure to QBW251, respectively, as compared to the fasted stated. Having demonstrated the impact of food on the PK of QBW251, it was recognized the need to modify protocol language to allow for dose and dosing frequency under food effect conditions to better represent a real-world clinical situation in Parts 2, 3, and 4. Thus this amendment was provided language that was to allow adaptive dose and dosing frequency in order to achieve optimal exposure below the imposed exposure cap.</p>   |
| 12 August 2013  | <p>Since the last amendment of this protocol two issues have occurred to justify changes, as follows: 1) The protocol underwent review by both the EU and US Cystic Fibrosis networks, and on the basis of these reviews, the protocol was amended to meet their proposed suggestions. 2) New scientific findings now support the rationale for using specific genotypes of CF patients in the current protocol. The new evidence supported that QBW251 would only benefit CF patients that have a mutation in CFTR that allows trafficking of CFTR to the cell membrane (e.g., class III, IV, V, VI CFTR mutations), but require potentiation of the receptor to repair function. On the basis of the above issues, this amendment implemented these changes relevant to Parts 3 and 4 of the protocol related to CF patients. Furthermore, while Part 2 was ongoing per protocol, the study had completed Part 1 of the study</p> |

|                   |  |
|-------------------|--|
| 15 April 2014     | <p>The purpose of this amendment was to address requests from FDA received on 01Apr 2014 regarding:</p> <ul style="list-style-type: none"> <li>•The maximum clinical exposure (exposure cap) supported by nonclinical data was based on the NOEL in monkeys (i.e., AUC0-24 = 47850 ng.hr/mL) instead of those observed at the rat no-observed-adverse-effect-level (i.e., AUC0-24 = 78850 ng×hr/mL). Healthy Volunteer data demonstrated that the exposure at 450 mg b.i.d. (AUC<sub>tau</sub>=12,100 ng×hr/mL or AUC0-24 = 24 200 ng×hr/mL), which was the highest dose planned in the study in CF patients, were approximately 2- and 3- fold below the exposures from monkeys and rats, respectively that produced no adverse findings. Based on this data, the highest planned dose in CF patients at 450 mg b.i.d. was still expected to result in exposures less than the new exposure cap of 47 850 ng×hr/mL.</li> <li>•Use of hyperpolarized helium-3 MRI (exploratory objective). This assessment was removed from Part 4 as the 3He MRI methodology is available only at limited number of centers globally. For the type of CF patient population targeted in this protocol, only three 3He MRI centers could potentially be utilized such that the number of subjects receiving the assessment would not be statistically meaningful. Hence this technology was not deployed in this trial.</li> <li>•Dose-escalation stopping rules</li> <li>•Other minor administrative aspects are clarified.</li> </ul> <p>A copy of this amended protocol was sent to the IRBs / IECs and Health Authorities for approval prior to implementation</p> |
| 15 September 2014 | <p>The purpose of this amendment was to address requests from the Irish Health Authorities regarding the Screening period that was changed from Day –28 to Day –2 to Day –28 to Day –7. This was done in order to minimize risks of early pregnancy by the urine pregnancy test at Baseline (Day –1) in case Screening visit (formal latest start of contraception) was done less than 7 days prior to Baseline (Day –1). The seven days between end of Screening and first study treatment was sufficient for newly started contraception to be effective, and an early pregnancy would not be missed by a negative hCG at baseline visit (Day –1) one day prior to dosing.</p> <p>This amendment also stipulated that patients that were included in Part 3 could not be enrolled in Part 4. At that time, only 28 days of toxicology data was available which was not a sufficient coverage for patients to participate in both, Parts 3 and 4 (total 6 weeks duration).</p> <p>The assessment of effect of QBW251 on height was removed from the exploratory objective.</p> <p>The effect of QBW251 was evaluated on weight and BMI only as we don't expect to see a change in height in the short period of the study.</p>  |

|                  |  |
|------------------|--|
| 16 February 2015 | <p>The purpose of this amendment was to include the assessment of safety, tolerability and efficacy of QBW251 in adult CF patients who are homozygous for the F508del mutation (F508del/F508del). These patients were previously not included in the study due to insufficient pre-clinical data. QBW251 was developed and optimized to potentiate the F508del-CFTR in vitro. Pre-clinical studies had demonstrated that QBW251, as compared to a competitor drug, does not have the same negative effect on cell surface expression and potentiation of human bronchial epithelial cells that express F508del/F508del CFTR (Veit et al 2014 and Cholon et al 2014). In addition, PK studies had showed that QBW251 had an excellent PK profile with lower plasma protein binding and increased free fraction, which supports the notion that a larger proportion of the administered dose may reach the target. Therefore, the inclusion of F508del homozygous patients was based on the rationale that through providing sustained potentiation of F508del-CFTR, QBW251 as monotherapy may provide a clinical benefit to the F508del homozygous patient population without the need to co-administer a corrector to improve surface trafficking of F508del-CFTR. These F508del homozygous patients (n=32) were included in Cohort 3 of Part 3 of the study. Cohort 2 and Cohort 3 of Part 3 of the study were conducted in parallel. In addition to the above rationale for this amendment, this amendment increased the age range for inclusion in Part 3 for Cohort 2 and Cohort 3 from 18 - 55 years to 18 - 65 years. Based on good safety/tolerability profile in 18-55 year olds, and because there was no mechanistic reason to expect a different safety profile in individuals between 55 - 65 years, the upper age limit had been increased to 65 years.</p> |
|------------------|--|

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date             | Interruption  | Restart date |
|------------------|---|--------------|
| 16 November 2015 | An interim analysis was conducted during Part 3 of the study, which demonstrated evidence of efficacy in Cohorts 1 and 2, but futility in cohort 3; hence the study was terminated in Nov 2015 before Cohort 3 was completed. | -            |

Notes:

## Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.

Notes:

