

**Sponsor**

Novartis

**Generic drug name**

QAX576

**Trial indication(s)**

Pulmonary fibrosis secondary to systemic sclerosis

**Protocol number**

CQAX576A2201

**Protocol title**

A randomized, double-blinded, placebo controlled, multiple-dose, multi-center pilot study, to assess safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous doses of QAX576 in patients with pulmonary fibrosis secondary to systemic sclerosis (SSc)

**Clinical trial phase**

Phase IIa

**Study Start/End Dates**

21 Dec 2007 to 08 Apr 2009

**Reason for Termination**

The study was terminated given concerns raised about the risk of the bronchoscopy procedure in the selected patient population and the frequency of SAEs observed to date.

**Study Design/Methodology**

This was a randomized, double-blinded, placebo controlled trial with 3 mg/kg QAX576 or placebo given intravenously once every 3 weeks for a total of 3 doses (over 6 weeks) to patients with pulmonary fibrosis secondary to SSc. The study comprised of a screening period of up to 4 weeks (Day -29 to -5), a baseline (Day -4 to Day -1, which was one to four days before the first dose) and a treatment period consisting of one dose every 3 weeks for a total duration of 6 weeks. Patients had a follow-up visit 4 weeks following completion of the last dose (week 11) and an end-of-study evaluation conducted 24 weeks following completion of the last dose (week 31). In the treatment period, three doses of study drug were given: once each on the first day of week 1, week 4 and week 7 respectively (Days 1, 22 and 43). The study drug was administered as an intravenous infusion over 2 hours. Patients were domiciled at the investigational site for 24 hours after each dose. Patients were to return to the investigational site for the 24 hours post-dose evaluations.

**Centers**

The study was conducted at 6 centres in the United States of America.

**Objectives:****Primary objective(s)**

- To evaluate the safety and tolerability of multiple intravenous doses of QAX576 in patients with pulmonary fibrosis secondary to systemic sclerosis.
- To evaluate the pharmacokinetics of multiple intravenous doses of QAX576 in patients with pulmonary fibrosis secondary to systemic sclerosis.
- To test the hypothesis that QAX576 (3 mg/kg x 3 doses) will neutralize IL-13 in patients with pulmonary fibrosis secondary to systemic sclerosis.

**Secondary objective(s)****Key secondary objectives:**

- To evaluate the effect of multiple intravenous doses of QAX576 on disease modification including pulmonary function tests (PFT), 6 minute walk test (6MWT), oxygen saturation (SpO<sub>2</sub>).

**Test Product (s), Dose(s), and Mode(s) of Administration**

QAX576 (3 mg/kg) as an intravenous infusion was administered over two hours.

**Reference therapy, Dose and Mode of Administration**

Placebo was administered as an intravenous infusion over two hours.

**Statistical Methods**

All patients with evaluable PK concentration data were included in the PK data analysis. All patients who received at least one dose of the study medication with at least one post-baseline safety assessment were included in the safety analysis set.

All safety and clinical laboratory data were listed by treatment and subject. The number of patients with AEs was counted by body system and preferred term. A subject with multiple AEs within a body system is only counted once towards the total of this body system.

Total QAX576 concentrations in plasma were summarized by descriptive statistics including minimum and maximum values, mean (arithmetic and geometric), standard deviation (SD) and coefficient of variation (CV). Concentrations below the limit of quantification were treated as zero in summary statistics.

The secondary pharmacodynamic variables like pulmonary function test, systemic scleroderma assessments, 6 minute walking test (6MWT), oxygen saturation (SpO<sub>2</sub>) were summarized by descriptive statistics.

**Study Population: Key Inclusion/Exclusion Criteria****Inclusion criteria:**

- Men and women between the ages of 18 and 65 years with a confirmed diagnosis of pulmonary fibrosis secondary to systemic sclerosis

## Clinical Trial Results Website

- Both men and women must be willing to use two forms of contraception. Additional information regarding this requirement is available at screening

### Exclusion criteria:

- Certain medical conditions may exclude patients from participation.
- Should not have participated in another clinical study within 4 weeks of study start
- Smokers are not eligible for participation
- Blood loss of donation of 400 mL or more within 2 months of study start
- Pregnant women or women who are breast feeding
- Past medical history of clinically significant ECG abnormalities
- Connective tissue disorders other than systemic sclerosis.
- Active infection or history of systemic parasitic infection
- History of immunodeficiency diseases, including a positive HIV test result
- History of drug or alcohol abuse within 12 months of study start
- Any condition that may compromise patient safety

Other protocol-defined inclusion/exclusion criteria may apply.

### Patient Flow Table (safety analysis set)

|                                      | QAX576     | Placebo    | Total      |
|--------------------------------------|------------|------------|------------|
| <b>Patients</b>                      |            |            |            |
| Completed                            | 5 (83.3%)  | 2 (100.0%) | 7 (87.5%)  |
| Discontinued                         | 1 (16.7%)  | 0          | 1 (12.5%)  |
| <b>Main cause of discontinuation</b> |            |            |            |
| Death                                | 0          | 0          | 0          |
| Adverse events(s)                    | 0          | 0          | 0          |
| Lack of efficacy                     | 0          | 0          | 0          |
| Protocol violation(s)                | 0          | 0          | 0          |
| Other                                | 0          | 0          | 0          |
| Lost to follow-up                    | 0          | 0          | 0          |
| Administrative problems              | 1 (100.0%) | 0          | 1 (100.0%) |

## **Baseline Characteristics**

### **Demographic summary by treatment group (safety analysis set)**

|                         |                  | <b>QAX576<br/>N=6</b> | <b>Placebo<br/>N=2</b> | <b>Total<br/>N=8</b> |
|-------------------------|------------------|-----------------------|------------------------|----------------------|
| <b>Age (years)</b>      | Mean (SD)        | 48.2 (11.92)          | 51.0 (5.66)            | 48.9 (10.38)         |
|                         | Median           | 51.0                  | 51.0                   | 51.0                 |
|                         | Range            | 32, 65                | 47, 55                 | 32, 65               |
| <b>Gender - n(%)</b>    | Female           | 5 (83.3%)             | 2 (100.0%)             | 7 (87.5%)            |
|                         | Male             | 1 (16.7%)             | 0                      | 1 (12.5%)            |
| <b>Race - n(%)</b>      | Asian            | 0                     | 1 (50.0%)              | 1 (12.5%)            |
|                         | Caucasian        | 5 (83.3%)             | 1 (50.0%)              | 6 (75.0%)            |
|                         | Pacific islander | 1 (16.7%)             | 0                      | 1 (12.5%)            |
| <b>Ethnicity - n(%)</b> | Hispanic/Latino  | 2 (33.3%)             | 0                      | 2 (25.0%)            |
|                         | Other            | 4 (66.7%)             | 2 (100.0%)             | 6 (75.0%)            |
| <b>Weight (kg)</b>      | Mean (SD)        | 62.55 (6.984)         | 76.30 (18.809)         | 65.99 (11.220)       |
|                         | Median           | 66.00                 | 76.30                  | 66.00                |
|                         | Range            | 50.0, 68.0            | 63.0, 89.6             | 50.0, 89.6           |
| <b>Height (cm)</b>      | Mean (SD)        | 159.7 (3.83)          | 155.0 (4.24)           | 158.5 (4.21)         |
|                         | Median           | 162.0                 | 155.0                  | 160.0                |
|                         | Range            | 153, 162              | 152, 158               | 152, 162             |

## **Summary of Efficacy**

### **Primary Outcome Result(s):**

Refer to Safety Result section for primary outcome results.

**Summary statistics for total QAX576 PK parameters directly taken from analytical data after repeat administration (3 x 3 mg/kg, 21-day dosing interval, 2-hour intravenous infusion) (PK set)**

|                         |          | <b>C<sub>max</sub><br/>(µg/mL)</b> | <b>C<sub>trough</sub> (first and second<br/>dose), or<br/>C<sub>day28</sub>* (after third dose)<br/>(µg/mL)</b> |
|-------------------------|----------|------------------------------------|---|
|                         | N        | 5                                  | 5   |
| Dose 1 (Day 1, Week 1)  | Mean     | 50.7                               | 9.0   |
|                         | SD       | 16.2                               | 2.9   |
|                         | CV% mean | 31.9                               | 32.4  |
|                         | N        | 5                                  | 5   |
| Dose 2 (Day 22, Week 4) | Mean     | 66.7                               | 13.1  |
|                         | SD       | 12.6                               | 3.8   |
|                         | CV% mean | 18.9                               | 29.2  |
|                         | N        | 5                                  | 4   |
| Dose 3 (Day 43, Week 7) | Mean     | 66.6                               | 15.3  |
|                         | SD       | 16.0                               | 7.2   |
|                         | CV% mean | 24.1                               | 47  |

(\*) : closest time point relative to the dosing interval (21-day)

## Secondary Outcome Result(s)

### Summary of pulmonary function tests – spirometry assessments

| Treat<br>ment | Visit |         | Predicted<br>FEV1<br>(L) | Predicted<br>FVC<br>(L) | FEV1<br>(L) | FVC<br>(L) | Percent<br>predicted<br>FEV1 | Percent<br>predicted<br>FVC | FEV1/FVC |
|---------------|-------|---------|--------------------------|-------------------------|-------------|------------|------------------------------|-----------------------------|----------|
| QAX576        | SCR   | n       | 6                        | 6                       | 6           | 6          | 6                            | 6                           | 6        |
|               |       | mean    | 2.860                    | 3.325                   | 1.932       | 2.193      | 68.073                       | 66.263                      | 0.934    |
|               |       | SD      | 0.5708                   | 0.4365                  | 0.4968      | 0.5797     | 14.2935                      | 16.7041                     | 0.0702   |
|               |       | minimum | 2.13                     | 2.71                    | 1.35        | 1.47       | 48.07                        | 47.88                       | 0.83     |
|               |       | median  | 2.890                    | 3.340                   | 1.985       | 2.165      | 70.670                       | 67.635                      | 0.945    |
|               |       | maximum | 3.77                     | 3.93                    | 2.47        | 2.96       | 85.45                        | 92.26                       | 1.01     |
|               | BAS   | n       | 6                        | 6                       | 6           | 6          | 6                            | 6                           | 6        |
|               |       | mean    | 2.755                    | 3.402                   | 1.985       | 2.293      | 72.032                       | 67.188                      | 0.918    |
|               |       | SD      | 0.4119                   | 0.4579                  | 0.6073      | 0.7115     | 18.0280                      | 17.1762                     | 0.0660   |
|               |       | minimum | 2.13                     | 2.71                    | 1.33        | 1.43       | 45.11                        | 46.36                       | 0.80     |
|               |       | median  | 2.870                    | 3.515                   | 2.015       | 2.265      | 77.865                       | 71.070                      | 0.932    |
|               |       | maximum | 3.18                     | 3.93                    | 2.75        | 3.27       | 90.05                        | 87.95                       | 0.98     |
|               | DAY8  | n       | 6                        | 6                       | 6           | 6          | 6                            | 6                           | 6        |
|               |       | mean    | 2.755                    | 3.402                   | 1.975       | 2.265      | 71.608                       | 66.383                      | 0.922    |
|               |       | SD      | 0.4119                   | 0.4579                  | 0.6245      | 0.7074     | 18.4671                      | 17.1045                     | 0.0641   |
|               |       | minimum | 2.13                     | 2.71                    | 1.29        | 1.42       | 44.12                        | 44.83                       | 0.81     |
|               |       | median  | 2.870                    | 3.515                   | 2.020       | 2.175      | 78.685                       | 70.540                      | 0.934    |
|               |       | maximum | 3.18                     | 3.93                    | 2.76        | 3.21       | 88.19                        | 86.34                       | 0.98     |
|               | DAY29 | n       | 5                        | 5                       | 5           | 5          | 5                            | 5                           | 5        |
|               |       | mean    | 2.692                    | 3.286                   | 2.134       | 2.416      | 78.598                       | 72.558                      | 0.938    |
|               |       | SD      | 0.4250                   | 0.4102                  | 0.5890      | 0.7253     | 14.0507                      | 15.1161                     | 0.0270   |
|               |       | minimum | 2.13                     | 2.71                    | 1.32        | 1.46       | 54.37                        | 48.39                       | 0.90     |
|               |       | median  | 2.700                    | 3.420                   | 2.410       | 2.730      | 81.270                       | 76.780                      | 0.938    |
|               |       | maximum | 3.15                     | 3.67                    | 2.75        | 3.24       | 89.30                        | 88.33                       | 0.97     |
|               | DAY50 | n       | 5                        | 5                       | 5           | 5          | 5                            | 5                           | 5        |
|               |       | mean    | 2.692                    | 3.286                   | 2.070       | 2.352      | 76.286                       | 70.636                      | 0.938    |
|               |       | SD      | 0.4250                   | 0.4102                  | 0.5485      | 0.6998     | 12.6977                      | 14.4933                     | 0.0401   |
|               |       | minimum | 2.13                     | 2.71                    | 1.32        | 1.43       | 54.37                        | 47.40                       | 0.87     |

| Treat<br>ment | Visit |         | Predicted<br>FEV1<br>(L) | Predicted<br>FVC<br>(L) | FEV1<br>(L) | FVC<br>(L) | Percent<br>predicted<br>FEV1 | Percent<br>predicted<br>FVC | FEV1/FVC |
|---------------|-------|---------|--------------------------|-------------------------|-------------|------------|------------------------------|-----------------------------|----------|
| QAX576        | DAY50 | median  | 2.700                    | 3.420                   | 2.350       | 2.680      | 80.370                       | 75.110                      | 0.954    |
|               |       | maximum | 3.15                     | 3.67                    | 2.57        | 3.12       | 87.08                        | 85.06                       | 0.97     |
|               | WK15  | n       | 5                        | 5                       | 5           | 5          | 5                            | 5                           | 5        |
|               |       | mean    | 2.658                    | 3.238                   | 2.058       | 2.354      | 76.406                       | 71.508                      | 0.935    |
|               |       | SD      | 0.3860                   | 0.3618                  | 0.6167      | 0.8005     | 14.7885                      | 18.3325                     | 0.0441   |
|               |       | minimum | 2.13                     | 2.71                    | 1.25        | 1.33       | 51.49                        | 44.08                       | 0.89     |
|               |       | median  | 2.700                    | 3.420                   | 2.220       | 2.560      | 82.270                       | 74.900                      | 0.917    |
|               |       | maximum | 3.08                     | 3.57                    | 2.65        | 3.17       | 87.50                        | 88.84                       | 0.99     |
|               | WK23  | n       | 5                        | 5                       | 5           | 5          | 5                            | 5                           | 5        |
|               |       | mean    | 2.810                    | 3.434                   | 2.106       | 2.366      | 74.584                       | 68.042                      | 0.948    |
|               |       | SD      | 0.6033                   | 0.6309                  | 0.6710      | 0.8073     | 15.8226                      | 16.3926                     | 0.0397   |
|               |       | minimum | 2.11                     | 2.69                    | 1.29        | 1.38       | 53.13                        | 45.74                       | 0.90     |
|               |       | median  | 2.700                    | 3.420                   | 2.210       | 2.550      | 77.300                       | 64.860                      | 0.943    |
|               |       | maximum | 3.63                     | 4.32                    | 3.01        | 3.37       | 94.70                        | 90.64                       | 0.99     |
|               | EOS   | n       | 6                        | 6                       | 6           | 6          | 6                            | 6                           | 6        |
|               |       | mean    | 2.748                    | 3.395                   | 1.928       | 2.250      | 70.015                       | 66.032                      | 0.909    |
|               |       | SD      | 0.4152                   | 0.4622                  | 0.5883      | 0.6907     | 16.5653                      | 16.4891                     | 0.0611   |
|               |       | minimum | 2.11                     | 2.69                    | 1.32        | 1.42       | 44.45                        | 45.85                       | 0.80     |
|               |       | median  | 2.865                    | 3.505                   | 1.890       | 2.160      | 77.840                       | 69.415                      | 0.915    |
|               |       | maximum | 3.18                     | 3.93                    | 2.66        | 3.13       | 83.69                        | 84.18                       | 0.98     |
| Placebo       | SCR   | n       | 2                        | 2                       | 2           | 2          | 2                            | 2                           | 2        |
|               |       | mean    | 2.695                    | 2.735                   | 1.395       | 1.730      | 51.810                       | 65.765                      | 0.856    |
|               |       | SD      | 0.0071                   | 0.7283                  | 0.1202      | 0.0283     | 4.5962                       | 18.5333                     | 0.0559   |
|               |       | minimum | 2.69                     | 2.22                    | 1.31        | 1.71       | 48.56                        | 52.66                       | 0.82     |
|               |       | median  | 2.695                    | 2.735                   | 1.395       | 1.730      | 51.810                       | 65.765                      | 0.856    |
|               |       | maximum | 2.70                     | 3.25                    | 1.48        | 1.75       | 55.06                        | 78.87                       | 0.90     |
|               | BAS   | n       | 2                        | 2                       | 2           | 2          | 2                            | 2                           | 2        |
|               |       |         |                          |                         |             |            |                              |                             |          |
|               |       |         |                          |                         |             |            |                              |                             |          |
|               |       |         |                          |                         |             |            |                              |                             |          |



| Treat<br>ment | Visit |         | Predicted<br>FEV1<br>(L) | Predicted<br>FVC<br>(L) | FEV1<br>(L) | FVC<br>(L) | Percent<br>predicted<br>FEV1 | Percent<br>predicted<br>FVC | FEV1/FVC |
|---------------|-------|---------|--------------------------|-------------------------|-------------|------------|------------------------------|-----------------------------|----------|
| Placebo       | BAS   | mean    | 2.460                    | 2.970                   | 1.310       | 1.720      | 53.970                       | 58.735                      | 0.812    |
|               |       | SD      | 0.3394                   | 0.3960                  | 0.0566      | 0.1131     | 9.7439                       | 11.6319                     | 0.0170   |
|               |       | minimum | 2.22                     | 2.69                    | 1.27        | 1.64       | 47.08                        | 50.51                       | 0.80     |
|               |       | median  | 2.460                    | 2.970                   | 1.310       | 1.720      | 53.970                       | 58.735                      | 0.812    |
|               |       | maximum | 2.70                     | 3.25                    | 1.35        | 1.80       | 60.86                        | 66.96                       | 0.82     |
|               |       |         |                          |                         |             |            |                              |                             |          |
|               | DAY8  | n       | 2                        | 2                       | 2           | 2          | 2                            | 2                           | 2        |
|               |       | mean    | 2.460                    | 2.970                   | 1.400       | 1.700      | 57.305                       | 57.510                      | 0.874    |
|               |       | SD      | 0.3394                   | 0.3960                  | 0.0707      | 0.1273     | 5.0275                       | 3.3800                      | 0.0198   |
|               |       | minimum | 2.22                     | 2.69                    | 1.35        | 1.61       | 53.75                        | 55.12                       | 0.86     |
|               |       | median  | 2.460                    | 2.970                   | 1.400       | 1.700      | 57.305                       | 57.510                      | 0.874    |
|               |       | maximum | 2.70                     | 3.25                    | 1.45        | 1.79       | 60.86                        | 59.90                       | 0.89     |
|               | DAY29 | n       | 2                        | 2                       | 2           | 2          | 2                            | 2                           | 2        |
|               |       | mean    | 2.460                    | 2.060                   | 1.450       | 1.815      | 59.635                       | 98.300                      | 0.850    |
|               |       | SD      | 0.3394                   | 0.8910                  | 0.0283      | 0.0919     | 9.3692                       | 46.9519                     | 0.0566   |
|               |       | minimum | 2.22                     | 1.43                    | 1.43        | 1.75       | 53.01                        | 65.10                       | 0.81     |
|               |       | median  | 2.460                    | 2.060                   | 1.450       | 1.815      | 59.635                       | 98.300                      | 0.850    |
|               |       | maximum | 2.70                     | 2.69                    | 1.47        | 1.88       | 66.26                        | 131.50                      | 0.89     |
|               | DAY50 | n       | 2                        | 2                       | 2           | 2          | 2                            | 2                           | 2        |
|               |       | mean    | 2.445                    | 2.960                   | 1.440       | 1.780      | 59.595                       | 60.590                      | 0.859    |
|               |       | SD      | 0.3182                   | 0.3818                  | 0.0566      | 0.0424     | 10.0621                      | 6.3781                      | 0.0509   |
|               |       | minimum | 2.22                     | 2.69                    | 1.40        | 1.75       | 52.48                        | 56.08                       | 0.82     |
|               |       | median  | 2.445                    | 2.960                   | 1.440       | 1.780      | 59.595                       | 60.590                      | 0.859    |
|               |       | maximum | 2.67                     | 3.23                    | 1.48        | 1.81       | 66.71                        | 65.10                       | 0.90     |
|               | WK15  | n       | 2                        | 2                       | 2           | 2          | 2                            | 2                           | 2        |
|               |       | mean    | 2.445                    | 2.960                   | 1.485       | 1.795      | 61.470                       | 61.055                      | 0.878    |
|               |       | SD      | 0.3182                   | 0.3818                  | 0.0636      | 0.0636     | 10.5925                      | 5.7205                      | 0.0651   |
|               |       | minimum | 2.22                     | 2.69                    | 1.44        | 1.75       | 53.98                        | 57.01                       | 0.83     |
|               |       | median  | 2.445                    | 2.960                   | 1.485       | 1.795      | 61.470                       | 61.055                      | 0.878    |

| Treat<br>ment | Visit |         | Predicted<br>FEV1<br>(L) | Predicted<br>FVC<br>(L) | FEV1<br>(L) | FVC<br>(L) | Percent<br>predicted<br>FEV1 | Percent<br>predicted<br>FVC | FEV1/FVC |
|---------------|-------|---------|--------------------------|-------------------------|-------------|------------|------------------------------|-----------------------------|----------|
| <hr/>         |       |         |                          |                         |             |            |                              |                             |          |
| Placebo       | WK15  | maximum | 2.67                     | 3.23                    | 1.53        | 1.84       | 68.96                        | 65.10                       | 0.92     |
|               | WK23  | n       | 2                        | 2                       | 2           | 2          | 2                            | 2                           | 2        |
|               |       | mean    | 2.445                    | 2.960                   | 1.500       | 1.870      | 62.030                       | 63.565                      | 0.853    |
|               |       | SD      | 0.3182                   | 0.3818                  | 0.0424      | 0.0849     | 9.8005                       | 5.3245                      | 0.0594   |
|               |       | minimum | 2.22                     | 2.69                    | 1.47        | 1.81       | 55.10                        | 59.80                       | 0.81     |
|               |       | median  | 2.445                    | 2.960                   | 1.500       | 1.870      | 62.030                       | 63.565                      | 0.853    |
|               |       | maximum | 2.67                     | 3.23                    | 1.53        | 1.93       | 68.96                        | 67.33                       | 0.90     |
|               | EOS   | n       | 2                        | 2                       | 2           | 2          | 2                            | 2                           | 2        |
|               |       | mean    | 2.430                    | 2.945                   | 1.415       | 1.765      | 59.115                       | 60.490                      | 0.852    |
|               |       | SD      | 0.3394                   | 0.4031                  | 0.0919      | 0.0212     | 12.0279                      | 7.5519                      | 0.0615   |
|               |       | minimum | 2.19                     | 2.66                    | 1.35        | 1.75       | 50.61                        | 55.15                       | 0.81     |
|               |       | median  | 2.430                    | 2.945                   | 1.415       | 1.765      | 59.115                       | 60.490                      | 0.852    |
|               |       | maximum | 2.67                     | 3.23                    | 1.48        | 1.78       | 67.62                        | 65.83                       | 0.90     |

**Summary of 6 minute walking test (6MWT) and oxygen saturation (SpO2)**

| Treat<br>ment | Visit |         | Pre-test<br>heart<br>rate<br>(bpm) | Pre-test<br>SpO2<br>(%) | Post-test<br>heart<br>rate<br>(bpm) | Post-test<br>Inspired<br>oxygen | Post-test<br>SpO2<br>(%) | Number<br>of<br>laps | Total<br>distance<br>walked<br>(meters) |
|---------------|-------|---------|------------------------------------|-------------------------|-------------------------------------|---------------------------------|--------------------------|----------------------|---|
| QAX576        | SCR   | n       | 6                                  | 6                       | 6                                   | 6                               | 6                        | 6                    | 6                                       |
|               |       | mean    | 87.2                               | 98.33                   | 101.3                               | 0.000                           | 96.50                    | 5.5                  | 351.8                                   |
|               |       | SD      | 13.45                              | 1.506                   | 11.86                               | 0.0000                          | 2.345                    | 1.38                 | 84.29                                   |
|               |       | minimum | 72                                 | 97.0                    | 84                                  | 0.00                            | 93.0                     | 3                    | 198                                     |
|               |       | median  | 84.0                               | 98.00                   | 101.0                               | 0.000                           | 96.00                    | 6.0                  | 384.0                                   |
|               |       | maximum | 106                                | 100.0                   | 121                                 | 0.00                            | 100.0                    | 7                    | 424                                     |
|               | DAY50 | n       | 5                                  | 5                       | 5                                   | 5                               | 5                        | 5                    | 5                                       |
|               |       | mean    | 91.2                               | 97.80                   | 100.2                               | 0.000                           | 89.20                    | 6.2                  | 407.0                                   |
|               |       | SD      | 7.26                               | 1.483                   | 26.32                               | 0.0000                          | 13.664                   | 1.30                 | 58.81                                   |
|               |       | minimum | 80                                 | 96.0                    | 63                                  | 0.00                            | 68.0                     | 5                    | 347                                     |
|               |       | median  | 92.0                               | 98.00                   | 105.0                               | 0.000                           | 96.00                    | 6.0                  | 400.0                                   |
|               |       | maximum | 98                                 | 100.0                   | 134                                 | 0.00                            | 100.0                    | 8                    | 488                                     |
|               | WK23  | n       | 5                                  | 5                       | 5                                   | 5                               | 5                        | 5                    | 5                                       |
|               |       | mean    | 86.4                               | 95.40                   | 103.4                               | 0.000                           | 91.00                    | 6.2                  | 391.8                                   |
|               |       | SD      | 21.24                              | 1.342                   | 35.89                               | 0.0000                          | 6.442                    | 1.30                 | 77.64                                   |
|               |       | minimum | 62                                 | 94.0                    | 48                                  | 0.00                            | 83.0                     | 5                    | 309                                     |
|               |       | median  | 96.0                               | 96.00                   | 125.0                               | 0.000                           | 89.00                    | 6.0                  | 378.0                                   |
|               |       | maximum | 106                                | 97.0                    | 130                                 | 0.00                            | 99.0                     | 8                    | 486                                     |
|               | EOS   | n       | 6                                  | 6                       | 6                                   | 6                               | 6                        | 6                    | 6                                       |
|               |       | mean    | 88.8                               | 95.17                   | 104.3                               | 0.000                           | 85.50                    | 5.7                  | 367.7                                   |
|               |       | SD      | 22.34                              | 6.242                   | 29.85                               | 0.0000                          | 17.421                   | 1.51                 | 101.93                                  |
|               |       | minimum | 54                                 | 83.0                    | 49                                  | 0.00                            | 53.0                     | 3                    | 192                                     |
|               |       | median  | 89.0                               | 98.00                   | 111.0                               | 0.000                           | 90.50                    | 6.0                  | 384.5                                   |
|               |       | maximum | 115                                | 99.0                    | 130                                 | 0.00                            | 99.0                     | 7                    | 463                                     |
| Placebo       | SCR   | n       | 2                                  | 2                       | 2                                   | 2                               | 2                        | 2                    | 2                                       |
|               |       | mean    | 76.5                               | 98.00                   | 98.0                                | 0.000                           | 95.00                    | 6.0                  | 373.5                                   |
|               |       | SD      | 2.12                               | 1.414                   | 28.28                               | 0.0000                          | 7.071                    | 0.00                 | 10.61                                   |

| Treat<br>ment | Visit |         | Pre-test<br>heart<br>rate<br>(bpm) | Pre-test<br>SpO2<br>(%) | Post-test<br>heart<br>rate<br>(bpm) | Post-test<br>Inspired<br>oxygen | Post-test<br>SpO2<br>(%) | Number<br>of<br>laps | Total<br>distance<br>walked<br>(meters) |
|---------------|-------|---------|------------------------------------|-------------------------|-------------------------------------|---------------------------------|--------------------------|----------------------|---|
| Placebo       | SCR   | minimum | 75                                 | 97.0                    | 78                                  | 0.00                            | 90.0                     | 6                    | 366                                     |
|               |       | median  | 76.5                               | 98.00                   | 98.0                                | 0.000                           | 95.00                    | 6.0                  | 373.5                                   |
|               |       | maximum | 78                                 | 99.0                    | 118                                 | 0.00                            | 100.0                    | 6                    | 381                                     |
|               | DAY50 | n       | 2                                  | 2                       | 2                                   | 2                               | 2                        | 2                    | 2                                       |
|               |       | mean    | 92.0                               | 95.50                   | 82.5                                | 0.000                           | 92.00                    | 6.0                  | 372.0                                   |
|               |       | SD      | 9.90                               | 6.364                   | 23.33                               | 0.0000                          | 66.468                   | 1.41                 | 77.78                                   |
|               |       | minimum | 85                                 | 91.0                    | 66                                  | 0.00                            | 45.0                     | 5                    | 317                                     |
|               |       | median  | 92.0                               | 95.50                   | 82.5                                | 0.000                           | 92.00                    | 6.0                  | 372.0                                   |
|               |       | maximum | 99                                 | 100.0                   | 99                                  | 0.00                            | 139.0                    | 7                    | 427                                     |
|               | WK23  | n       | 2                                  | 2                       | 2                                   | 2                               | 2                        | 2                    | 2                                       |
|               |       | mean    | 93.0                               | 97.50                   | 119.5                               | 0.000                           | 96.00                    | 5.0                  | 322.5                                   |
|               |       | SD      | 18.38                              | 0.707                   | 12.02                               | 0.0000                          | 0.000                    | 0.00                 | 7.78                                    |
|               |       | minimum | 80                                 | 97.0                    | 111                                 | 0.00                            | 96.0                     | 5                    | 317                                     |
|               |       | median  | 93.0                               | 97.50                   | 119.5                               | 0.000                           | 96.00                    | 5.0                  | 322.5                                   |
|               |       | maximum | 106                                | 98.0                    | 128                                 | 0.00                            | 96.0                     | 5                    | 328                                     |
|               | EOS   | n       | 2                                  | 2                       | 2                                   | 2                               | 2                        | 2                    | 2                                       |
|               |       | mean    | 103.0                              | 96.50                   | 125.0                               | 0.000                           | 95.50                    | 6.0                  | 388.5                                   |
|               |       | SD      | 5.66                               | 4.950                   | 15.56                               | 0.0000                          | 3.536                    | 1.41                 | 75.66                                   |
|               |       | minimum | 99                                 | 93.0                    | 114                                 | 0.00                            | 93.0                     | 5                    | 335                                     |
|               |       | median  | 103.0                              | 96.50                   | 125.0                               | 0.000                           | 95.50                    | 6.0                  | 388.5                                   |
|               |       | maximum | 107                                | 100.0                   | 136                                 | 0.00                            | 98.0                     | 7                    | 442                                     |

## Summary of Safety

### Safety Results

Adverse events overall and frequently affected system organ classes - n (%) of patients (all patients)

|  | <b>QAX576</b><br><b>N=6</b><br><b>n (%)</b> | <b>Placebo</b><br><b>N=2</b><br><b>n (%)</b> | <b>Total</b><br><b>N=8</b><br><b>n (%)</b> |
|--|---|--|--|
| Patients with AE(s)                                  | 6 (100.0)                                   | 2 (100.0)                                    | 8 (100.0)                                  |
| <b>System organ class</b>                            |   |  |  |
| Infections and infestations                          | 5 (83.3)                                    | 1 (50.0)                                     | 6 (75.0)                                   |
| Gastrointestinal disorders                           | 5 (83.3)                                    | 0  | 5 (62.5)                                   |
| Musculoskeletal and connective tissue disorders      | 3 (50.0)                                    | 2 (100.0)                                    | 5 (62.5)                                   |
| Injury, poisoning and procedural complications       | 4 (66.7)                                    | 0  | 4 (50.0)                                   |
| Respiratory, thoracic and mediastinal disorders      | 2 (33.3)                                    | 2 (100.0)                                    | 4 (50.0)                                   |
| Skin and subcutaneous tissue disorders               | 3 (50.0)                                    | 1 (50.0)                                     | 4 (50.0)                                   |
| General disorders and administration site conditions | 1 (16.7)                                    | 2 (100.0)                                    | 3 (37.5)                                   |
| Eye disorders  | 1 (16.7)                                    | 1 (50.0)                                     | 2 (25.0)                                   |
| Investigations                                       | 1 (16.7)                                    | 1 (50.0)                                     | 2 (25.0)                                   |
| Nervous system disorders                             | 2 (33.3)                                    | 0  | 2 (25.0)                                   |
| Vascular disorders                                   | 2 (33.3)                                    | 0  | 2 (25.0)                                   |
| Cardiac disorders                                    | 1 (16.7)                                    | 0  | 1 (12.5)                                   |
| Metabolism and nutrition disorders                   | 1 (16.7)                                    | 0  | 1 (12.5)                                   |
| Psychiatric disorders                                | 1 (16.7)                                    | 0  | 1 (12.5)                                   |

**Adverse events overall and most frequent events - n (%) of patients (safety set)**

|                               | <b>QAX576</b><br><b>N=6</b><br><b>n (%)</b> | <b>Placebo</b><br><b>N=2</b><br><b>n (%)</b> | <b>Total</b><br><b>N=8</b><br><b>n (%)</b> |
|-------------------------------|---|--|--|
| Patients with AE(s)           | 6 (100.0)                                   | 2 (100.0)                                    | 8 (100.0)                                  |
| <b>Preferred term</b>         |   |  |  |
| Abdominal distension          | 1 (16.7)                                    | 0  | 1 (12.5)                                   |
| Abdominal pain                | 1 (16.7)                                    | 0  | 1 (12.5)                                   |
| Anxiety                       | 1 (16.7)                                    | 0  | 1 (12.5)                                   |
| Arthralgia                    | 1 (16.7)                                    | 0  | 1 (12.5)                                   |
| Arthropod bite                | 1 (16.7)                                    | 0  | 1 (12.5)                                   |
| Blood triglycerides increased | 1 (16.7)                                    | 0  | 1 (12.5)                                   |
| Bronchitis                    | 2 (33.3)                                    | 0  | 2 (25.0)                                   |
| Chills                        | 1 (16.7)                                    | 0  | 1 (12.5)                                   |
| Constipation                  | 1 (16.7)                                    | 0  | 1 (12.5)                                   |
| Cough                         | 1 (16.7)                                    | 0  | 1 (12.5)                                   |
| Device breakage               | 1 (16.7)                                    | 0  | 1 (12.5)                                   |
| Diarrhea                      | 1 (16.7)                                    | 0  | 1 (12.5)                                   |
| Dyspnea                       | 1 (16.7)                                    | 0  | 1 (12.5)                                   |
| Eye pruritus                  | 0   | 1 (50.0)                                     | 1 (12.5)                                   |
| Fatigue                       | 0   | 1 (50.0)                                     | 1 (12.5)                                   |
| Flatulence                    | 1 (16.7)                                    | 0  | 1 (12.5)                                   |
| Food poisoning                | 1 (16.7)                                    | 0  | 1 (12.5)                                   |
| Hemoglobin decreased          | 0   | 1 (50.0)                                     | 1 (12.5)                                   |

|                        |          |          |          |
|------------------------|----------|----------|----------|
| Headache               | 1 (16.7) | 0        | 1 (12.5) |
| Helicobacter infection | 1 (16.7) | 0        | 1 (12.5) |
| Hyperesthesia          | 1 (16.7) | 0        | 1 (12.5) |
| Hypotension            | 1 (16.7) | 0        | 1 (12.5) |
| Influenza              | 0        | 1 (50.0) | 1 (12.5) |
| Intestinal obstruction | 1 (16.7) | 0        | 1 (12.5) |
| Lung infection         | 1 (16.7) | 0        | 1 (12.5) |
| Mouth ulceration       | 1 (16.7) | 0        | 1 (12.5) |
| Muscle spasms          | 0        | 1 (50.0) | 1 (12.5) |
| Muscular weakness      | 1 (16.7) | 0        | 1 (12.5) |
| Musculoskeletal pain   | 1 (16.7) | 0        | 1 (12.5) |
| Myalgia                | 0        | 1 (50.0) | 1 (12.5) |
| Nasopharyngitis        | 1 (16.7) | 0        | 1 (12.5) |
| Non-cardiac chest pain | 0        | 1 (50.0) | 1 (12.5) |
| Oropharyngeal pain     | 0        | 1 (50.0) | 1 (12.5) |
| Pain                   | 1 (16.7) | 0        | 1 (12.5) |
| Photophobia            | 1 (16.7) | 0        | 1 (12.5) |
| Pneumonia              | 1 (16.7) | 0        | 1 (12.5) |
| Procedural pain        | 1 (16.7) | 0        | 1 (12.5) |
| Productive cough       | 1 (16.7) | 1 (50.0) | 2 (25.0) |
| Pruritus               | 0        | 1 (50.0) | 1 (12.5) |
| Pyrexia                | 1 (16.7) | 1 (50.0) | 2 (25.0) |
| Rash pruritic          | 1 (16.7) | 0        | 1 (12.5) |

|                                   |          |          |          |
|-----------------------------------|----------|----------|----------|
| Raynaud's phenomenon              | 1 (16.7) | 0        | 1 (12.5) |
| Red blood cell count decreased    | 0        | 1 (50.0) | 1 (12.5) |
| Sinus tachycardia                 | 1 (16.7) | 0        | 1 (12.5) |
| Skin irritation                   | 1 (16.7) | 0        | 1 (12.5) |
| Skin laceration                   | 1 (16.7) | 0        | 1 (12.5) |
| Skin ulcer                        | 2 (33.3) | 0        | 2 (25.0) |
| Staphylococcal infection          | 2 (33.3) | 0        | 2 (25.0) |
| Tachycardia                       | 1 (16.7) | 0        | 1 (12.5) |
| Tooth injury                      | 1 (16.7) | 0        | 1 (12.5) |
| Upper respiratory tract infection | 1 (16.7) | 1 (50.0) | 2 (25.0) |
| Urinary tract infection           | 2 (33.3) | 0        | 2 (25.0) |
| Vitamin D deficiency              | 1 (16.7) | 0        | 1 (12.5) |

**Number of patients with serious adverse events and deaths (safety set)**

No deaths were reported in this study. Seven SAEs were reported in two patients.

**Other Relevant Findings**

None

**Date of Clinical Trial Report**