| Clinical Study Report N° QGC001/2QG1 | |
|---|---|
| Title: | **Multicenter, randomized, double-blind, two-period, placebo controlled, forced-titration proof of concept crossover study to compare QGC001 with placebo in patients with grade I or II essential hypertension** |
| Protocol code: | **QGC001/2QG1** |
| EudraCT Number: | **2014-003071-37** |
| Study drug: | **QGC001** |
| Clinical phase: | IIa |
| Study initiation date: | 23FEB2015 |
| Study completion date: | 13APR2016 |
| Principal investigator: | Pr M. Azizi, MD, PhD<br>Clinical Investigation Center and European Society of Hypertension Excellence Center, Hôpital Européen Georges Pompidou, 75015 Paris, FRANCE |
| Study location | Hôpital Européen Georges Pompidou, Paris,<br>Hôpital Cardiologique, CHRU, Lille<br>Hôpital de la Croix Rousse, Lyon,<br>Hôpital Arthur Gardiner, Dinard |
| Company/Sponsor: | Quantum Genomics |
| Responsible medical officer: | Dr. Olivier Madonna<br>Tour Montparnasse, 33 avenue du Maine, 75015 Paris, France |
| Sponsor address: | 2-12 rue du chemin des Femmes<br>91300 Massy<br>FRANCE |
| Document version: | Final |
| Date of the report: | 13DEC2016 |

| |
|---|
| This study was performed in accordance with the principles of Good Clinical Practice including the archiving of essential documents. |
| This report contains confidential information that should only be disclosed to those persons responsible for execution and organisation of the study. This information cannot be disclosed to any third party without prior written authorisation from the Sponsor. |

# 2. SYNOPSIS

| | | |
|---|---|---|
| **Name of Company:**<br>Quantum Genomics<br>2-12 rue du chemin des Femmes<br>91300 Massy<br>France | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:**<br>QGC001 | **Volume:** | |
| **Name of active ingredient:**<br>(3S,3'S)-4,4'-dithiobis(3-aminobutane-1-sulfonic acid) | **Page:** | |
| **Title of Study:** Multicenter, randomized, double-blind, two-period, placebo controlled, forced-titration proof of concept crossover study to compare QGC001 with placebo in patients with grade I or II essential hypertension. | | |
| **Principal investigator:**<br>Pr M. Azizi, MD, PhD | | |
| **Study centre(s):**<br>The study was a multicenter study carried out in France under the supervision of Pr M. Azizi at the Clinical Investigation Center and European Society of Hypertension Excellence center at the HEGP (Hôpital Européen Georges Pompidou, 20-40 rue Leblanc, 75015 Paris France).<br>The other 3 investigating centers were : Hôpital Cardiologique, CHRU, Boulevard du Professeur Jules Leclercq, 59037 Lille Cedex, Hôpital de la Croix Rousse, 103, Grande Rue de la Croix Rousse, 69317 Lyon cedex 4 and Hôpital Arthur Gardiner,1 rue Henri Dunant, 35800 Dinard. | | |
| **Publication (reference):** NA | | |
| **Studied period (years):**<br>date of first enrolment: 23FEB2015<br>date of last completed: 13APR2016 | **Phase of development**:<br>**IIa** | |
| **Objective(s)**<br>***Primary:***<br>To assess the BP lowering effect of 4-week administration of QGC001 oral doses in patients with grade I or II essential hypertension compared to placebo.<br>***Secondary:***<br>To assess the safety and tolerability of 4-week administration of QGC001 oral doses in patients with grade I or II essential hypertension compared to placebo<br>To obtain preliminary PK information for QGC001 given as multiple oral doses<br>To determine preliminary PD profile of QGC001 multiple oral doses on plasma and urine hormones, to be compared with that of placebo. | | |

| | | |
|---|---|---|
| **Name of Company:**<br>Quantum Genomics<br>2-12 rue du chemin des Femmes<br>91300 Massy<br>France | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:**<br>QGC001 | **Volume:** | |
| **Name of active ingredient:**<br>(3S,3'S)-4,4'-dithiobis(3-aminobutane-1-sulfonic acid) | **Page:** | |

**Methodology:**

Multicenter, randomized, double-blind, two-period of 4-week duration each, placebo controlled, forced-titration crossover pilot study to compare QGC001 (250 mg b.i.d. over 1 week and then 500 mg b.i.d. over a 3-week period) with placebo:

An initial screening period included a period of tapering and discontinuation of current antihypertensive therapy for two weeks if needed, before starting the placebo run-in period of 2 weeks (Run-in Period).

Patients untreated at screening directly entered the two-week placebo run-in period. At the end of the placebo run-in period, baseline measurements of BP and HR as well as blood samplings were performed.

Once the baseline evaluations were performed, the patients were randomly assigned in a double-blind manner at the end of the run-in period to receive one of the two following treatment sequences including two-period of 4-week duration each (total of 8 weeks) with a 2 week washout period intercalated between the two periods, during which placebo was administered:

- A: (P1, QGC001) – (Washout, placebo) – (P2, placebo)
- B: (P1, placebo) – (Washout, placebo) – (P2, QGC001).

The first period (P1) corresponded either to QGC001 or placebo, the second period (P2) corresponded either to QGC001 or placebo.

The starting dose of QGC001 was one fourth of the maximum dose tested in phase I, i.e, 250 mg b.i.d. during one week, followed by a forced titration after one week to 500 mg b.i.d. which was administered for three weeks.

**Number of subjects (planned and analysed):**

Planned:

36 patients were planned in order to retain at least 24 evaluable patients.

Analysed:

34 patients

**Diagnosis and main criteria for inclusion:**

Patients were required to satisfy the following criteria:

1) Male and female of non-childbearing potential patients (post-menopausal since at least 12 months or surgically sterilized) aged 18 to 75 years;
2) Body weight ≥50 kg with a body mass index (BMI) calculated as weight in kg/(height in $m^2$) from 18 to 40 $kg/m^2$ at screening;
3) A signed and dated informed consent form before any study-specific screening procedure is performed;
4) With a diagnosis of essential grade I or II hypertension defined as:
    a. a supine office systolic BP (SBP) of 140–159 mmHg or diastolic BP (DBP) of 90-99 mmHg who should have an additional clinical indication according to ESH guidelines for antihypertensive treatment after a 2-week placebo run-in period,
    b. or a supine office SBP of 160-179 mmHg or DBP of 100–109 mmHg after a 2-week placebo run-in period with a diagnosis of essential grade II hypertension;
5) Diagnosis of permanent hypertension confirmed by a mean SBP or DBP higher than 135 or 85 mmHg on daytime ambulatory blood pressure monitoring (ABPM) after a 2-week placebo run-in period;
6) Estimated glomerular filtration rate (Modification of Diet in Renal Disease (MDRD) formula) ≥ 60 ml/min/1.73 $m^2$.

| | | |
|---|---|---|
| **Name of Company:**<br>Quantum Genomics<br>2-12 rue du chemin des Femmes<br>91300 Massy<br>France | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:**<br>QGC001 | **Volume:** | |
| **Name of active ingredient:**<br>(3S,3'S)-4,4'-dithiobis(3-aminobutane-1-sulfonic acid) | **Page:** | |

**Test product, dose and mode of administration, batch number:**

| Name | Formulation | Dose | Mode of Administration | Batch Number |
|---|---|---|---|---|
| QCG001 | Capsule | 250 mg | oral | Run-in period : 1319414297<br>First period of cross-over : 1319414298<br>Wash out period : 1319414299<br>Second period of cross-over : 1319414300 |
| Placebo | Capsule | na | oral | |

**Duration of treatment:**

Each patient took part in the study for a maximum screening period of four weeks (including, if needed, 2 weeks of tapering/discontinuation of previous antihypertensive treatments) followed by:

- a two-week Run-in period and
- two four-week treatment periods separated by a two-week washout period.

The following schedule of administrations applied:

| | **Run-in Period** ***single blind*** | | **Cross-over (Period 1 or Period 2)** ***double blind*** | | | | | | **Washout Period** ***single blind*** | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **Placebo** | | **QGC001** | | | **Placebo** | | | **Placebo** | |
| ***Duration*** | ***week 1*** | ***week 2*** | ***week 1*** | ***week2*** | ***week 3 to week 4*** | ***week 1*** | ***week 2*** | ***week 3 to week 4*** | ***week 1*** | ***week 2*** |
| **QGC001 250 mg** | 0 capsule | 0 capsule | 1 capsule every 12 hours | 2 capsules every 12 hours | 2 capsules every 12 hours | 0 capsule | 0 capsule | 0 capsule | 0 capsule | 0 capsule |
| **placebo** | 1 capsule every 12 hours | 2 capsules every 12 hours | 0 capsule | 0 capsule | 0 capsule | 1 capsule every 12 hours | 2 capsules every 12 hours | 2 capsules every 12 hours | 1 capsule every 12 hours | 2 capsules every 12 hours |

The patients were instructed to take their medication at ≈ 08:00 and 20:00, and to follow lifestyle measures throughout the study according to European Society of Hypertension (ESH) recommendations. The compliance was evaluated by the following methods: pill counting, Morisky questionnaire, QGC001 level by LC-MS/MS and exact time of drug intake (as recorded by the patients in individual diaries).

**Criteria for evaluation:**

| | |
|---|---|
| Safety | Safety was evaluated from reported signs and symptoms (Adverse events), scheduled physical examination findings, vital sign measurements (office BP (OBP) and HR), electrocardiogram (ECG) and clinical laboratory tests |
| Pharmacokinetics | Four (4) PK blood samples were taken on P1 and P2 on D15 (+/-2) and D28 (+/-2) before morning dose. Plasma levels of QGC001 and its metabolite EC33 were measured using validated LC/MS/MS methods. |

<table>
<tr><td>Name of Company:<br>Quantum Genomics<br>2-12 rue du chemin des Femmes<br>91300 Massy<br>France</td><td>Individual Study Table Referring to Part of the Dossier</td><td>(For National Authority Use only)</td></tr>
<tr><td>Name of Finished Product:<br>QGC001</td><td>Volume:</td><td></td></tr>
<tr><td>Name of active ingredient:<br>(3S,3'S)-4,4'-dithiobis(3-aminobutane-1-sulfonic acid)</td><td>Page:</td><td></td></tr>
<tr><td><u>Pharmacodynamics:</u></td><td colspan="2">Primary efficacy criteria<br>24h ABPM (primary efficacy criteria):<br>24h ABPM started/did the last day of the Run-in Period, the last day of the P1 Period, the last day of the Washout Period and the last day of the P2 Period.<br>A portable recording system was used to perform 24h ABPM with the cuff placed on the non-dominant arm. Measurements included mean 24h systolic and diastolic pressures, and daytime values (measured every 15 min from 07:00 am to 10:00 pm) and night-time values (measured every 20 min from 10:00 pm to 07:00 am). Only ambulatory BP recordings with a minimum of 24 measurements were considered as successful. In case of non-valid ABPM, a new ABPM was scheduled on the next day.<br><br>Secondary efficacy criteria<br>Self BP measurements at home:<br>Additional information were obtained from self-measurement of BP at home (HBP) with an automatic validated device. After education by a trained nurse, HBP monitoring (using a validated semiautomatic, oscillometric, digitized device equipped with an electronic memory enabling storage of the BP measurements with the adapted cuff placed at the level of the brachial artery) were performed during the Run-in period for 7 consecutive days from D7 to D13 and during P1 and P2 every two weeks during 7 consecutive days (just before the planned hospital visit when applicable) i.e, during P1 and P2 from D8 to D14 (visit planned on D15) and from D21 to D27 (visit planned on D28).<br>The device had a built-in function, making it possible to take two consecutive measurements, at one-minute intervals. On each monitoring day at home, the patient was requested to perform a series of 2 consecutive measurements in the sitting position after a 5-minute rest in the morning before drug intake and breakfast and in the evening before drug intake. HBP values will be calculated as the mean of the measurements after discarding the first day of measurement (n=24).<br><br>Office BP measurements<br>Office SBP, DBP and HR measured after resting in the semi-recumbent position for at least 5 min. Office SBP, DBP and HR measured after 1 min in a standing position will be recorded at each visit. These assessments will be made immediately before the administration of the study drug in order to match subsequent assessments of BP and HR at trough levels of the study drug.</td></tr>
</table>

| | | |
|---|---|---|
| **Name of Company:**<br>Quantum Genomics<br>2-12 rue du chemin des Femmes<br>91300 Massy<br>France | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:**<br>QGC001 | **Volume:** | |
| **Name of active ingredient:**<br>(3S,3'S)-4,4'-dithiobis(3-aminobutane-1-sulfonic acid) | **Page:** | |
| Pharmacodynamics (cont'd): | *Hormonal measurements:*<br>The pharmacodynamic neurohormonal effects of QGC001 were assessed by measurements of plasma active renin, aldosterone, cortisol, adrenocorticotropic hormone (ACTH), apelin and copeptin as well as urine aldosterone, cortisol, creatinine, sodium and potassium using commercially available validated assays. | |
| **Statistical methods:** | All data were analyzed by Biostatistics Unit of BIOTRIAL using SAS® software 9.4 release or higher (SAS Institute Inc. Cary NC USA).<br>*Analysis Sets:*<br>Run-in included set: all the subjects eligible for the Run-in period and who received at least one dose of the treatment (placebo in the run-in period).<br>Randomised set (RS): defined as all subjects randomised in the study.<br>Intention to treat set (ITT): defined as all randomised patients who received at least one treatment after the Run-in period and for whom the primary efficacy criterion is available at baseline (evaluable ABPM at D14 of Run-in period).<br>Per-Protocol set (PP): defined as all patients in the ITT population who completed the study without any major protocol deviations that can be source of bias for ABPM evaluation.<br>Safety set (SP): defined as all patients who received at least one dose of the treatment after randomization.<br>Subject 11001 was not included in the safety tables, sorted by treatment group: following a protocol deviation, he received two different treatments in Period 2 and therefore cannot be allocated to a single treatment group for a statistical analysis. His safety results are however presented in the safety listings.<br>*Baseline definition:*<br>For all parameters, baseline was defined as the last available measurement prior to the first IMP administration in each period. For HBP parameters, baseline was defined as the value before the first intake of treatment in the first 4-week treatment period (Run-in period).<br>*Demography and safety variables:*<br>Descriptive statistics were supplied according to the nature of the criteria (quantitative or qualitative variable).<br>Adverse events, including pre-treatment events, were recorded from the time of consent through 30 days after the end of treatment period and coded according to MedDRA® Version 17.1.<br>When applicable for haematology, blood chemistry, vital signs and ECG parameters, specific listings with the PCSA values with clinical significance information were generated. Values (raw data and changes from baseline) were listed and data out of normal/PCSA ranges were flagged with clinical significance information. | |

| | | |
|---|---|---|
| **Name of Company:**<br>Quantum Genomics<br>2-12 rue du chemin des Femmes<br>91300 Massy<br>France | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:**<br>QGC001 | **Volume:** | |
| **Name of active ingredient:**<br>(3S,3'S)-4,4'-dithiobis(3-aminobutane-1-sulfonic acid) | **Page:** | |
| | *Pharmacokinetic data*<br>Only the plasma levels of QGC001 and its metabolite EC33 were determined. The mean plasma concentrations were calculated and the plasma concentration versus time profiles of QGC001 and EC33 were presented graphically on linear and semi-logarithmic coordinates for each subject as well as arithmetic mean (±SEM) and arithmetic mean (±SEM) with all analytes on the same graph. Individual plasma concentration-time profiles (spaghetti plots) of QGC001 and EC33 were also presented<br><br>*Efficacy (Pharmacodynamic) data*<br>The pharmacodynamic analysis was performed on the ITT set. The primary efficacy analysis was also performed on the PP set to assess robustness of the primary results.<br>The primary pharmacodynamic endpoint was the comparison of change from baseline of daytime mean SBP as calculated from the individual ABPM after 4 weeks of treatment between treatments.<br><br>The secondary pharmacodynamic endpoints were the comparison of changes from baseline to 4 weeks of treatment between treatments on the following parameters:<br>- Hourly mean SBP/DBP/HR, 24h mean SBP/DBP/HR, daytime mean DBP/HR and night-time mean SBP/DBP/HR, systolic and diastolic load.<br>- Office SBP/DBP/HR<br>- The time course of the effect was examined through home BP response every two weeks. The parameters were the morning mean BP, evening mean BP, and total day mean BP, after discarding the values of the first day.<br>- Blood (renin, aldosterone, cortisol, ACTH, apelin and copeptin) and urinary (aldosterone, cortisol, creatinine, sodium and potassium) parameters<br><br>*Statistical analysis of blood pressure and Heart rate PD parameters*<br>For ABPM and OBP parameters, baseline was defined as the value before the first intake of treatment in each 4-week treatment period (Daytime, nighttime and 24-hour value at D-1) (=D14 of run-in or washout period).<br>For HBP parameters, baseline was defined as the value before the first intake of treatment in the first 4-week treatment period (Run-in period). | |

| | | |
|---|---|---|
| **Name of Company:**<br>Quantum Genomics<br>2-12 rue du chemin des Femmes<br>91300 Massy<br>France | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:**<br>QGC001 | **Volume:** | |
| **Name of active ingredient:**<br>(3S,3'S)-4,4'-dithiobis(3-aminobutane-1-sulfonic acid) | **Page:** | |
| **Statistical methods (cont'd):** | *Statistical analysis of blood pressure and Heart rate PD parameters (cont'd)*<br>The comparison between treatments of 24h mean SBP/DBP/HR, daytime mean SBP/DBP/HR, nighttime SBP/DBP/HR, and OBP was analyzed using an analysis of variance (ANOVA) on change from baseline to 4 weeks of treatment with treatment group, sequence, period and center as fixed effects and subject within sequence as random effect. The estimate and the 95% CI of the difference between QGC001 and placebo was provided.<br>The comparison between treatments of the smoothness index was analyzed using an analysis of variance (ANOVA) on value at 4 weeks of treatment with treatment group, sequence, period and center as fixed effects and subject within sequence as random effect. The estimate and the 95% CI of the difference between QGC001 and placebo were provided.<br>The comparison between treatments of trough to peak ratio was analyzed using a Wilcoxon signed-rank test for paired data, because the distribution of this parameter is not normal (Omboni et al, "The trough:peak ratio and the smoothness index in the evaluation of control of 24h blood pressure by treatment in hypertension",1998).<br>The comparison between treatments of systolic and diastolic loads were analyzed using an analysis of covariance (ANCOVA) on value at 4 weeks of treatment with treatment group, sequence, period, center and systolic or diastolic load at baseline as fixed effects and subject within sequence as random effect. The estimate and the 95% CI of the difference between QGC001 and placebo were provided.<br>The HBP parameters were compared between treatments after 2 weeks and after 4 weeks of treatment using an analysis of variance on change from baseline with treatment group, sequence, period, center as fixed effect and subject within sequence as random effect. Estimates and corresponding 95% CIs were provided.<br>*Blood and urinary parameters:*<br>Baseline was defined as the last available value before the first intake of treatment in each 4-week treatment period (D14 of Run-in period or wash-out period).<br>Blood (raw data and changes from baseline) and urinary PD parameters (raw data and data corrected by the concentration of creatinine) were listed and described overall in the run-in period and by treatment group and measurement time otherwise. | |

| | | |
|---|---|---|
| **Name of Company:**<br>Quantum Genomics<br>2-12 rue du chemin des Femmes<br>91300 Massy<br>France | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:**<br>QGC001 | **Volume:** | |
| **Name of active ingredient:**<br>(3S,3'S)-4,4'-dithiobis(3-aminobutane-1-sulfonic acid) | **Page:** | |
| **Statistical methods (cont'd):** | For these parameters, descriptive statistics included number of available data, geometric mean, 95% CI, CV%, median, IQR, minimum, and maximum.<br>A graphical description over time of raw data, geometric mean and 95% CI for each treatment was also performed.<br>Statistical comparisons were performed between treatments at each time point using an ANOVA, on changes from baseline calculated on log-transformed raw data for blood parameters and on log-transformed raw data for urinary parameters, with treatment group, sequence, period and center as fixed effects and subject within sequence as random effect. The geometric mean ratios and their corresponding 95% confidence intervals were provided. | |
| **SUMMARY -CONCLUSIONS** | | |
| BASELINE AND DEMOGRAPHY | A total of 50 volunteers were screened for the study and 40 patients were included in the Run-in period. Six patients were not included in Period 1 after the completion of the Run-in period.<br>34 patients were therefore included in the study and randomized. Four patients discontinued the study: two patients following a SAE (one episode of macular rash and one episode of right atypical vestibular syndrome during the QGC001 period), one patient following a TEAE (arthralgia in the QGC001 period) and one patient in compliance with withdrawal procedures following an increase in home-base assessed blood pressures, in the placebo period. The remaining 30 patients completed the study.<br>Two patients presented deviations from the schedule of treatment administrations: a temporary IMP withdrawal for 4 days (minor deviation) in one patient during the placebo period and two different treatments (placebo and QGC001) administered in Period 2 (major) for one patient who completed the study but was withdrawn from all statistical analyses. With the exception of these two cases, the overall compliance to treatment was high.<br>The patients were 56.6 ± 9.1 years old; 73.5% were male and 88.2% white. The mean± SD screening BMI was 26.766 ± 3.322 kg/$m^2$.<br>The medical history and previous and concomitant medications recorded were consistent with the diagnosis of essential grade I or II hypertension. | |
| PK RESULTS | PK data were missing in the case of investigating center n°4, because the iodoacetamide solution could not be prepared. Data were obtained from the other 3 centers.<br>Most QGC001 concentrations were BLQ, which is consistent with the short halve-lives observed in the previous study.<br>No relevant difference in EC33 concentrations was observed between the D15 and D28 assays. | |

| | | |
|---|---|---|
| **Name of Company:**<br>Quantum Genomics<br>2-12 rue du chemin des Femmes<br>91300 Massy<br>France | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:**<br>QGC001 | **Volume:** | |
| **Name of active ingredient:**<br>(3S,3'S)-4,4'-dithiobis(3-aminobutane-1-sulfonic acid) | **Page:** | |
| EFFICACY (PD) RESULTS | ***24h ABPM (primary efficacy criteria):***<br>• **Day-Time Blood Pressures and Heart Rate**<br>- *Primary endpoint analysis: day-time mean SBP changes from baseline*<br>The primary efficacy analysis was the comparison of change from baseline of daytime mean SBP as calculated from the individual ABPM after 4 weeks of treatment between treatments, in the ITT set.<br>The baseline values taken after the run-in period confirmed the requested diagnosis of essential grade I or II hypertension prior to inclusion. The baseline values of each treatment period were also very close, which confirmed that the duration of the washout period had been sufficient. Standard deviations were also smaller than the hypothesis of 15 mmHg that had been used when designing the study.<br>On D28, a decrease of day-time SBP was observed following QGC001 administration compared to placebo (-1.88 ± 8.13 mmHg versus +0.68 ± 9.34 mmHg respectively); the ANOVA estimated difference was -2.69 mmHg, however no statistically significant difference was found (p=0.1573).<br>- *Secondary endpoint analysis: day-time mean DBP and HR changes from baseline in the ITT set and SBP changes from baseline in the PP set*<br>The daytime mean DBP and heart rate in the ITT set constituted secondary endpoints. On D28, a decrease of day-time DBP was observed following QGC001 administration compared to placebo (-2.02 ± 6.70 mmHg versus -0.24 ± 6.27 mmHg respectively), however no statistically significant difference was found (p=0.2351).<br>On D28, day-time heart rate remained unchanged following QGC001 administration, whereas a decrease was observed following placebo administration (-0.51 ± 6.63 bpm versus -1.30 ± 8.60 bpm respectively), no statistically significant difference was found (p=0.6392).<br>The analysis of the daytime mean SBP in the PP set constituted a secondary analysis. As was the case in the ITT set, the ANOVA estimated difference was also -3.18 mmHg, and no statistically significant difference was found (p=0.1097).<br>• **Night-Time Blood Pressures and Heart Rate**<br>The changes that had been observed in day-time data were not observed in night-time data: in particular, the decrease in day-time SBP after QGC001 administration was not present during night-time, when SBP values returned to baseline: +0.69 ± 11.42 mmHg versus +1.29 ± 9.44 mmHg respectively; the ANOVA estimated difference was -0.51 mmHg, and no statistically significant difference was found (p=0.8483).<br>Similarly, no statistically significant difference was found in night-time DBP and heart rate when comparing changes from baseline on D28 in each treatment period. | |

<table>
<tr><td>Name of Company:<br>Quantum Genomics<br>2-12 rue du chemin des Femmes<br>91300 Massy<br>France</td><td>Individual Study Table<br>Referring to Part<br>of the Dossier</td><td>(For National Authority<br>Use only)</td></tr>
<tr><td>Name of Finished Product:<br>QGC001</td><td>Volume:</td><td></td></tr>
<tr><td>Name of active ingredient:<br>(3S,3'S)-4,4'-dithiobis(3-aminobutane-1-sulfonic acid)</td><td>Page:</td><td></td></tr>
<tr><td><u>EFFICACY (PD) RESULTS (cont'd)</u></td><td colspan="2">
<ul>
<li>24h mean Blood Pressures and Heart Rate</li>
</ul>
The decrease in day-time SBP after QGC001 administration and the baseline-like values of night-time SBP lead to a stable 24h- mean SBP on D28 compared to baseline, when a small increase was observed on D28 of the placebo period: -0.82 ± 8.80 mmHg versus +1.09 ± 8.97 mmHg respectively; the ANOVA estimated difference was -2.0 mmHg, and no statistically significant difference was found (p=0.3163).
<ul>
<li>Trough to peak ratio</li>
</ul>
No statistically significant difference was found.
<ul>
<li>Smoothness Index</li>
</ul>
No statistically significant difference was found.
<ul>
<li>Blood pressure loads:</li>
</ul>
A small reduction in day-time blood pressure loads was observed following QGC001 administration compared to placebo:
<ul>
<li>Day-time SBP: 78.25 ± 19.42% versus 82.16 ± 18.45% respectively; the ANOVA estimated difference was -3.77%.</li>
<li>Day-time DBP: 73.97 ± 25.56% versus 77.02 ± 20.59% respectively; the ANOVA estimated difference was -4.32%.</li>
</ul>
However none of these reductions were statistically significant: p=0.3247 and 0.2737 respectively.<br>
Similar results were found in 24h-mean BP loads, and no statistically significant difference was found.<br>
No nocturnal decrease was observed.
<ul>
<li>Time Course Of Treatment Effect (Home Blood Pressure)</li>
</ul>
No statistically significant difference was found.
<ul>
<li>Office Blood Pressures and heart rate</li>
</ul>
Office semi-recumbent measurements show similar results to the 24-ABPM derived results: a decrease of SBP was observed following QGC001 administration compared to placebo, on D15 (-1.4 ± 11.7 mmHg versus +2.9 ± 10.9 mmHg respectively) and on D28 (-4.7 ± 11.9 mmHg versus +0.1 ± 12.4 mmHg respectively); on D28, the ANOVA estimated difference was 4.65 mmHg, but no statistically significant difference was found (p=0.1512).<br>
No change and no statistically significant difference was observed in any of the other investigated parameters.
</td></tr>
</table>

| | | |
|---|---|---|
| **Name of Company:**<br>Quantum Genomics<br>2-12 rue du chemin des Femmes<br>91300 Massy<br>France | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:**<br>QGC001 | **Volume:** | |
| **Name of active ingredient:**<br>(3S,3'S)-4,4'-dithiobis(3-aminobutane-1-sulfonic acid) | **Page:** | |
| EFFICACY (PD) RESULTS (cont'd) | • **Blood PD Parameters**<br>No statistically significant effect was found on D15 and D28 in the case of active renin, aldosterone, cortisol, copeptin and apelin.<br>In the case of ACTH, an increase from baseline was observed following QGC001 administration on D15 (+0.3ng/L) and D28 (+1.15ng/L) and a decrease following placebo administration on D15 (-0.2ng/L) and D28 (-0.5ng/L): this difference was not statistically significant on D15 (p=0.5171) but became significant on D28 (p=0.0246).<br>• **Urinary PD Parameters**<br>No statistically significant effect was found on D15 and D28 in any of the investigated parameters (aldosterone, cortisol, sodium and potassium and creatinine).<br>• **Post-hoc analyses:**<br>The analysis of the mean day-time, night-time and 24h mean SBP for subjects with no ongoing antihypertensive treatment at inclusion, in the PP set showed no statistically significant difference between the treatment periods.<br>The multivariate analyses of day-time mean SBP changes from baseline, in the PP set, with and without adjustment on sequence and period showed no statistically significant effect. | |
| SAFETY RESULTS | Two SAEs were reported during the study, each SAE in a different patient, both patients fully recovered: both SAEs, a vestibular disorder and a rash macular, were reported during the QGC001 period of administration.<br>The case of vestibular disorder (verbatim: right atypical vestibular syndrome) was considered possibly related to treatment because no other aetiology could be proposed. The case of rash macular (verbatim: verbatim: generalised macular erythematous rash with facial periorbital edema) was considered probably related to treatment.<br>A patient also presented two AESIs during the study: a pruritic rash taking place during a blinded placebo administration period, considered possibly related to treatment, and a pruritic rash taking place during the washout period.<br>One patient was also withdrawn shortly after the initiation of QGC001 administrations, due to moderate arthralgia, possibly related to treatment. | |

| | | |
|---|---|---|
| **Name of Company:**<br>Quantum Genomics<br>2-12 rue du chemin des Femmes<br>91300 Massy<br>France | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:**<br>QGC001 | **Volume:** | |
| **Name of active ingredient:**<br>(3S,3'S)-4,4'-dithiobis(3-aminobutane-1-sulfonic acid) | **Page:** | |
| SAFETY RESULTS (cont'd) | Overall, 14 patients (42.4%) presented a total of 16 TEAEs during the study:<br>The most TEAEs were gastroenteritis and headache, both reported in one patient (3.1%) in each treatment period. The other AEs were only reported in isolated patients.<br>The intensity of most TEAEs was mild; only 2 patients (6.3%) in the QGC001 treatment period and one patient (3.1%) in the placebo treatment period presented a TEAE of moderate intensity. There was no AE of severe intensity.<br>Only one TEAE was considered as probably related to treatment during the study: a rash macular reported in one patient (3.1%) in the QGC001 treatment period.<br>The assessment of haematology, blood chemistry and urinalysis laboratory safety parameters showed no relevant difference between the QGC001 treatment period and the placebo treatment period at baseline, and no trend was observed after baseline.<br>PCSA values were reported but none of them were considered clinically significant.<br>Blood pressures and heart rate were efficacy (PD) parameters but were also monitored for safety:<br>The office measurement of semi-recumbent blood pressures showed a more pronounced decrease of SBP following QGC001 administration on D15 and D28, compared to placebo. The evolution of DBP and heart rate was similar in both treatment periods.<br>The home measurement of morning semi-recumbent blood pressures showed a decrease of SBP following placebo administration, compared to unchanged. On D15 however, an increase was seen in the evening SBP measurements following QGC001 administrations. No difference was found on D28. The 24-h mean semi-recumbent SBP combined both trends: on D15, a slight increase following QGC001 administration, versus a decrease following placebo administration; and no difference were found on D28.<br>The evolution of DBP and heart rate was similar in both treatment periods, in the morning, in the evening and for the 24-hour mean values.<br>None of the changes were clinically significant.<br>One patient (n°22002) was also withdrawn from the study for safety issues related to elevations of home-based vital signs assessments, in compliance with withdrawal procedures.<br>The analysis of ECG parameters showed no relevant difference between the QGC001 treatment period and the placebo treatment period at baseline, and no trend was observed after baseline. PCSA values were reported but none of them were considered clinically significant. | |

| | | |
|---|---|---|
| **Name of Company:**<br>Quantum Genomics<br>2-12 rue du chemin des Femmes<br>91300 Massy<br>France | **Individual Study Table Referring to Part of the Dossier** | *(For National Authority Use only)* |
| **Name of Finished Product:**<br>QGC001 | **Volume:** | |
| **Name of active ingredient:**<br>(3S,3'S)-4,4'-dithiobis(3-aminobutane-1-sulfonic acid) | **Page:** | |
| **CONCLUSION** | Four-week administration of the aminopeptidase inhibitor QGC001 at 1000 mg daily oral doses to patients with grade I to II hypertension decreased ambulatory daytime SBP by 2 to 3 mmHg compared to placebo, but the difference with placebo was not significant. QGC001 did not influence HR, or plasma/ urine hormones including renin, aldosterone, copeptin, apelin, ACTH. Four week QGC001 administration was safe, with the exception of occurrence of one episode of QGC001 probably-related macular rash.<br>The non-significant BP lowering effect of QGC001 may be of multifactorial origin including the small sample size of the study, the short duration of exposure to QGC001, the short PK half-life of QGC001 in its present formulation, the low penetration of QGC001 at the level of blood brain barrier especially if converted to its metabolite EC33 in the systemic circulation, and the large between-patient variability in BP levels.<br>The absence of any placebo effect on ambulatory BP measurements and the results of the multivariate analysis showing a 3 to 4 mmHg difference in daytime SBP in favor of QGC001, although not significant, suggest designing further studies in patients with grade I to II hypertension with the following conditions: larger adequate sample size, new formulation to increase plasma half-life, 8-week administration, parallel groups study design with a placebo and an active arm. | |
| **Date of the report:** ***13DEC2016*** | | |