Bromocriptine Safety Report - Unblinded

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# 1. Study description

This is a double-blind, random-order, cross-over design study of bromocriptine QR in type 1 diabetes funded by the JDRF (NCT02544321). Two cohorts, adult (age 22-50) and adolescent (age 12-21) are planned with a goal to complete 40 subjects in each cohort. The adult cohort was required to precede the adolescent cohort for safety reasons. An IND exemption was obtained for the adult cohort and an IND is in place for the adolescent cohort (sponsored by the study coPI, Kristen Nadeau). Primary outcomes include measures of glycemic control. Secondary measures include hypoglycemia, hypoglycemia awareness, sleep, vascular function and stiffness, and cardiac autonomic function.

# 2. Safety Officer Responsibilities

The responsibilities of the safety officers are as follows:

* Review unblinded safety data annually and report to the PI of the safety of the study
* Protect unblinding information from the PI and study team at all times prior to completion of the relevant cohort
* Work with the PI to protect the safety of the study participants
* Follow the below process annually:
* Review unblinded data reports sent by study-independent biostatistician
  + Hypoglycemia: number of events, severity, % time hypoglycemic
  + Symptom reports and adverse events
* Assess for future potential safety concerns
* Engage in conference call with study PI and team to discuss conduct, progress, and concerns of the study
* Write a formal letter with decision for recommendation of continuation of study, discussed safety concerns, suggestions for improvement, and plans of action, if applicable

# 3. Data management

First, all the data was gathered into a single folder for adults and a single folder for pediatric participants. Timestamp formats were inconsistent from file to file, so they were manually edited in order to be correctly read into R. Some of the files were also re-named to include subject ID, as this was how participants’ data were identified. Excel files were saved as CSV, to make importing them into R easier and faster.

Some pediatric participants’ data included summary tables that were not standard across the cohort. These were manually removed to help with formatting data in R. For the adults, BCQR-31’s second med start date was incorrectly listed in the enrollment log as 1/19/16, so it was manually changed to 1/19/17. When cleaning the CGM data, gaps <= 20 min were interpolated, and larger gaps were left in the data. “Low” sensor readings were converted to 40, and “High” to 400.

The cleaning function reads in everything in the respective input directories, and combines it into one big table. Then the table is first split by subject ID, then further split by pre/post med start, and unblinded drug phase. Cleaned files are written in the appropriate directories. This function is performed seperately for pediatric and adult participants.

After all of the CGM data was sorted, CGM summary variables were generated using modified code from the “cgmanalysis” package. Summary variables were compared between phases using a paired Wilcoxon test, so only participants with BCQR and placbo data were included.

# 4. Enrollment Log

Table 1 provides a count of the number of participants screened, enrolled, completed and withdrawn in the pediatric and adult cohorts.

Table 1. Count of participants by enrollment status.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Cohort | Screened | Enrolled | Completed | Withdrawn | Screen Failed | Active |
| Adult | 65 | 65 | 41 | 17 | 7 | 0 |
| Pediatric | 32 | 32 | 23 | 4 | 0 | 5 |

# Adverse Events

## Table 2

Symptoms reported in adult study participants.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Subject ID | Phase 1 Drug | Phase 1 Side Effects | Phase 1 Notes | Phase 2 Drug | Phase 2 Side Effects | Phase 2 Notes |
| BCQR-02 | BCQR | None |  | PLAC | None |  |
| BCQR-04 | BCQR | None |  |  | NA |  |
| BCQR-05 | BCQR | None |  | PLAC | None |  |
| BCQR-06 | PLAC | None |  | BCQR | None |  |
| BCQR-07 | BCQR | Gastrointestinal, Other | right ankle swelling? (had previous varicose vein), mild nausea with increase to 3.2mg | PLAC | None |  |
| BCQR-08 | BCQR | Gastrointestinal | Subj. thinks had food poisoning, led to emesis | PLAC | None |  |
| BCQR-10 | PLAC | Gastrointestinal, Orthostasis | nausea, low blood pressure | BCQR | Orthostasis |  |
| BCQR-12 | BCQR | None |  | PLAC | None |  |
| BCQR-15 | PLAC | Orthostasis, Other | joint pain, dizziness with 3.2 mg | BCQR | None |  |
| BCQR-16 | PLAC | None |  | BCQR | None |  |
| BCQR-18 | PLAC | None |  | BCQR | Gastrointestinal, Orthostasis | orthostatic, dizzy, nausea |
| BCQR-19 | PLAC | None |  | BCQR | None |  |
| BCQR-20 | BCQR | Gastrointestinal, Orthostasis, Fatigue |  | PLAC | None |  |
| BCQR-23 | BCQR | None |  | PLAC | None |  |
| BCQR-24 | PLAC | None |  | BCQR | Fatigue |  |
| BCQR-25 | BCQR | Gastrointestinal |  | PLAC | None |  |
| BCQR-26 | PLAC | Other | Has noticed no Reynaud’s Disease after morning runs per usual | BCQR | Gastrointestinal, Orthostasis, Fatigue, Other | Reynaud’s returned |
| BCQR-27 | BCQR | Gastrointestinal |  | PLAC | None |  |
| BCQR-28 | BCQR | Gastrointestinal, Orthostasis |  | PLAC | None |  |
| BCQR-29 | PLAC | None |  | BCQR | None |  |
| BCQR-31 | PLAC | None |  | BCQR | None |  |
| BCQR-32 | PLAC | Fatigue, Headache |  | BCQR | None | Bladder spasms reported in early washout phase. |
| BCQR-34 | BCQR | Gastrointestinal, Headache |  | PLAC | None |  |
| BCQR-35 | PLAC | Gastrointestinal, Headache |  | BCQR | Gastrointestinal |  |
| BCQR-36 | BCQR | None |  | PLAC | None |  |
| BCQR-40 | BCQR | Gastrointestinal, Orthostasis |  | PLAC | None |  |
| BCQR-42 | PLAC | None |  | BCQR | Gastrointestinal |  |
| BCQR-43 | PLAC | None |  | BCQR | None |  |
| BCQR-44 | BCQR | None |  | PLAC | None |  |
| BCQR-45 | BCQR | Gastrointestinal |  | PLAC | None |  |
| BCQR-47 | PLAC | None |  | BCQR | Gastrointestinal |  |
| BCQR-48 | BCQR | None |  | PLAC | None |  |
| BCQR-49 | PLAC | None |  | BCQR | None |  |
| BCQR-51 | PLAC | None |  | BCQR | Fatigue |  |
| BCQR-53 | PLAC | None |  | BCQR | None |  |
| BCQR-54 | BCQR | None |  | PLAC | None |  |
| BCQR-56 | BCQR | Fatigue, Headache | Foot & Mouth Disease during last 2 weeks of phase, on amoxicillin (day 5) at visit 4. | PLAC | None |  |
| BCQR-57 | PLAC | Gastrointestinal | constipation and weight gain | BCQR | Fatigue | weight gain |
| BCQR-59 | PLAC | Gastrointestinal, Fatigue |  | BCQR | Gastrointestinal | caught cold/flu virus |
| BCQR-61 | BCQR | None |  | PLAC | Headache |  |
| BCQR-62 | BCQR | Gastrointestinal, Headache | Related to Celiac’s? | PLAC | None |  |
| BCQR-64 | PLAC | None |  | BCQR | NA |  |
| BCQR-65 | PLAC | None |  | BCQR | None |  |

## Table 3.

Symptoms reported in pediatric study participants.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Subject ID | Phase 1 Drug | Phase 1 Side Effects | Phase 1 Notes | Phase 2 Drug | Phase 2 Side Effects | Phase 2 Notes |
| PBCQR-01 | BCQR | Other | Appetite Suppression week 3 | PLAC | None |  |
| PBCQR-02 | PLAC | None |  | BCQR | None |  |
| PBCQR-03 | PLAC | None |  | BCQR | None |  |
| PBCQR-04 | BCQR | Gastrointestinal, Orthostasis |  | PLAC | None |  |
| PBCQR-05 | PLAC | None |  | BCQR | None |  |
| PBCQR-06 | PLAC | None |  | BCQR | Gastrointestinal | Nausea when taken without food |
| PBCQR-07 | BCQR | None |  | PLAC | None |  |
| PBCQR-08 | BCQR | None |  | PLAC | None |  |
| PBCQR-09 | BCQR | None |  | PLAC | None |  |
| PBCQR-10 | PLAC | None |  | BCQR | None |  |
| PBCQR-11 | BCQR | None |  | PLAC | NA | Did not complete Phase 2 |
| PBCQR-12 | BCQR | None |  | PLAC | None |  |
| PBCQR-13 | BCQR | Gastrointestinal | nauseous in AM after taking pills | PLAC | None |  |
| PBCQR-14 | PLAC | None |  | BCQR | None |  |
| PBCQR-15 | PLAC | None |  | BCQR | None |  |
| PBCQR-16 | PLAC | None |  | BCQR | Orthostasis, Headache |  |
| PBCQR-17 | BCQR | Gastrointestinal | Stomach aches when meds are not taken with a large amount of food (started when taking full dose). | PLAC | None |  |
| PBCQR-18 | PLAC | None |  | BCQR | None |  |
| PBCQR-19 | BCQR | None |  | PLAC | None |  |
| PBCQR-20 | PLAC | Other | Numbness with lows | BCQR | None |  |
| PBCQR-21 | BCQR | None |  | PLAC | None |  |
| PBCQR-22 | PLAC | None |  | BCQR | Gastrointestinal, Orthostasis, Fatigue, Headache, Other | See AE log for this subject. When subject went to full dose she was very nauseous, light headed, and had headaches. She passed out when she was at Barre class and said she was very dizzy. We went back down to 2 pills and her symptoms subsided. Subject withdrawaled from study |
| PBCQR-23 | PLAC | None |  | BCQR | None |  |
| PBCQR-25 | PLAC | Gastrointestinal, Other | Decreased hypoglycemia awareness overnight; nausea when low after taking pills with food; nausea when pills taken without food | BCQR | Headache | Went to ER for a severe migrane and threw up at hospital. She said it was not study medication related. Felt better with Tylenol and Benadryl |
| PBCQR-26 | BCQR | Gastrointestinal | Nausea on first day of 2 pills, then subsided. Vomited on first day of 4 pills. Took 3 pills for remainder of study without complaint. | PLAC | None |  |
| PBCQR-27 | BCQR | Gastrointestinal | Nausea with full dose if participating in morning skate practice | PLAC | NA |  |
| PBCQR-28 | BCQR | Gastrointestinal | Subject felt nauseous when she did not take the meds with food | PLAC | NA |  |
| PBCQR-30 | BCQR | NA |  | PLAC | NA |  |
| PBCQR-31 | PLAC | NA |  | BCQR | NA |  |

# 6. Hypoglycemia data

Participants were asked to wear a CGM for 3 days prior to starting medication and 4 weeks after starting medication, in each phase of the study. For this study, hypoglycemia-related safety outcomes are defined as the number of glycemic excursions <50 mg/dL and <70 mg/dL per day, and the percent of time spent <50 mg/dL and <70 mg/dL. These outcomes are expressed as excursions per day or percent of time to account for the different length of time the CGM was worn by each participant in each phase. Tables 4 and 5 provide descriptive statistics for these outcomes for the adult and pediatric cohort, respectively. For the blinded version of the report, data from phases 1 and 2 are combined, so each participant has up to 2 sets of CGM data in each column of tables 4 and 5.

## Table 4.

Summary of hypoglycemia by CGM in adult cohort, by treatment assignment.

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | BCQR, Median (IQR) | Placebo, Median (IQR) | P-Value |
| num\_days\_good\_data | 26.70 (23.45, 27.31) | 26.63 (24.47, 27.65) | 0.483 |
| excursions\_under\_50\_per\_day | 0.18 (0.07, 0.48) | 0.32 (0.12, 0.59) | 0.321 |
| percent\_time\_under\_50 | 0.41 (0.15, 1.29) | 0.96 (0.24, 1.46) | 0.422 |
| excursions\_under\_70\_per\_day | 0.96 (0.68, 1.98) | 1.40 (0.74, 1.85) | 0.142 |
| percent\_time\_under\_70 | 3.88 (2.14, 7.62) | 4.81 (2.34, 7.49) | 0.712 |

## Table 5.

Summary of hypoglycemia by CGM in pediatric cohort, by treatment assignment.

|  |  |  |  |
| --- | --- | --- | --- |
| Variable | BCQR, Median (IQR) | Placebo, Median (IQR) | P-Value |
| num\_days\_good\_data | 22.38 (18.80, 24.40) | 22.93 (21.86, 26.69) | 0.344 |
| excursions\_under\_50\_per\_day | 0.18 (0.08, 0.40) | 0.20 (0.10, 0.44) | 0.165 |
| percent\_time\_under\_50 | 0.56 (0.21, 1.19) | 0.56 (0.25, 1.52) | 0.33 |
| excursions\_under\_70\_per\_day | 0.91 (0.41, 1.29) | 1.08 (0.52, 1.76) | 0.312 |
| percent\_time\_under\_70 | 3.59 (2.57, 5.73) | 3.85 (1.96, 7.27) | 0.409 |

# Clarification Questions

## 1. Enrolled numbers don’t = completed + withdrawn or active

The peds total enrollment should equal 32, which has been updated in the report. For the adult cohort, screen fails and withdrawals are separate categories, so in fact a total of 24 participants dropped out of the study, of which 7 were screen fails (as opposed to 17 total).

## 2. Screening numbers = enrolled numbers

Once the consent form is signed, they are considered “enrolled,” and screening labs cannot be drawn until the consent has been signed. Per Susan Gross: “If they signed a consent and then their screening labs came back ineligible or they withdrew after the screen then they would be a withdrawal or screen fail. They would still be counted in the enrolled #, but they would also be listed as a screen fail/withdrawn.”

## 3. Number withdrawn during therapy by treatment.

### Table 6.

Pediatric participants withdrawn during therapy by phase.

|  |  |  |
| --- | --- | --- |
| Subject ID | Withdrawal Treatment | Withdrawal Phase |
| PBCQR-06 | PLAC | 1 |
| PBCQR-11 | PLAC | 2 |
| PBCQR-22 | BCQR | 2 |
| PBCQR-24 | PLAC | 1 |

### Table 7.

Adult participants withdrawn during therapy by treatment.

|  |  |  |  |
| --- | --- | --- | --- |
| Subject ID | Withdrawal Phase | Withdrawal Treatment | Comments |
| BCQR-01 | 1 | PLAC | Family Emergency |
| BCQR-03 | 1 |  | No longer interested |
| BCQR-04 | 2 | BCQR | Was diagnosed with RA |
| BCQR-09 | 1 | PLAC | Had side effects with placebo |
| BCQR-11 | 1 |  | study team had ethical concerns |
| BCQR-13 | 1 |  | Scheduling conflicts |
| BCQR-14 | 1 |  | Scheduling conflicts |
| BCQR-21 | 1 |  | Decided to seek pregnancy after screening visit |
| BCQR-33 | 1 |  | No longer interested |
| BCQR-37 | 1 |  | No longer interested |
| BCQR-39 | 1 |  | Moved to California |
| BCQR-41 | 1 |  | Wanted to start exercise program |
| BCQR-50 | 1 | BCQR | Couldn’t tolerate symptoms |
| BCQR-55 | 1 |  | No longer interested |
| BCQR-63 | 1 |  | No longer interested |
| BCQR-64 | 2 | BCQR | No longer interested |

## 4. Tables for GI side effects and orthostasis symptoms

### Table 8a.

Adult cohort GI side effects by drug.

## GI.Symptoms  
## Med Yes No  
## PLAC 4 38  
## BCQR 16 27

## [1] "McNemar's P Value = 0.01"

\*BCQR-04 was never on placebo, but did start BCQR.

### Table 8b.

Adult cohort orthostasis side effects by drug.

## Ortho.Symptoms  
## Med Yes No  
## PLAC 2 40  
## BCQR 6 37

## [1] "McNemar's P Value = 0.22"

\*BCQR-04 was never on placebo, but did start BCQR.

### Table 9a.

Pediatric cohort GI side effects by drug.

## GI.Symptoms  
## Med Yes No  
## PLAC 1 28  
## BCQR 8 21

## [1] "McNemar's P Value = 0.05"

### Table 9b.

Pediatric cohort orthostasis side effects by drug.

## Ortho.Symptoms  
## Med Yes No  
## PLAC 0 29  
## BCQR 3 26

## [1] "Unable to perform significance test."

## 5. BP measures

### Table 10.

Adult BP comparisons by drug. Mean (SD) or median [IQR]. P Values adjusted using the Bonferroni method.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variables | PLAC | BCQR | Raw P Value | Adjusted P Value |
| supine.systolic | 116.37 (10.6) | 113.42 (12.31) | 0.07014 | 0.281 |
| standing.systolic | 120.95 (10.59) | 108.68 (15.76) | < 0.001 | <0.001 |
| end.systolic | 125.08 (12.33) | 121.39 (13.09) | 0.02942 | 0.118 |
| end.diastolic | 68.17 [11.25] | 64.33 [9.33] | 0.00425 | 0.017 |

### Table 11.

Pediatric BP comparisons by drug. Mean (SD) or median [IQR]. P Values adjusted using the Bonferroni method.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Variables | PLAC | BCQR | Raw P Value | Adjusted P Value |
| supine.systolic | 123.65 (10.5) | 116.3 (11.12) | <0.001 | <0.001 |
| standing.systolic | 122.6 (11.55) | 117.75 (15.77) | 0.257 | 0.514 |

\*Only two participants had end of visit BP readings, so the variables were excluded from this table.

## 6. Scale of symptoms

The scale of symptoms was not recorded, but all were mild except for those participants who withdrew as a result. In the pediatric cohort, only one participant withdrew due to symptoms. Per Susan Gross: “There was really just the one subject that withdrew due to symptoms (PBCQR-22). She did pass out and was very nauseous at the full dose 4 pills. This was resolved when she went back down to the 2 pills, but again, her parents would not allow her to continue.” This was the same for the adult cohort as well. Per Irene Schauer: “If they didn’t withdraw, the symptoms were always mild OR very transient (ie first dose or two and then gone).” See Table 7 for withdrawal reasons in the adult cohort.

## 7. Further BP clarification

### Table 11.

Adult Endopat BP comparisons by drug, median [IQR].

|  |  |  |  |
| --- | --- | --- | --- |
|  | BCQR | PLAC | p |
| n | 25 | 25 |  |
| SystolicPressure (median [IQR]) | 117.00 [113.00, 131.00] | 124.00 [114.00, 133.00] | 0.145 |
| DiastolicPressure (median [IQR]) | 63.00 [60.00, 70.00] | 67.00 [62.00, 74.00] | 0.002 |

### Table 12.

Pediatric Endopat BP comparisons by drug, median [IQR].

|  |  |  |  |
| --- | --- | --- | --- |
|  | BCQR | PLAC | p |
| n | 19 | 19 |  |
| SystolicPressure (median [IQR]) | 117.00 [106.50, 121.00] | 123.00 [116.50, 128.00] | 0.002 |
| DiastolicPressure (median [IQR]) | 58.00 [55.00, 64.00] | 63.00 [56.50, 67.00] | 0.061 |