EVALUATION OF RBP-6000 EFFECTS ON QT INTERVAL DURING TREATMENT FOR OPIOID USE DISORDER (OUD)

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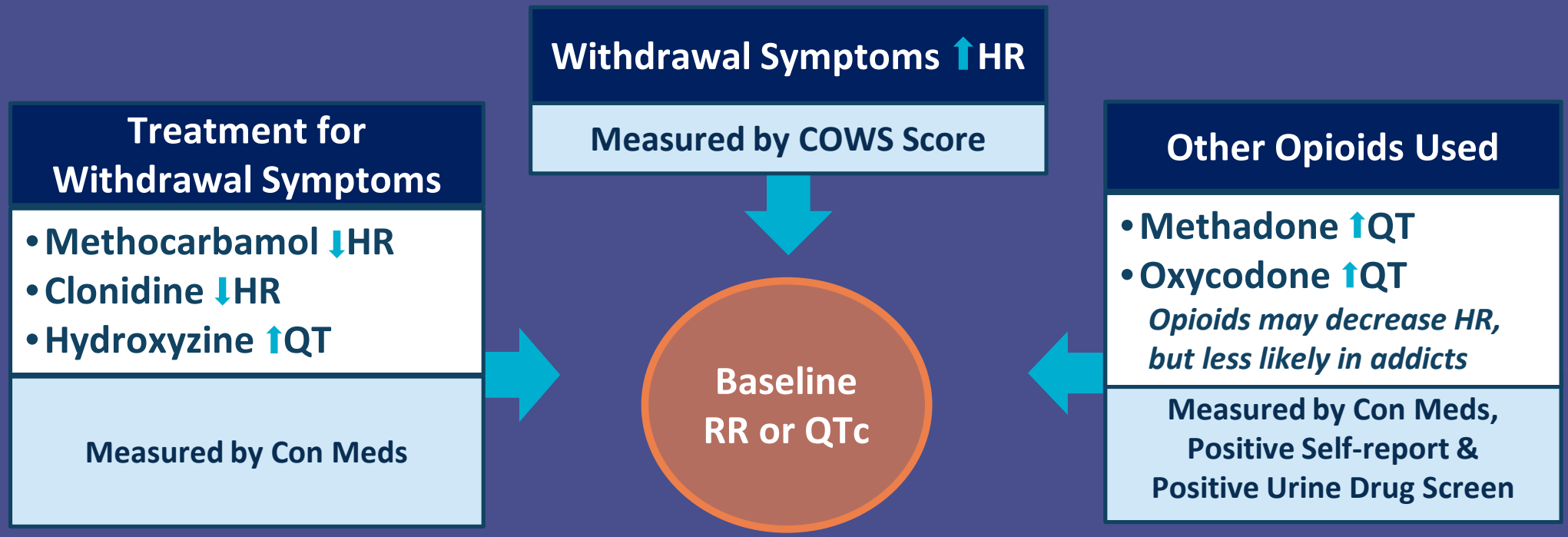
Introduction

- RBP-6000 is a monthly SC depot formulation of buprenorphine developed for the treatment of OUD
- The overall safety profile of buprenorphine is well established, but a recent report suggested a potential effect of buprenorphine on QT in healthy volunteers receiving naltrexone[1]
- Extensive robust 12-lead ECG monitoring & PK assessments were conducted from 5 Phase I-III studies as part of the RBP-6000 development program to evaluate the effects of RBP-6000 on QT:
  - includes **>11,000** C-QT observations before and after a wide range of RBP-6000 doses
- All clinical studies with RBP-6000 were conducted in subjects with moderate to severe OUD

[1]Darpo et al . *Clin Ther* **38**(2): 315-326

Challenges in Identifying Baseline HR & QT Interval and Evaluating Any Effects of Buprenorphine on HR & QT Interval



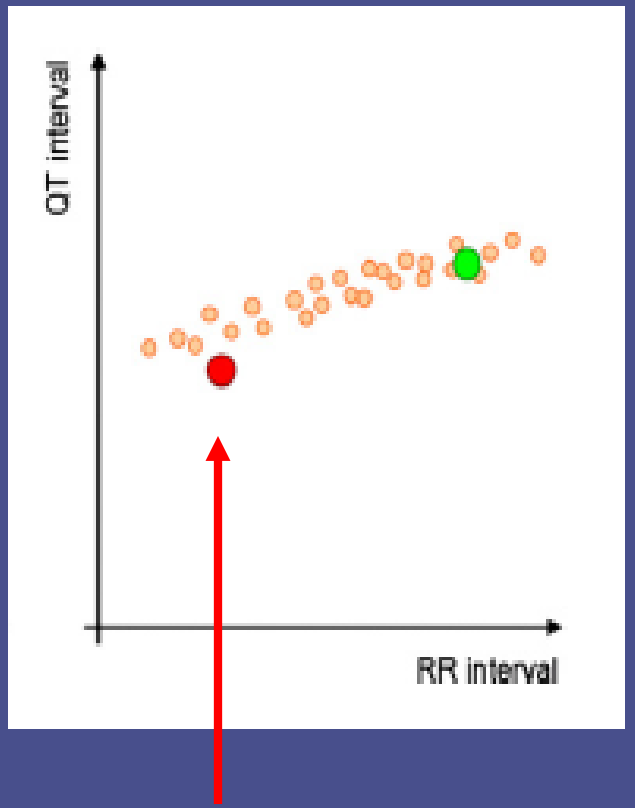
Patients with OUD do not have a true baseline prior to receiving RBP-6000 because they

- May be experiencing withdrawal
- Typically receive sublingual buprenorphine for induction
- May be receiving other con-meds
- May use illicit drugs (typical at screening)

COWS, Clinical Opioid Withdrawal Scale; HR, heart rate; QTc, QT-interval corrected for HR

Drugs that Affect HR

- Given the relationship between QT and RR, any drugs affecting HR can affect alpha



Garnett et al. *Am Heart J* **163**(6): 912-930.

Objectives

- To evaluate whether there is a concentration-related effect of buprenorphine on QT interval after accounting for the effect of relevant concomitant medications and illicit drug use on HR and/or QT in opioid-dependent subjects
- To predict the concentration-related effects of buprenorphine on QTc interval at therapeutic and supratherapeutic concentration levels after treatment with RBP-6000

Methods

- Matched robust 11,925 C-QT measurements from 1,114 subjects pooled from 5 Phase I-III studies of RBP-6000 in OUD subjects

A concentration-QT model developed in NONMEM

- to characterize the QTc in the absence of buprenorphine (QTc_{Abs}) & alpha
- to estimate concomitant medication effects on alpha or QTc_{Abs}
- to estimate buprenorphine-related slope

Covariates selected using individual steps of backward elimination

Effects on alpha if con-meds affect HR

Effects on QTc_{Abs} if con med effects QT

The concentration-related slope added and model refined

Sensitivity analysis

Bootstrap & VPC

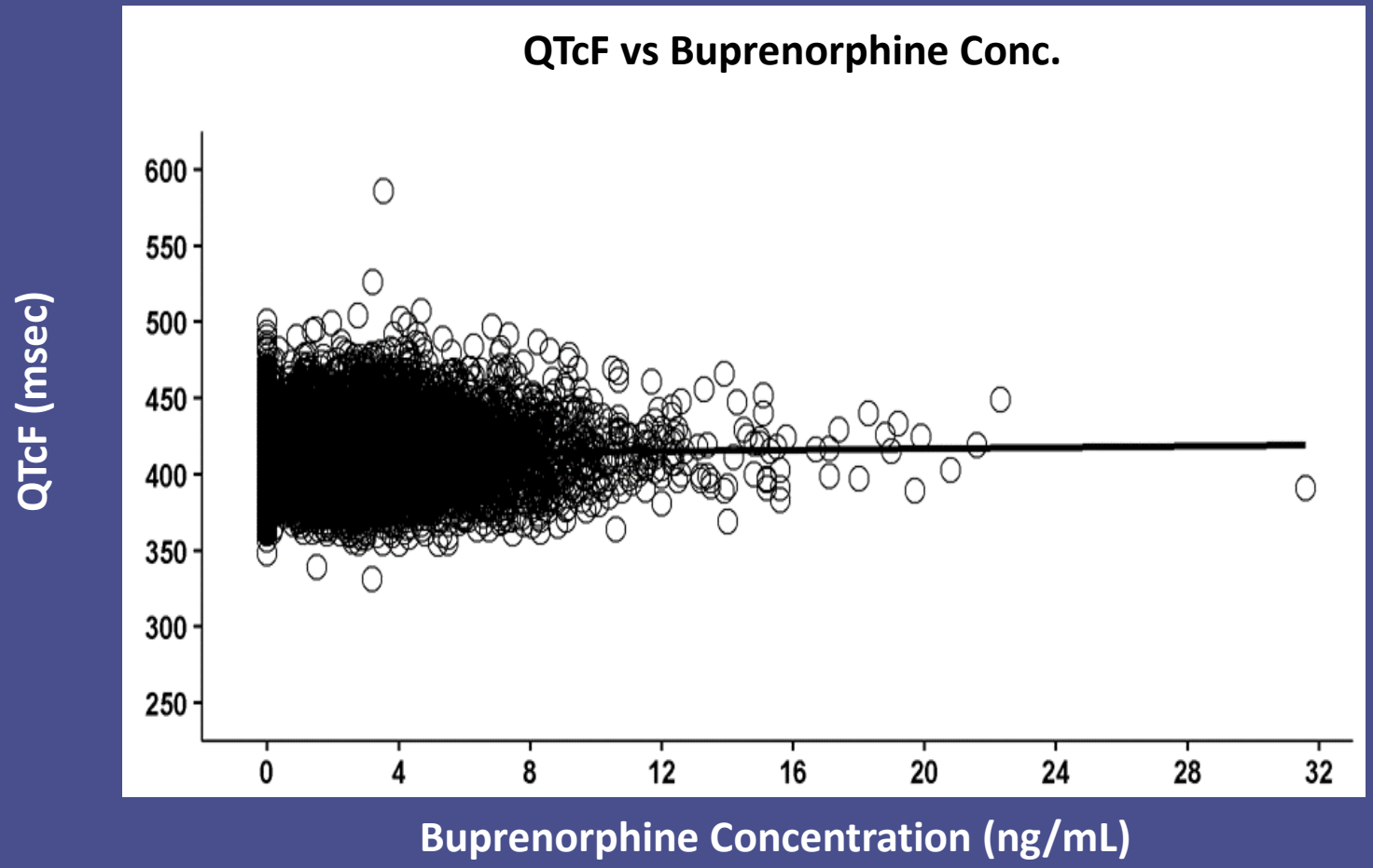
Predict ΔQTc at therapeutic & supratherapeutic doses

The 2-sided 90% confidence interval & a bias-corrected 2-sided 90% confidence interval of the mean ΔQTc at the:

- geometric mean C_{max} at 100 mg, 300 mg, and 2x300 mg doses

If the upper limit of the 90% confidence interval was <10 msec, then an effect of the RBP-6000 on QTc was to be ruled out

Time-matched Concentration-QTc Over the Clinical Program



Covariates Evaluated: The Final Concentration-QT Model Included Many Covariate Effects on QTc

Covariates	Effect on QTc
Age	16.8 msec difference between a 70-yr old and an 18-yr-old
Sex	+7.6 msec for females
ECG Reading: Central vs. non-central reading	-8.4 msec
Capturing of ECG: Holter vs. non-Holter	-1.7 msec
Methadone	+6.1 msec
Barbiturates	+5.0 msec
Phencyclidine	+3.4 msec
Hydroxyzine and Cocaine	+1.7 msec each
Oxycodone	-1.5 msec
Codeine	+1.3 msec

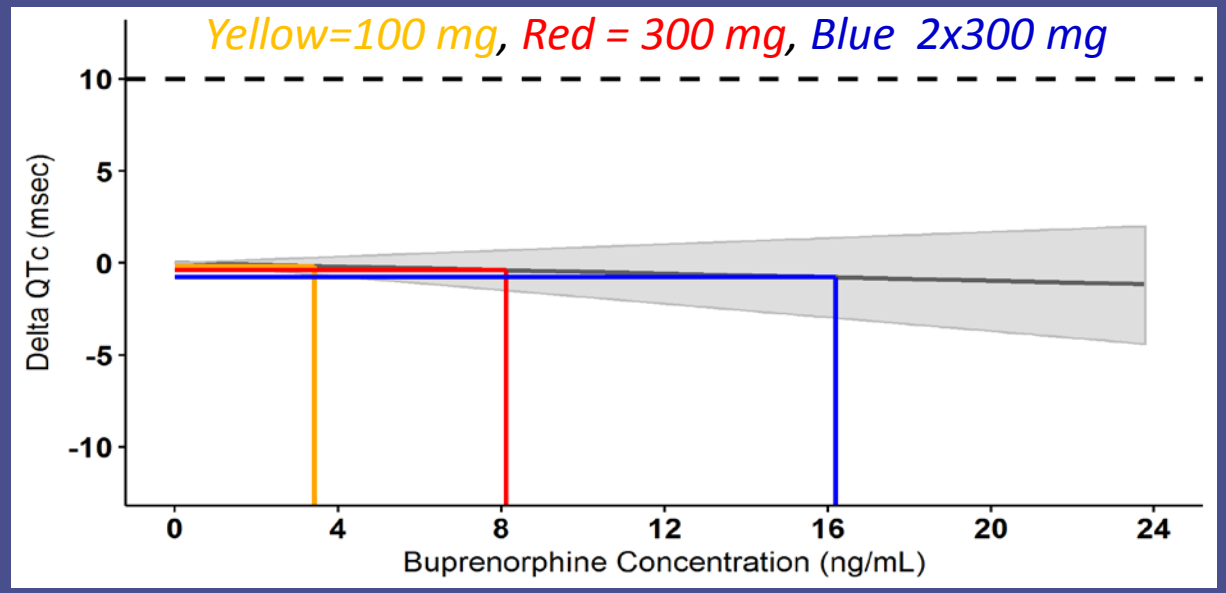
Results: Predicted ΔQTc (msec) at Therapeutic and Supratherapeutic Doses

	Geometric Mean C_{max} (ng/mL)			ΔQTc (msec)			
RBP-6000 DOSE	Mean	Median	90% Confidence Interval	Mean	Median	90% Confidence Interval	Bias-Corrected 90% Confidence Interval
100 mg Q28D	3.44	3.43	3.25 to 3.63	-0.17	-0.16	-0.65 to 0.29	-0.65 to 0.29
300 mg Q28D	8.12	8.12	7.54 to 8.72	-0.40	-0.38	-1.52 to 0.66	-1.52 to 0.67
2X300 mg Q28D[a]	16.2	16.2	15.1 to 17.4	-0.79	-0.75	-3.04 to 1.32	-3.05 to 1.34

[a]2x300 mg not studied

Results: Predicted Concentration-QT Results Consistent with Minimal Outliers using ICH-E14 Definitions

Predicted ΔQTc at Therapeutic and Supratherapeutic Concentrations



Observed Data

- Phase 3 study
  - 6 of 397 subjects had QTcF >60 msec. One of these subjects also had a QT >500 msec
- Long-term Safety study
  - 3 of 669 subjects had QTcF >60 msec. One of these subjects also had a QT >500 msec

Conclusion and Implications

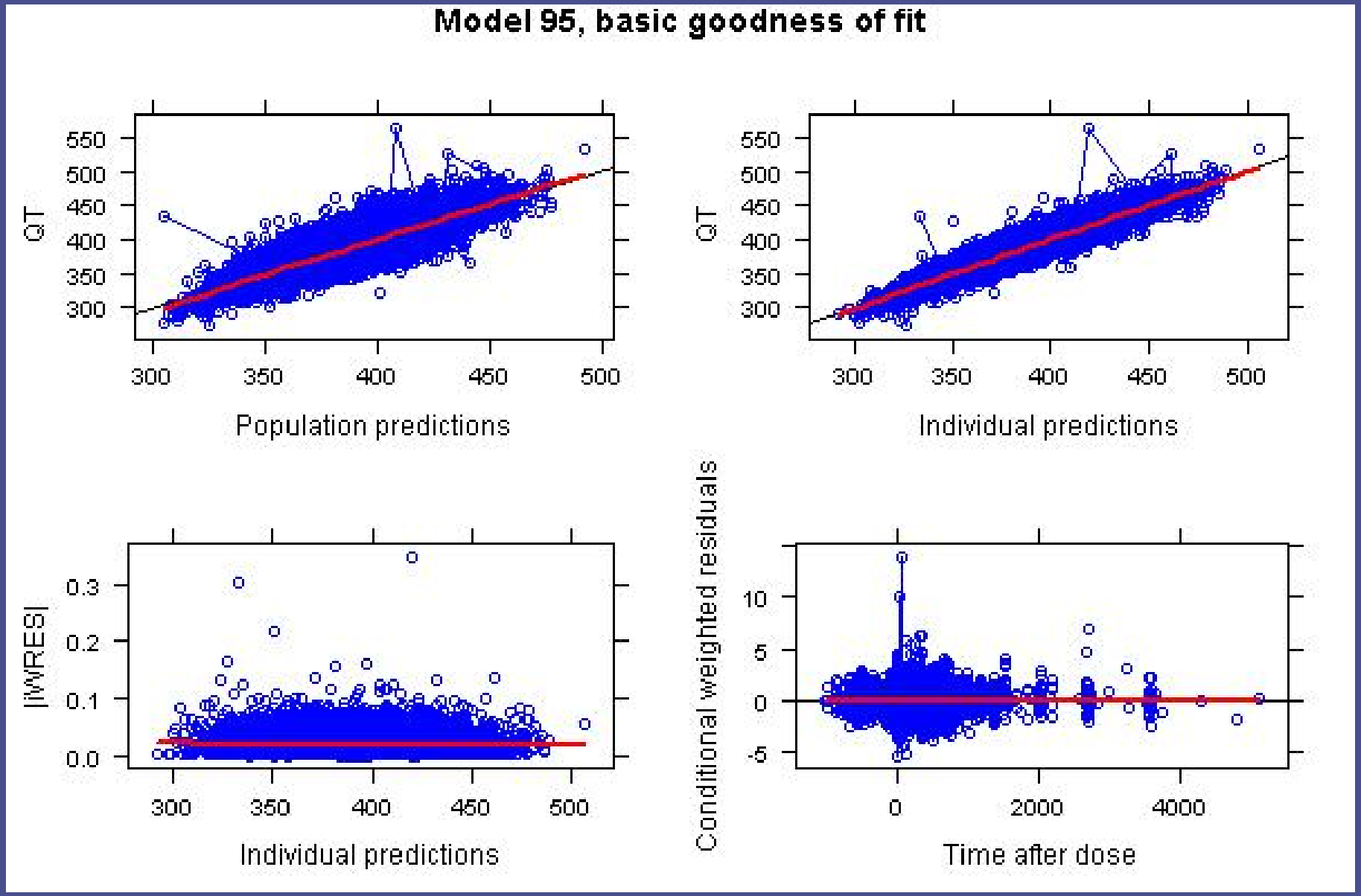
- Conclusion
  - An effect of buprenorphine on QT can be ruled out at therapeutic and supratherapeutic doses of RBP-6000, after accounting for the covariates that may influence HR and/or QT in subjects with OUD
- Implications
  - The collection of robust, high-quality ECG data (Holter and non-Holter, triplicate and single, central and non-central reading), with > **11,000** observations from **1114** subjects, allowed for a thorough evaluation of the relationship between concentration and QTc
  - The analysis plan outlined the modeling methods and assumptions, criteria for model selection, rationale for model components, and potential for pooling of data across studies prior to conducting the analysis to limit bias
  - Therefore, a thorough QT trial was avoided in the development of RBP-6000

Back-up slides

C-QT Analysis – Dataset

Study	12-Lead ECG	Holter	Time-matched QT-PK
FIM	✓		Screening, pre-dose, 3 hrs, 12 hrs, then Days 2, 3, 8, 14, 25-30, 32, 57, 85 and 120
SAD	✓		Screening, pre-dose, 3 hrs, 12 hrs, then Days 2, 3, 7, 14, 21, 35, 42, 63, 84, 112, and 150
MAD	✓		Screening, pre-dose, 12 hrs, then Days 3 (repeated for each cycle up to 4 doses)
MW	✓		Screening, pre-dose, 12 hrs, 24 hrs, 36 hrs, then Days 3, 4, 6, 14, 27, and 57
Ph 3 DB	✓	✓	Screening, pre-dose, 4 hrs, 24 hrs, then Days 8, 15, 22 and 29 (repeated for each cycle up to 6 doses)

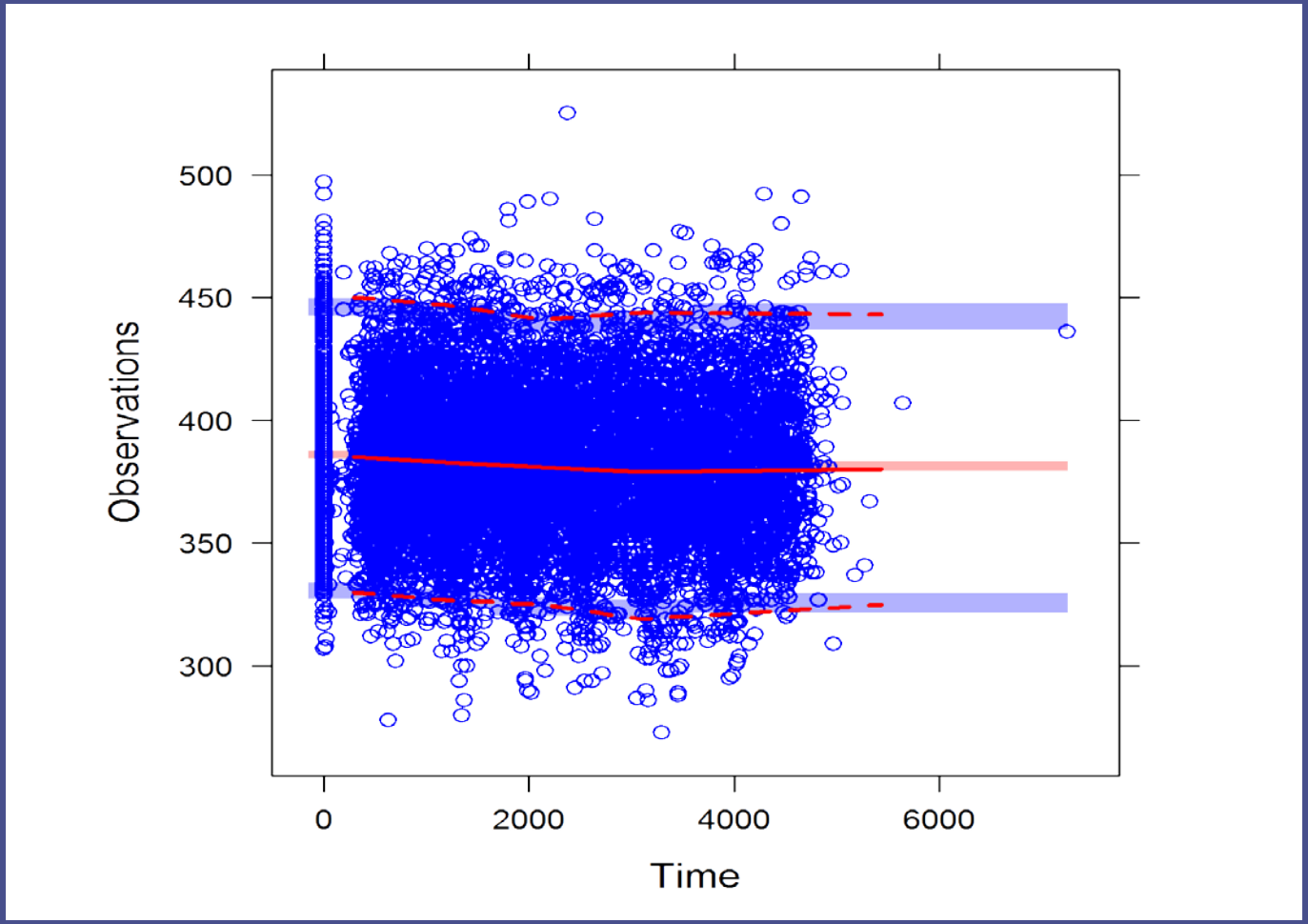
	NONMEM		Bootstrap			
	Estimate	%RSE[b]	Median	%RSE[b]	2.5th	97.5th
QTc_{Abs} (msec)	400	0.2	400	0.4	396	403
Alpha	0.333	fixed	0.333	fixed		
Sex on QTc_{Abs}[a]	0.0189	13.7	0.01911	13.8	0.0140	0.0241
COWS on alpha (slope)	0.00151	52.1	0.00151	51.5	-0.0000274	0.00307
Hydroxyzine on QTc_{Abs}[a]	0.00423	35.7	0.00422	36.3	0.00115	0.00715
Methadone on QTc_{Abs}[a]	0.0153	18.4	0.01522	17.4	0.0101	0.0210
Age on QTc_{Abs} (msec/yr)	0.324	7.0	0.32158	12.9	0.232	0.406
Holter vs computerized on QTc_{Abs}[a]	-0.00423	24.6	-0.00421	25.2	-0.00624	-0.00206
Central vs non-central reading on QTc_{Abs}[a]	-0.021	11.5	-0.02097	13.1	-0.0266	-0.0158
Concentration-related slope (msec/ng/mL)[a]	-0.0507	168.8	-0.04617	181.1	-0.225	0.110
Codeine on QTc_{Abs}[a`]	0.00327	35.2	0.00333	33.7	0.00102	0.00551
Oxycodone on QTc_{Abs}[a]	-0.00378	43.4	-0.00381	42.9	-0.00694	-0.000448
Phencyclidine on QTc_{Abs}[a]	0.00861	44.1	0.00902	42.3	0.000451	0.0159
Barbiturates on QTc_{Abs}[a]	0.0124	38.9	0.01223	40.4	0.00205	0.0219
Cocaine on QTc_{Abs}[a]	0.00428	28.0	0.00427	28.0	0.00193	0.00651
IIV on QTc_{Abs} (msec)	14.3	5.2	14.2	5.2	13.5	15
IIV on concentration-related slope (msec/ng/mL)	0.767	33.1	0.748	34.8	0.5	1
Residual Error (msec)	10.6	3.3	10.6	3.1	10.3	11


Model 95, basic goodness of fit
QT
Population predictions
QT
Individual predictions
|iWRES|
Individual predictions
Conditional weighted residuals
Time after dose

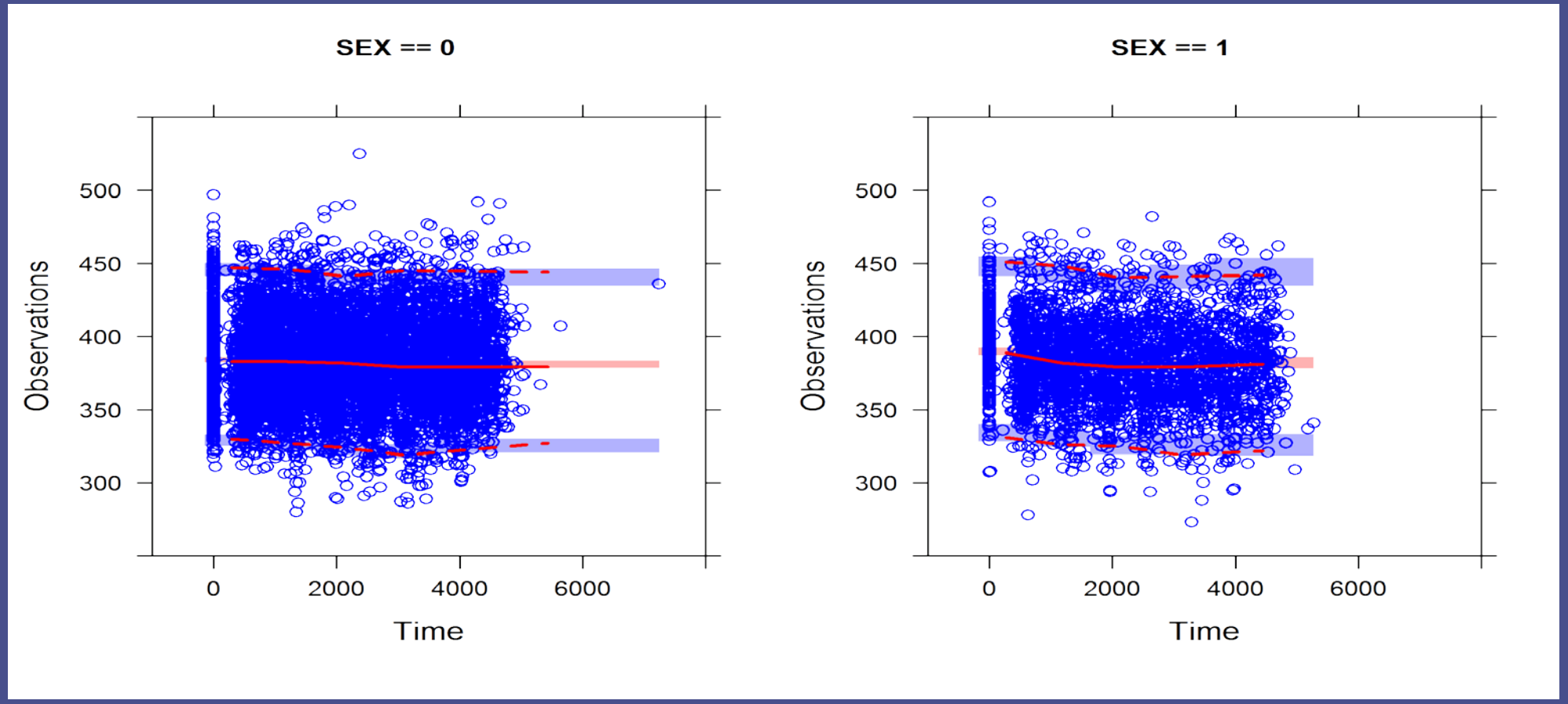
Sensitivity Analysis

- Three sensitivity analyses were conducted:
  - The use of a population alpha value equal to 0.333 (QTcF) vs an individual predicted value (QTcI).
  - The use of data across studies vs the Phase 3 (Study RB-US-13-0001) population alone.
  - The influence of the absence or presence of an age-related slope on QTc_{Abs}.
- Results showed:
  - Adding IIV to alpha (making it QTcI instead of QTcF) resulted in a slightly more negative slope for buprenorphine concentration (-0.0604 compared to -0.0507 for Model #95).
- Using the Phase 3 data only (Study RB-US-13-0001) resulted in a less negative slope (-0.0157 compared to -0.0507).
- Eliminating age from the model resulted in a highly statistically significant increase in the OFV ($P<0.0001$), did not substantially change the concentration-related slope (-0.0431 compared to -0.0507 for Model #95), and significantly increased the baseline QTcAbs in males to 411 msec (compared to 400 msec in Model #95).
  - These results were consistent with the exploratory plots showing that QTcF increases with increasing age where the age-related slopes were 0.357 msec/yr and 0.202 msec/yr for the reduced and full datasets, respectively, compared to the model-based slope of 0.324 msec/yr.

VPC: QTc Over Time Overall

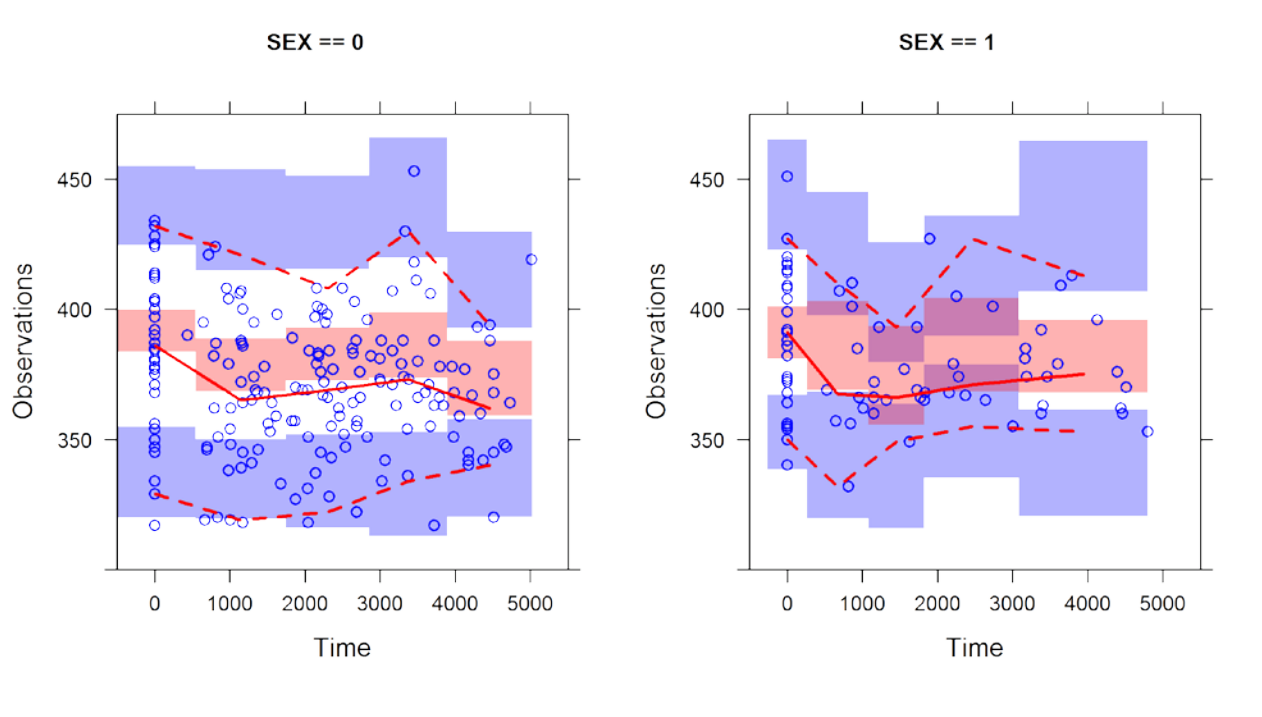


Visual Predictive Check: QTc Over Time by Sex (0=males; 1=females)



QTc Over Time with and without Methadone by Sex (0=males; 1=females)

With Methadone



Without Methadone