

Lack of Adherence to Treatment Drives Maraviroc Exposure-Response in the MERIT Study in Treatment-naïve HIV-1 Infected Subjects

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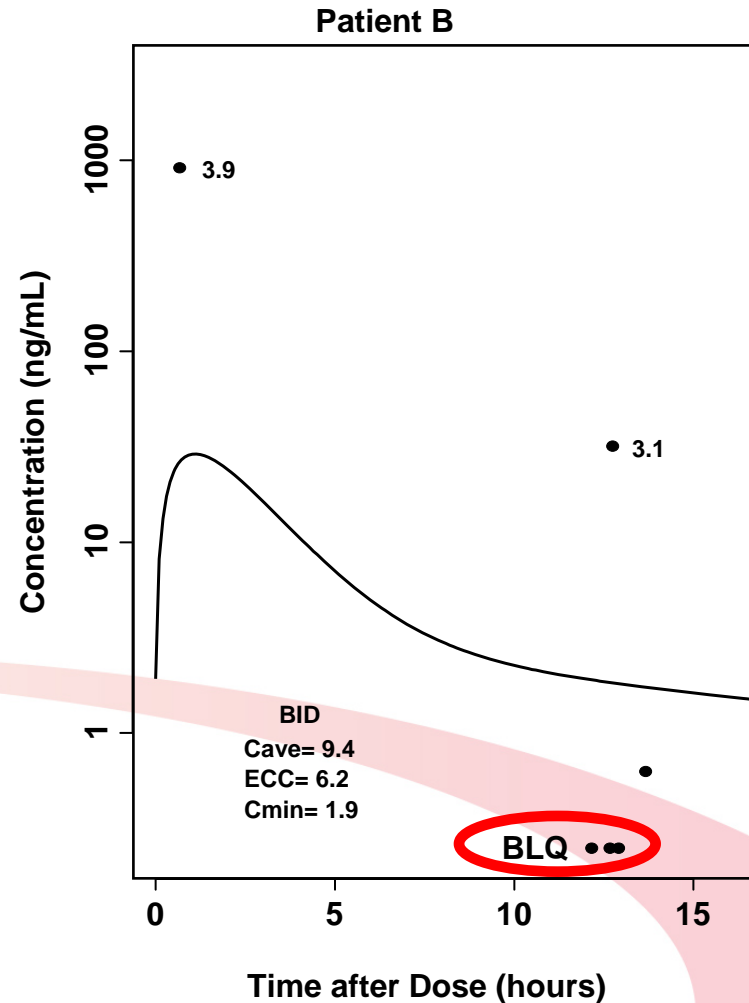
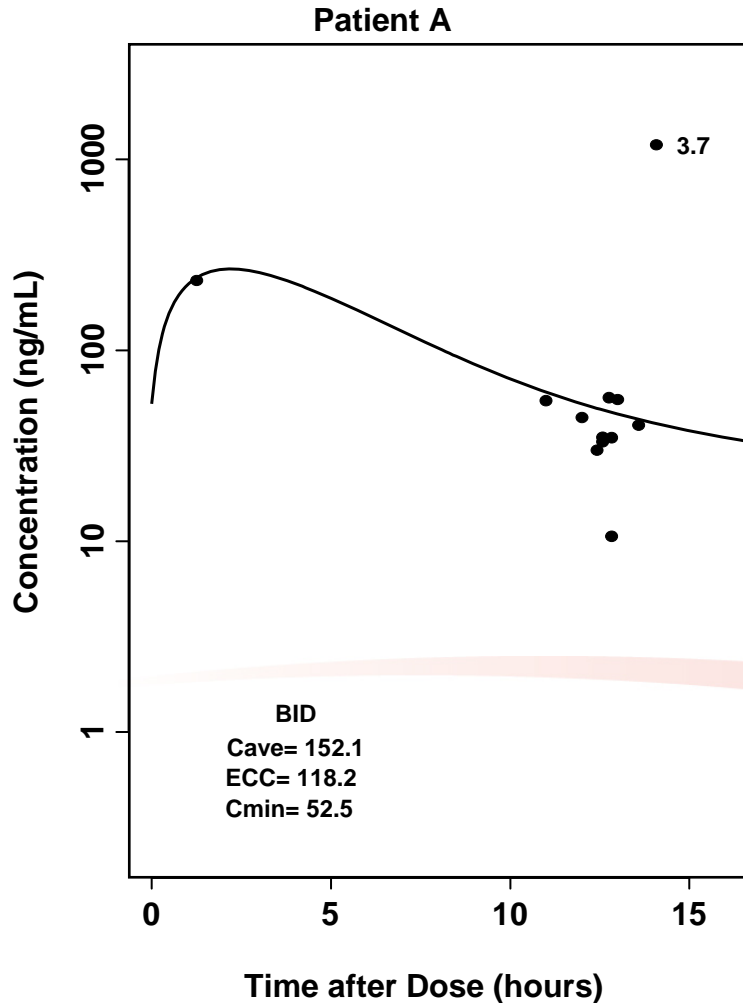
Background

- Exposure-response analyses of the maraviroc (MVC) 300mg BID (+ Combivir™) arm in the MERIT study have been previously reported¹.
- These analyses used:
 - **ITT population (original Trofile™ assay)** including those with PK and other covariates of interest (n=340)
 - **Endpoint:** Success = <50 copies/mL viral RNA (discontinuation=failure) at 48 weeks
 - **Methods:** Logistic regression with generalised additive modelling (GAM)
 - **Covariates:** MVC Cavg; other possible predictive baseline factors (baseline tropism, CD4, viral load, time since diagnosis, age, etc).
- Two major factors were identified (decrease in Akaike Information Criterion):
 - **Tropism switch** at baseline to dual/mixed (DM) from CCR5-tropic (R5) at screening and
 - **MVC exposure:**
 - Probability of failure greatly increased below MVC average concentration (Cavg) of approximately 75ng/mL (or Cmin of 25 ng/mL).
 - **Sigmoid-like non-linear relationship for Cavg**

¹McFadyen L et al. XVII IAC, Mexico, August 2008 (Poster TUPE0055)

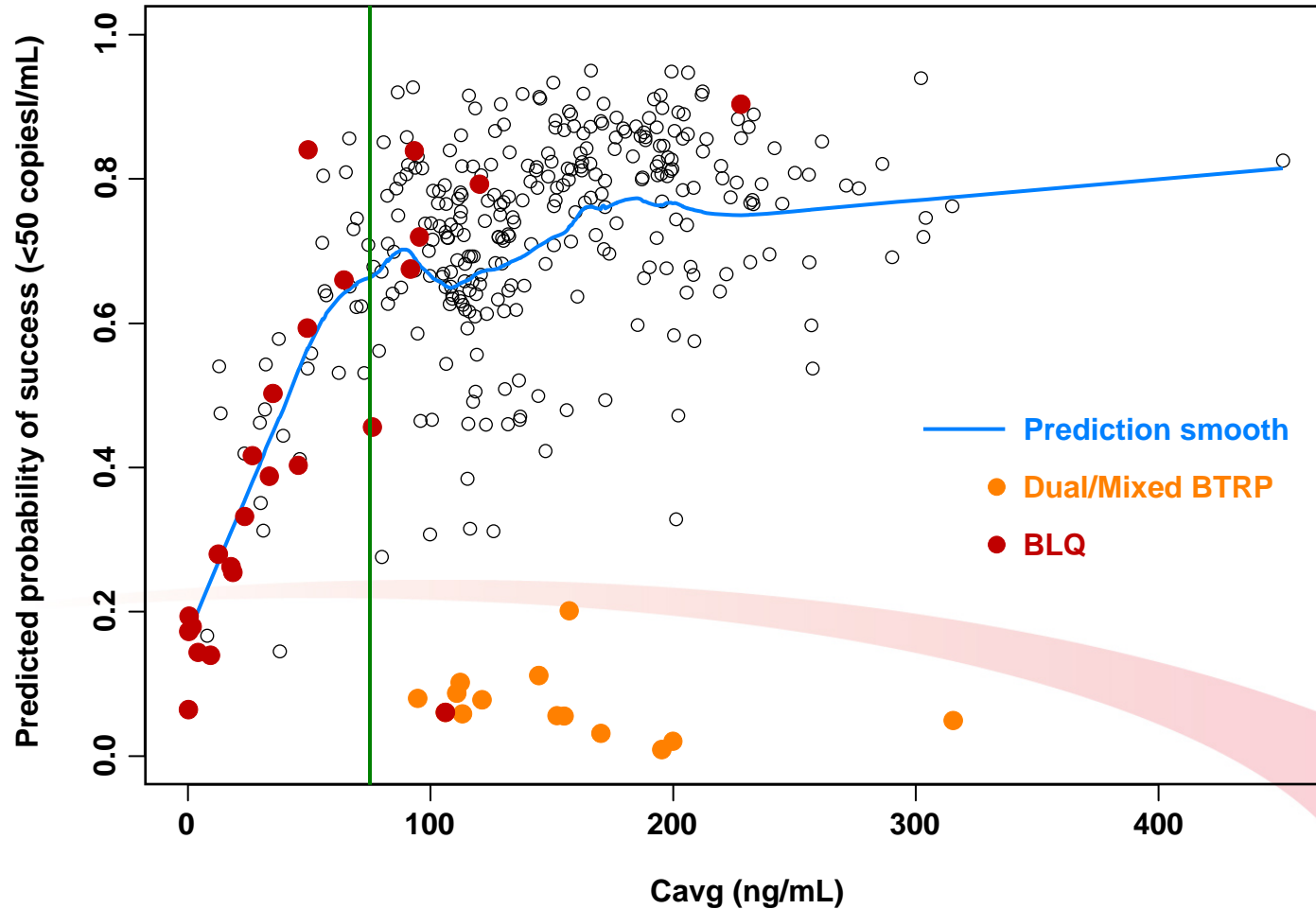
MVC Cavg or Cmin derivation²:

Population PK modelling of sparse PK (1 or 2 samples per visit over 48 weeks); patient-reported dosing; BLQ (below limit of quantification) set to 0.25ng/mL (1/2BLQ) for exposure response PK.



²Weatherley B et al. IWCPHIVT, New Orleans 2008 (Poster 17B)

Model predicted probability of success (< 50 copies/mL of viral RNA; discontinuation=failure)



ITT population, original Trofile™

Aims of the new analyses

1. Examine phase 1/2a PK data (carefully controlled dosing) to assess the likelihood of observing BLQ values.
2. Re-assess exposure-response in MERIT using:
 - ESTA* censored subset
 - a) MVC BLQ as a separate predictive factor from C_{avg} and
 - b) censoring subjects with BLQ
3. Assess virology at failure in relation to MVC exposure and BLQ values.

*ESTA Trofile™=Enhanced sensitivity Trofile (30-fold more sensitive) for re-screening of baseline samples to exclude low level X4 virus

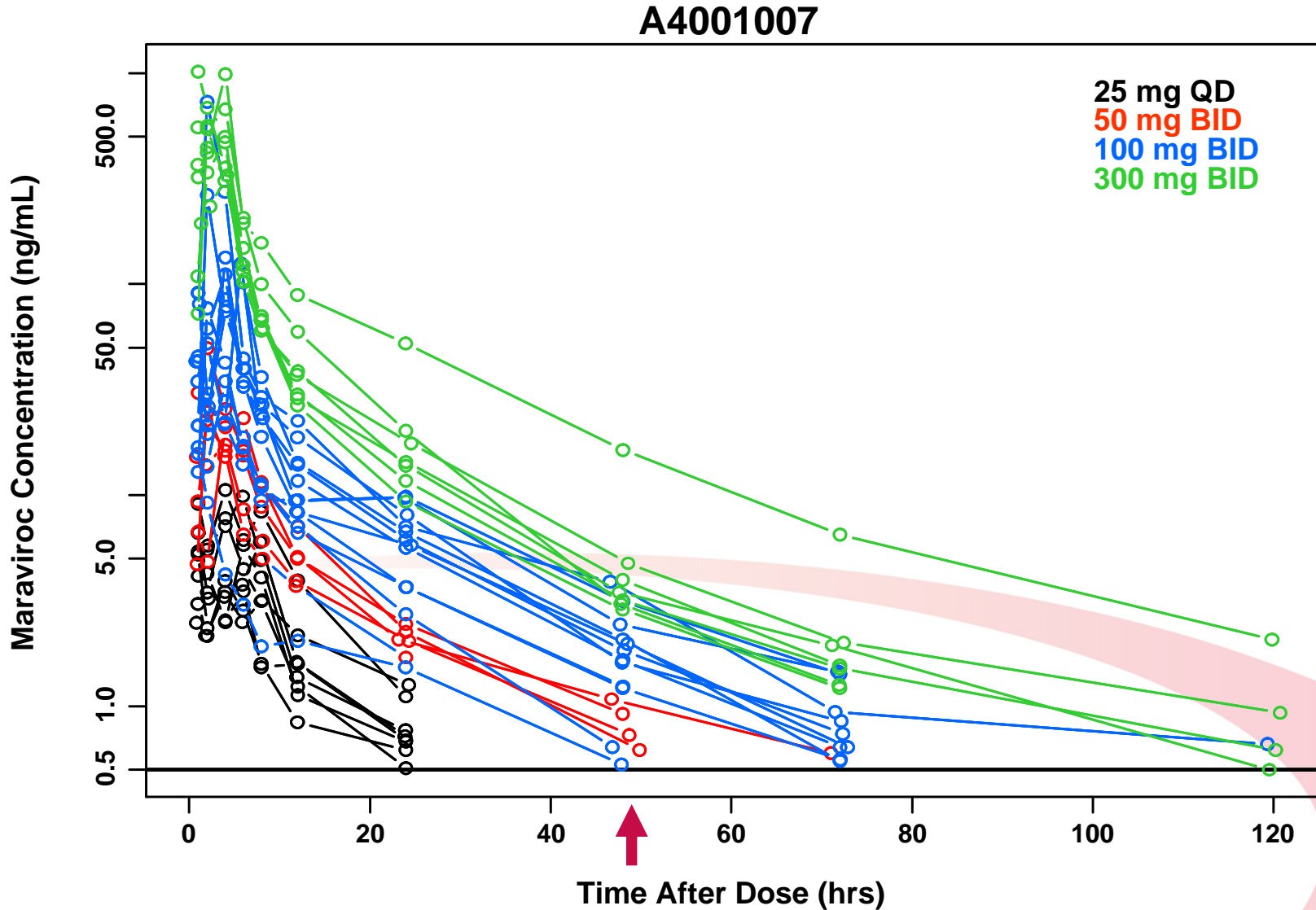
Methods

- Exposure-response analyses using logistic regression and GAM (SPLUS 7) were performed as before on (< 50 copies/mL at 48 weeks; D=F) :
 - ESTA-censored Dataset and
 - BLQ as a separate categorical covariate from Cavg or
 - Dataset censored for subjects with MVC BLQ values (n=273).
- Virology: Subjects defined as virologic failures (TLOVR <50 copies/mL at 48 weeks) were assessed for patterns or trends on cumulative Cavg plots according to virology resistance characteristics at failure.

Results

Study A4001007: Multiple Dose, Phase 2a in Patients

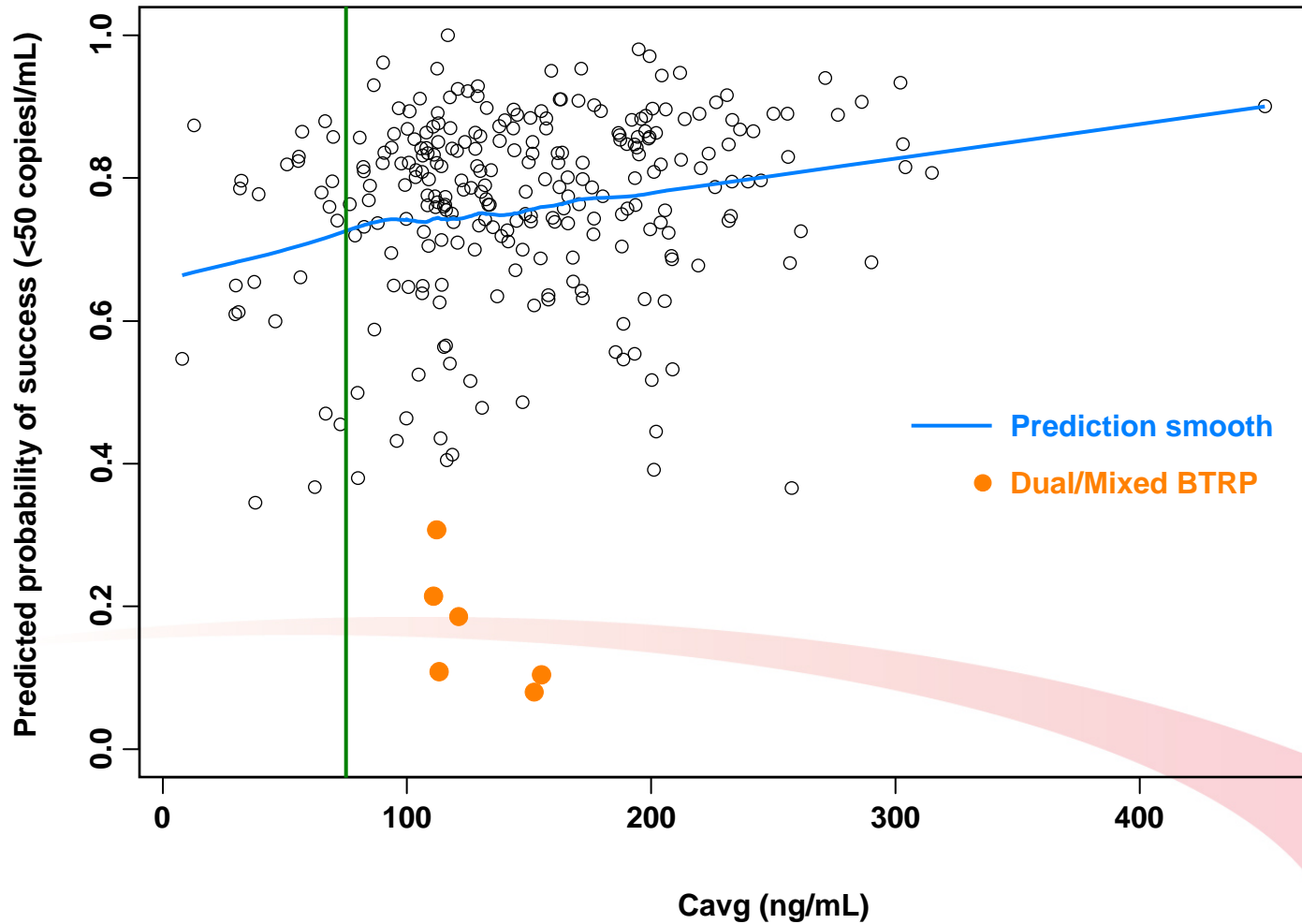
No BLQ values were observed within 48 hours after 300 mg BID doses



Results: GAM analysis (significance based on bootstrap CI)

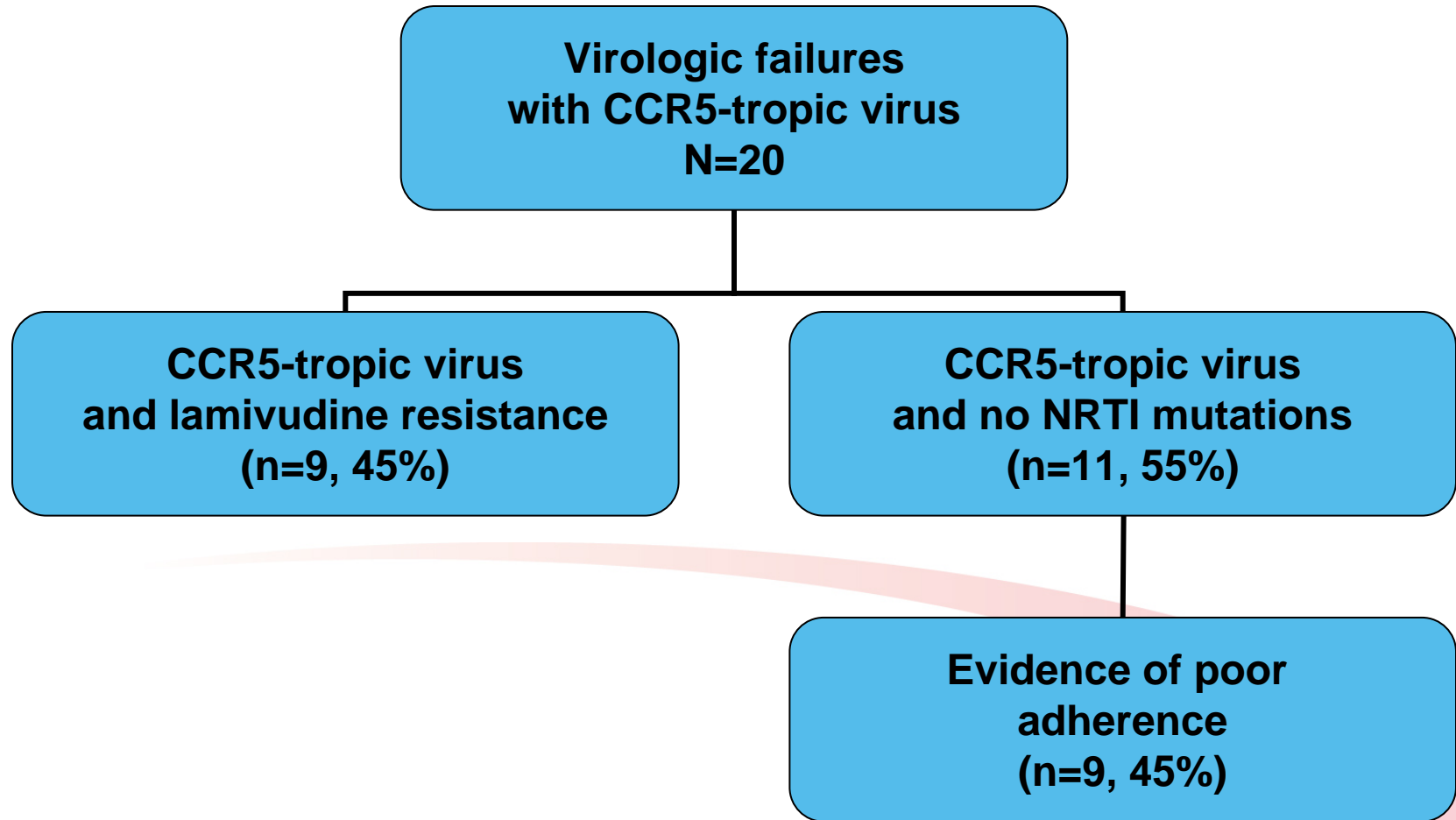
1. Original ITT analysis: Cavg (nonlinear sigmoid shaped relationship) and baseline tropism most significant factors
2. ESTA censored dataset with BLQ as a factor: BLQ and baseline tropism most significant with linear Cavg relationship borderline of significance
3. ESTA censored dataset + BLQ subjects censored: Cavg no longer significant leaving baseline tropism as most important predictor of failure.

Model predicted Exposure Response for Cavg

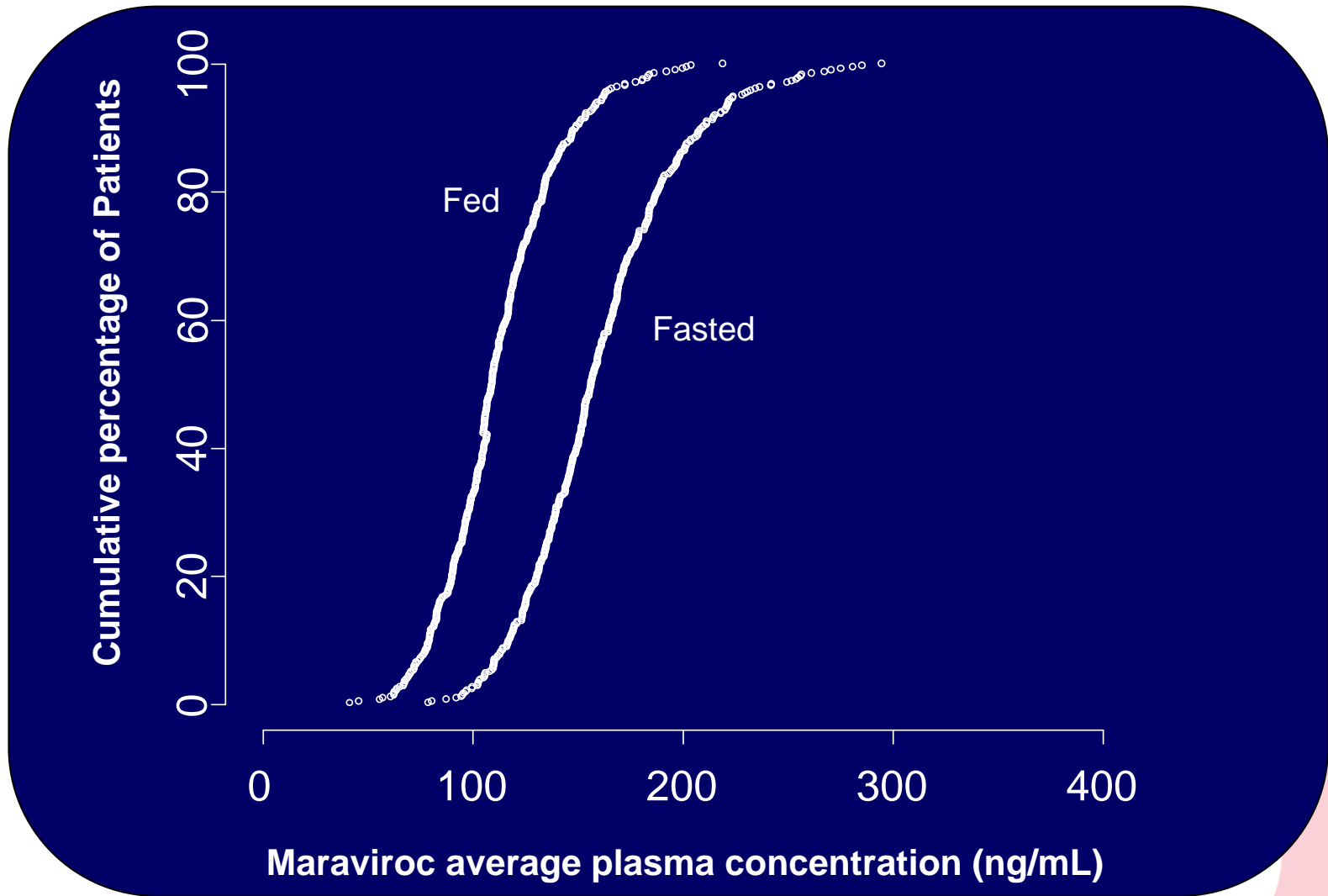


ITT ESTA , BLQ removed, n=273

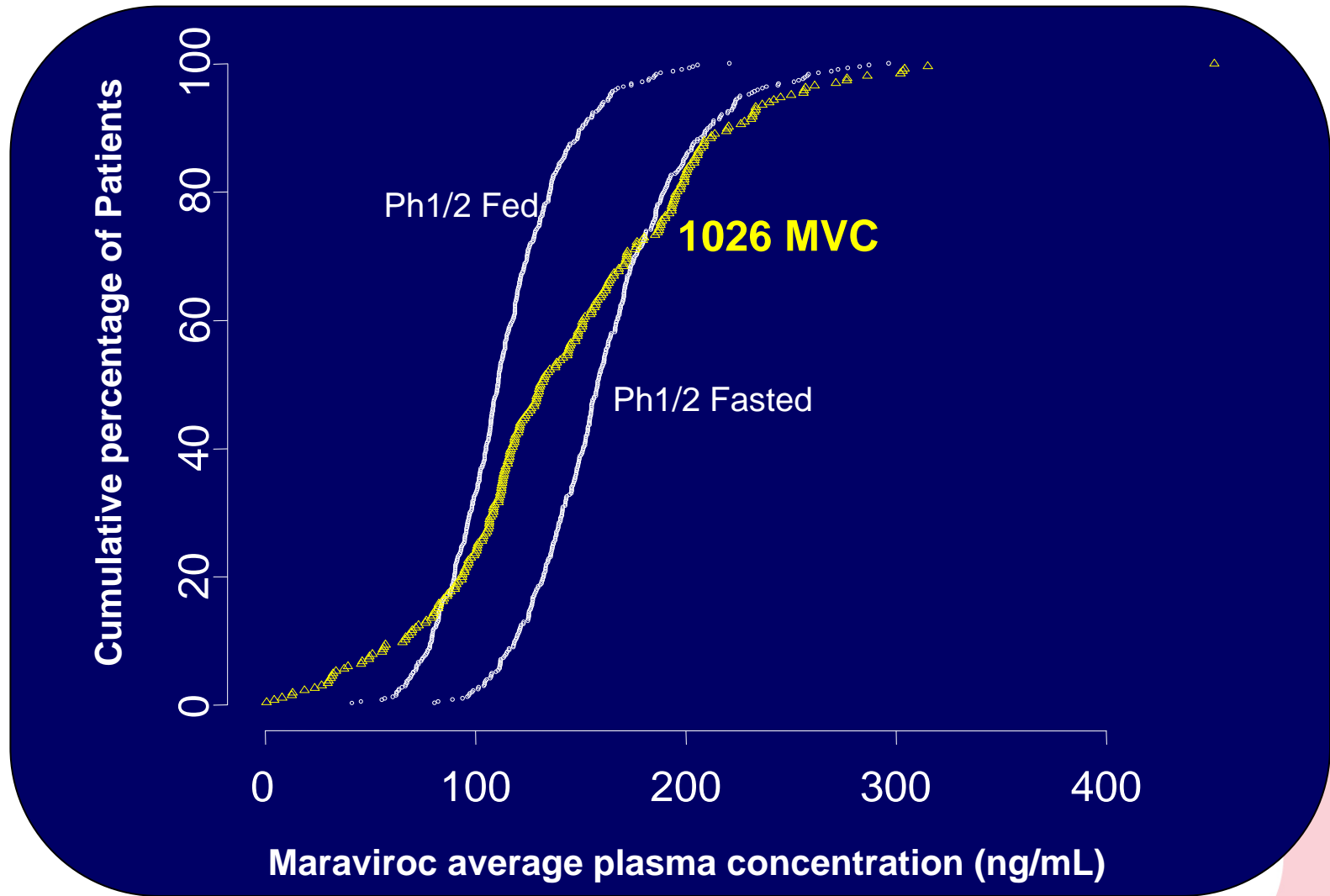
Virologic Outcomes in Maraviroc-treated Patients Failing with CCR5-tropic Virus (TLOVR <50 copies/mL, 48 weeks, with samples for virology at baseline and failure)



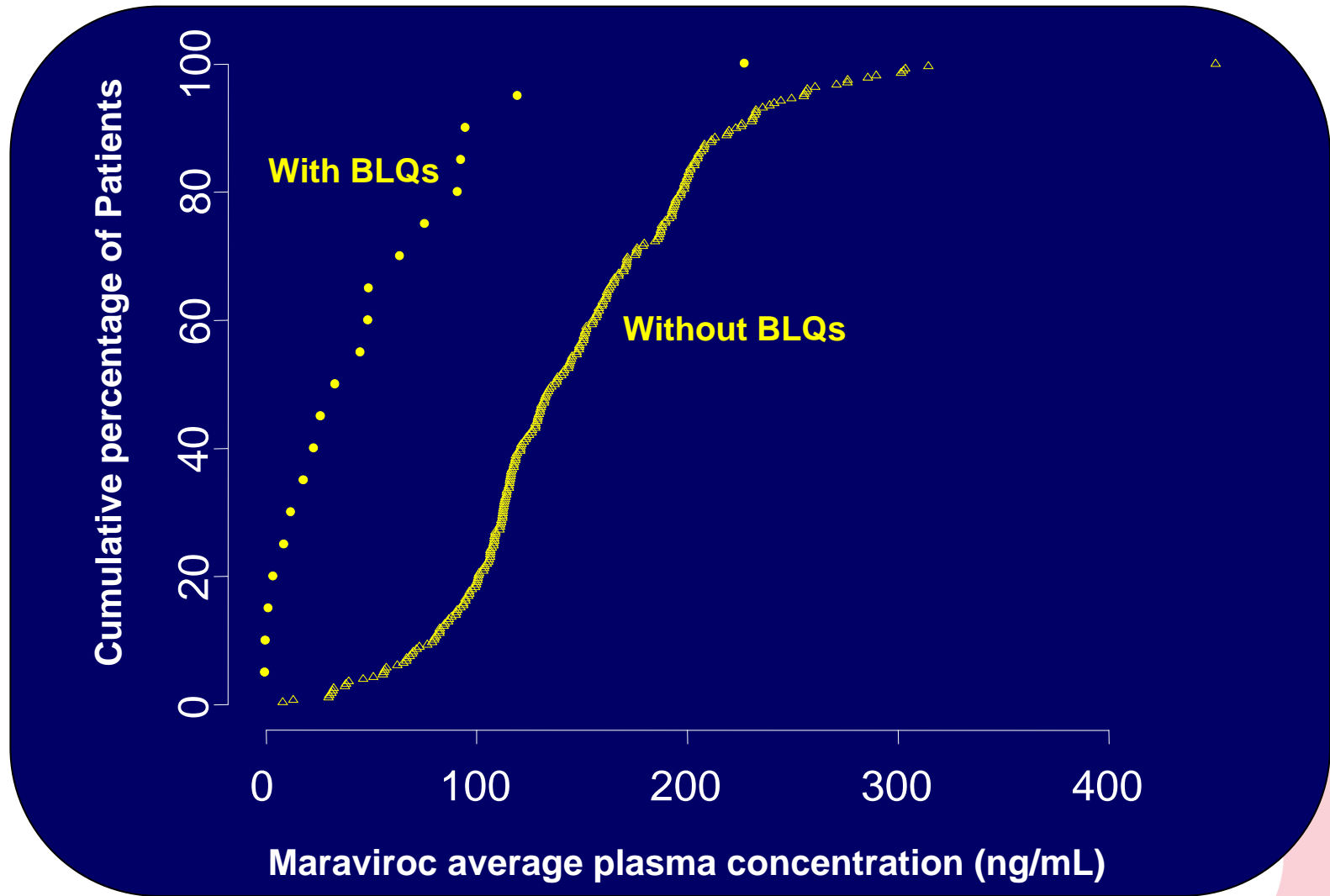
Cumulative Predicted Average Plasma Concentrations (C_{avg}) for 300 mg BID with Monitored Dosing (Ph1/2a)



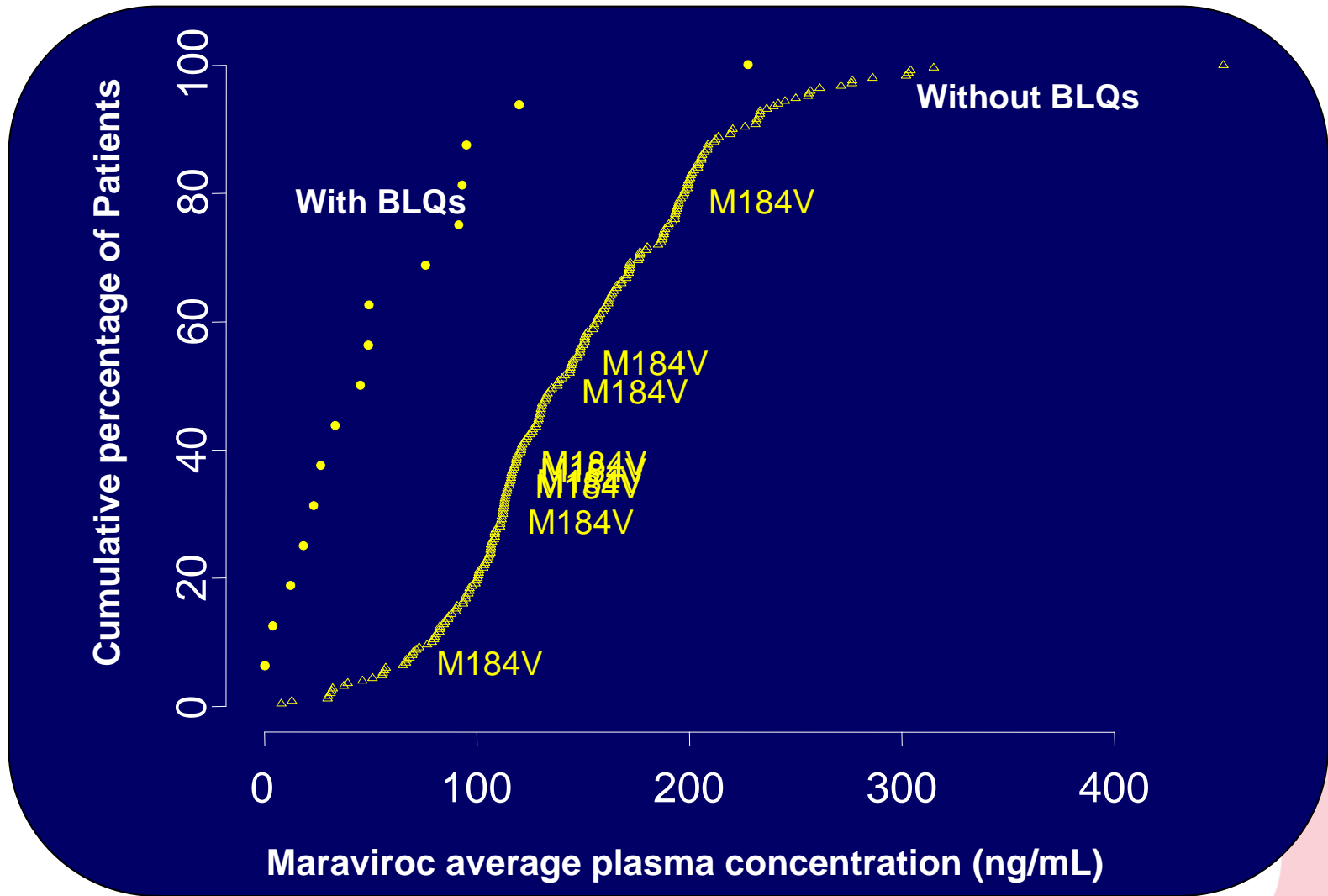
Cumulative Predicted Cavg for Maraviroc in Study 1026 (no food restrictions)



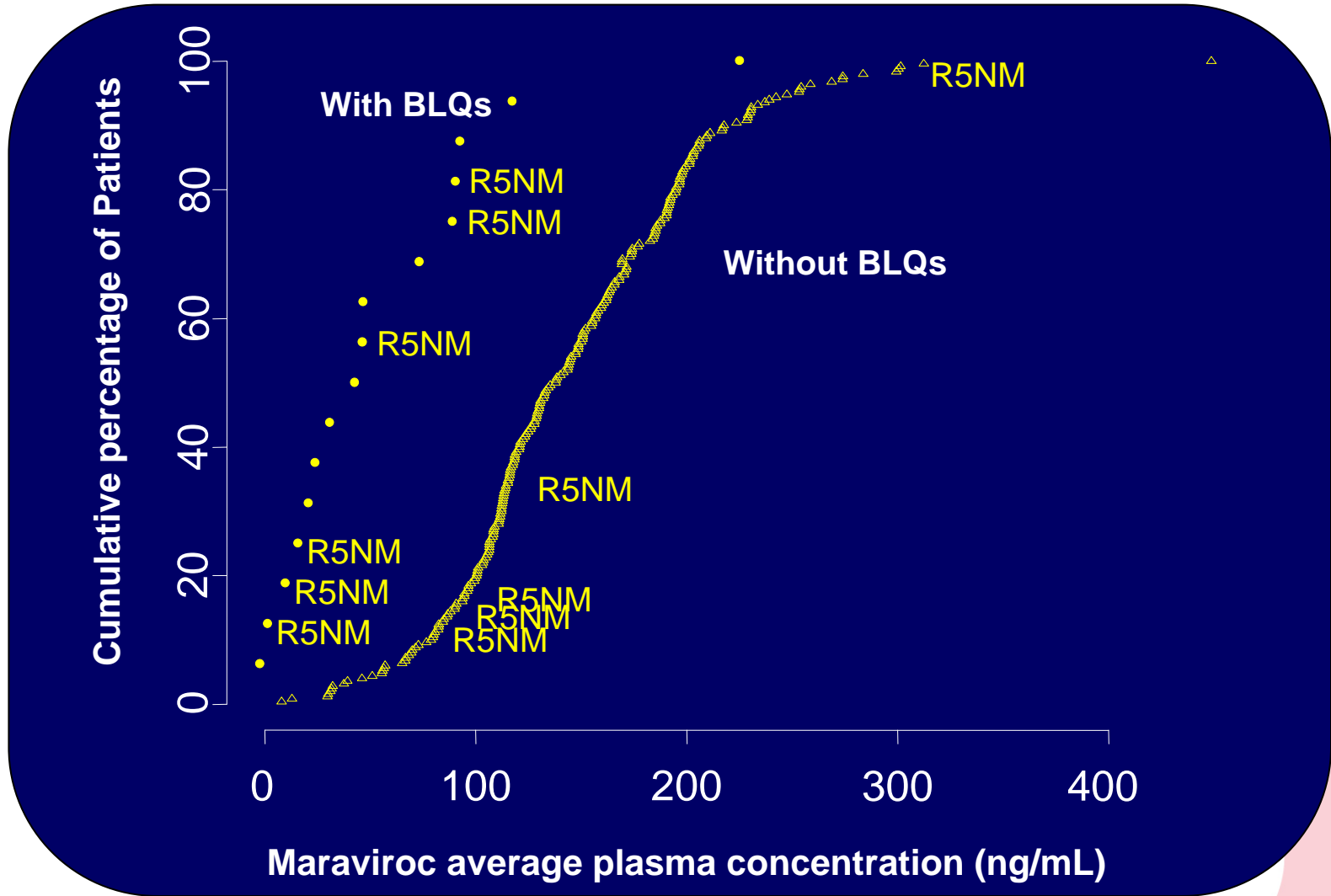
Patients with MVC BLQ values had lower MVC average concentrations



No virus from patients with a MVC BLQ value had Lamivudine Resistance (M184V) at Failure



Lack of Resistance at Failure (R5NM=CCR5 tropic with no mutations) is Largely Explained by Poor Adherence



Quartile analysis in USPI³ is NOT helpful for therapeutic drug monitoring unless used for adherence checking

	n	Median Cmin (ng/mL)	% patients with virologic success (<50 copies/mL)
Q1*	75	23	57.3
Q2	72	39	72.2
Q3	73	56	74.0
Q4	74	81	83.8

*18 of 20 subjects with BLQ values in Q1; Only 3 of 18 in Q1 achieved < 50 copies/mL at 48 weeks

³ Maraviroc (Selzentry) Label: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022128s002lbl.pdf

Conclusions

- BLQ concentrations are unlikely to be observed within 48 hours of 300 mg MVC doses; BLQ values suggest at least 3 missed 12 hourly doses prior to the clinic visit.
- Subjects with MVC BLQ values were mainly responsible for driving the previously reported exposure-response relationship for both quartile and GAM analyses for MVC in the MERIT study.
- Consistent with poor adherence, patients with BLQ values are likely to fail with MVC-sensitive virus (and no NRTI mutations).
- Adherence information is critical in understanding/interpreting exposure response data and warrants appropriate collection especially in HIV treatment.

Acknowledgements

- We acknowledge and thank all Patients, Investigators and the many other colleagues who worked on the Merit study.