

# Pharmacokinetics/Pharmacodynamics of Bevirimat (BVM) in a 14-day Functional Monotherapy Trial in HIV-infected Patients

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## Abstract

**Background:** BVM is a novel HIV-1 maturation inhibitor in Phase II development that targets the capsid SP-1 cleavage site of Gag. Recent analysis has shown that the antiviral activity of BVM is attenuated by the presence of baseline polymorphisms in the SP1 region of Gag; specifically at amino acid residues 369, 370, and 371. The purpose of this study was to characterize the PK/PD of BVM when administered as functional monotherapy.

**Methods:** A total of 72 HIV infected adults received 14 days of BVM QD at 400 mg (tablet), 250, 300, 350, or 400 mg (liquid doses). Plasma viral load and BVM concentrations were determined frequently over the dosing period.

**Results:** The mean log<sub>10</sub> viral load change from baseline on Day 15 for patients without changes at positions 369-371 was -1.13 and it was -0.38 for patients with changes at positions 369-371. The maximum antiviral effect of BVM was observed with an estimate for E<sub>max</sub> of -1.27 log<sub>10</sub>. The 50% effective trough concentration (EC<sub>50</sub>) was estimated to be 21.2 µg/mL. When individual patients were examined, 100% of responders (>0.5 log<sub>10</sub>) had trough concentrations >20 µg/mL while 60% of non-responders (<0.5 log<sub>10</sub>) had trough concentrations <20 µg/mL.

**Conclusions:** The maximum antiviral effect of BVM was observed at doses ≤400 mg/day. Patients without polymorphisms at Gag residues 369-371 that achieved trough concentrations >20 µg/mL were more likely to respond. This is consistent with the estimated EC<sub>50</sub>. These concentrations were achievable in all patients at doses >250 mg/day.

## Background

HIV infection continues to be a major health challenge; with many newly infected patients and patients developing antiretroviral resistance. New antiretrovirals with novel mechanisms of action are particularly important, as they are unlikely to develop cross-resistance to existing agents.

Except for agents classed as entry inhibitors (e.g., maraviroc and enfuvirtide), currently available antiretroviral drugs all target the HIV enzymes; integrase (integrase inhibitors, INSTIs), reverse transcriptase (reverse transcriptase inhibitors, RTIs) and protease (protease inhibitors, PIs). Both INSTIs and RTIs inhibit the early stages of HIV replication whereas PIs target later stage processes. The viral protease is responsible for cleaving the HIV Gag polyprotein precursor molecules prior to assembly into new virions. Maturation of the precursor proteins involves a regulated cleavage cascade which is governed by the processing rates at each cleavage site, the slowest being the one between CA and the spacer peptide, SP1 (also known as p2).

Bevirimat (BVM) belongs to a new class of anti-HIV agents, known as maturation inhibitors. BVM targets the late stages of viral replication and shows potent activity against wild-type HIV-1 as well as antiretroviral resistant strains of virus. BVM blocks the conversion of the HIV-1 capsid precursor CA-SP1 (p25) to the mature capsid protein (p24). This results in the release of non-infectious viral particles and the termination of viral replication with immature viral particles rapidly cleared from the plasma by the immune system. Unlike PIs, BVM binds to the substrate of the HIV protease, rather than the protease itself, only affecting processing at the CA-SP1 junction. This unique specificity results in activity against PI-resistant HIV-1, while BVM-resistant HIV-1 shows no cross-resistance with PIs.

BVM is currently undergoing Phase II clinical development; studies conducted to date in healthy volunteers and HIV-positive patients have shown BVM to be well tolerated with good oral bioavailability and favorable pharmacokinetics. A Phase II, proof-of-concept study in HIV-positive patients showed a median viral load reduction of ~1.0 log<sub>10</sub> at 200 mg QD, the highest dose tested. Since the plateau of the dose-response curve was not identified in that study, the current study was undertaken to further explore the dose response curve and to identify the plasma BVM concentrations associated with response.

## Methods

### Study Design:

This was a Phase II, randomized, placebo-controlled, double-blind, multiple-dose, dose-escalation study in HIV treatment experienced patients on a failing antiretroviral regimen. The study was conducted in three parts. The first part (Part A) utilized a tablet formulation at a BVM dose of 400 mg QD for 14 days (Days 1 to 14), but due to lower than expected plasma concentrations only this one tablet dose was evaluated. The second part (Part B) was conducted with an oral solution and evaluated BVM doses of 250, 300, 350, and 400 mg QD for 14 days. The third part (Part C) evaluated a single BVM dose (300 mg QD for 14 days) but stratified patients based on treatment history: treatment-naïve, treatment-experienced patients without genotypic evidence of Gag polymorphisms at either positions 369, 370 or 371, and treatment-experienced patients with genotypic evidence of Gag polymorphisms at positions 369, 370 or 371. In all study parts, pre-dose blood samples for HIV RNA and BVM concentrations were obtained daily from Days 1-15.

### Study Population:

Eligible patients included adult patients with documented HIV-1 infection, plasma HIV-1 RNA levels between 2,000 and 250,000 log<sub>10</sub> copies/mL, on a stable highly active antiretroviral therapy (HAART) containing at least three drugs for at least 8 weeks prior to initial screening and harboring at least one major resistance mutation from the IAS-USA list of drug resistance mutations (Johnson V, et al, Top HIV Med 2007;15(4): 119-125). Naïve patients enrolled in Part C met the same entrance criteria as other patients except they had no history of receiving HAART. Ineligible patients included those with active AIDS defining illnesses, laboratory parameters outside pre-specified limits and those taking concurrent prescription or investigational medications restricted by the protocol.

### Sample Analysis:

BVM concentrations in plasma were quantified by a validated LC/MS/MS method. HIV RNA in plasma was measured by the Roche Amplicor HIV-1 RNA Assay with a dynamic range of 400 to 750,000 copies/mL. Samples with HIV RNA below 400 copies/mL were also analyzed by the Roche Amplicor Ultrasensitive HIV-1 RNA Assay with a dynamic range of 50 to 100,000 copies/mL. All samples obtained after screening were analyzed for HIV RNA in duplicate, with geometric mean of the duplicates used for all statistical analysis. Baseline HIV RNA was determined by geometric mean of the average HIV RNA levels from Day 0 (the day before dosing) and Day 1 (prior to dosing).

### Pharmacokinetic/Pharmacodynamic Analysis:

PK-PD analysis was performed to identify plasma BMV concentrations that correlate with response. Response was determined by HIV RNA reduction from baseline and the PK parameter was the average plasma trough (C<sub>min</sub>) BMV concentration at Day 14 and 15.

PK-PD data from all patients in all three parts were first analyzed, followed by subgroup analyses. Scatter plots were evaluated to identify factors important for subgroup analysis, such as with or without polymorphisms in the SP1 region of Gag, and a potential threshold BVM concentration (i.e., 18 µg/mL) as shown in Figure 1.

Various pharmacological models were explored, including linear, simple E<sub>max</sub> and sigmoidal E<sub>max</sub> models along with different statistical functions. The sigmoidal E<sub>max</sub> model was found to best describe the PK-PD relationship for data obtained from patients without polymorphisms in the SP1 region of Gag. The sigmoidal E<sub>max</sub> model is defined as follows:

$$\text{Response} = \text{PD Effect (E)} = \text{Antiviral Activity} = (\text{Emax} * \text{Cmin}^\gamma) / (\text{EC50}^\gamma + \text{Cmin}^\gamma)$$

- Antiviral activity is determined by the HIV-RNA reduction from baseline at Day 15
- C<sub>min</sub> is steady-state plasma trough (pre-dose) BVM concentration, mean value of Days 14 and 15
- E<sub>max</sub> is the maximal or plateau anti-HIV activity or viral load reduction from baseline
- EC<sub>50</sub> is the C<sub>min</sub> required to produce 50% of the maximal anti-HIV activity
- $\gamma$  is the Hill factor, representing the slope of the Effect vs. log(C<sub>min</sub>) curve

## Results

A total of 72 patients had available plasma HIV RNA and BVM C<sub>min</sub> data for PK-PD analysis. Valid data of baseline polymorphism status in the SP1 region of Gag were available from 69 patients.

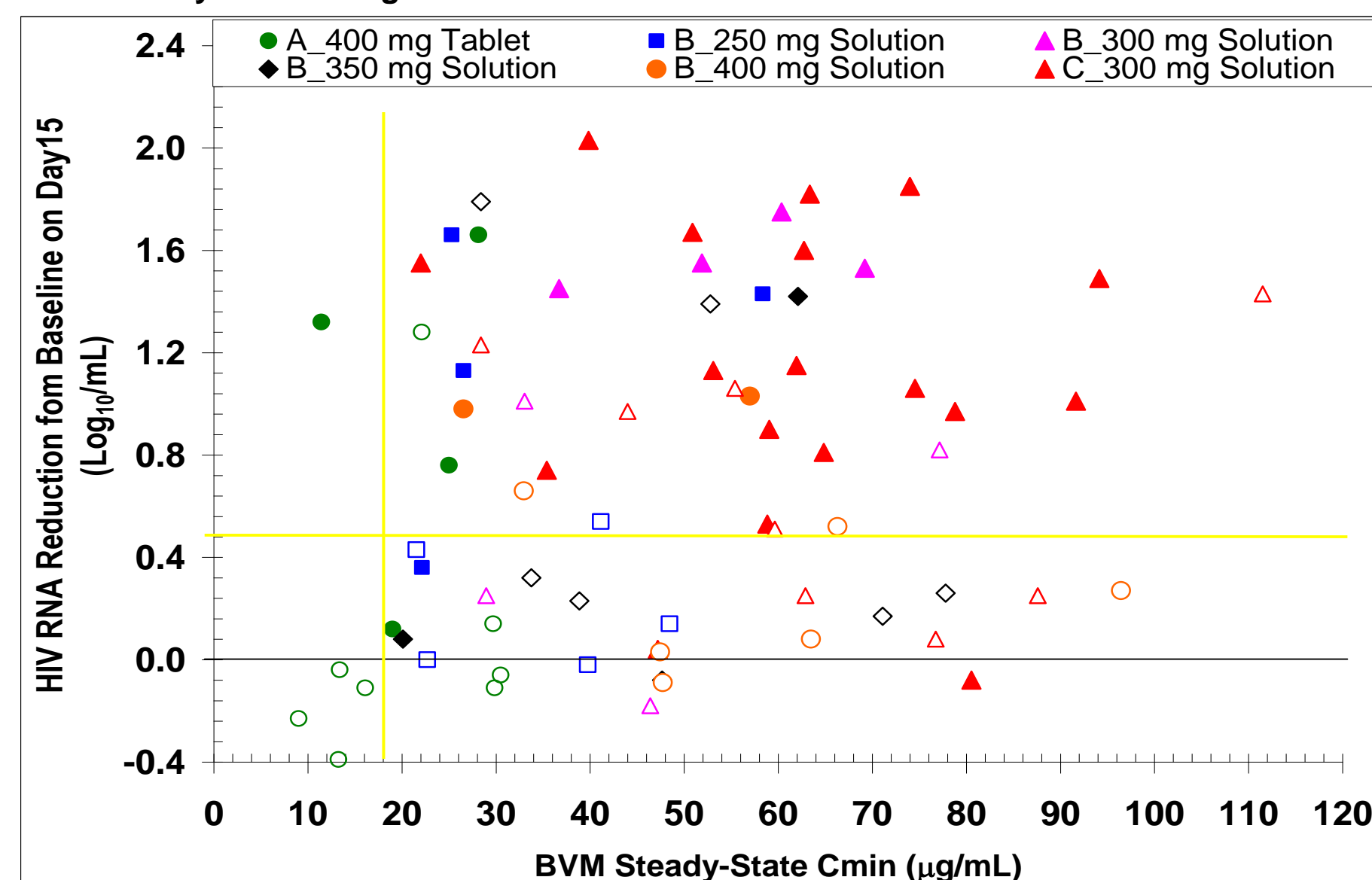
Table 1. Demographics and Key Response Variables for All Patients

	Part A		Part B (Oral Solution)				Part C (Solution, 300 mg QD)		
	Tablet 400 mg QD	250 mg QD	300 mg QD	350 mg QD	400 mg QD	Naïve	Pts w/o Poly-morphisms	Pts w/ Poly-morphisms	
N	12	9	8	9	8	9	10	7	
Age (years)	46.5 (40-52)	47.0 (39-55)	47.6 (36-60)	50.6 (39-70)	49.6 (27-65)	40.3 (25-54)	43.2 (28-54)	44.6 (31-60)	
Gender (M, F)	12M	9M	7M, 1F	9M	8M	9M	8M, 2F	6M, 1F	
Baseline CD4 (cells/mm <sup>3</sup> )	491 (307-864)	237 (120-491)	353 (185-514)	245 (30-393)	270 (53-537)	366 (135-708)	372 (156-930)	349 (150-588)	
Baseline Viral Load (log <sub>10</sub> copies/mL)	3.97 (3.35-4.61)	4.45 (3.65-5.17)	4.15 (3.24-5.17)	4.12 (2.93-5.16)	4.18 (2.67-5.33)	4.53 (4.09-5.11)	4.39 (3.31-5.10)	3.91 (3.09-5.18)	
Day 15 Viral Load Reduction from BL (log <sub>10</sub> copies/mL)	-0.36 (-1.66, 0.39)	-0.63 (-1.66, 0.02)	-1.02 (-1.75, 0.18)	-0.62 (-1.79, 0.08)	-0.44 (-1.03, 0.09)	-1.04 (-1.85, -0.04)	-1.10 (-2.03, 0.08)	-0.81 (-1.43, -0.25)	
BVM Steady-State C <sub>min</sub> (µg/mL)	20.6 (9.00-30.5)	34.0 (21.6-58.4)	50.5 (29.0-77.2)	48.1 (20.1-77.8)	54.7 (26.6-96.5)	67.1 (47.2-94.2)	58.6 (22.0-91.7)	64.2 (38.4-112)	
# W/O Polymorphisms	4	4	4	2	2	8	10	1	

Table 2. Demographics and Key Response Variables by Polymorphism Status in the SP1 Region of Gag

	Pts w/o Polymorphisms	Pts w/ Polymorphisms at a.a. 369, 370 and 371
N	34	35
Age (years)	45.5 (25-70)	46.6 (27-65)
Gender (M, F)	32M, 2F	33M, 2F
Baseline Viral Load (log <sub>10</sub> copies/mL)	4.23 (2.67-5.17)	4.17 (2.93-5.33)
Day 15 Viral Load Reduction from BL (log <sub>10</sub> copies/mL)	-1.13 (-2.03, 0.08)	-0.38 (-1.79, 0.39)
BVM Steady-State C <sub>min</sub> (µg/mL)	50.4 (11.4-94.2)	47.1 (9.03-112)

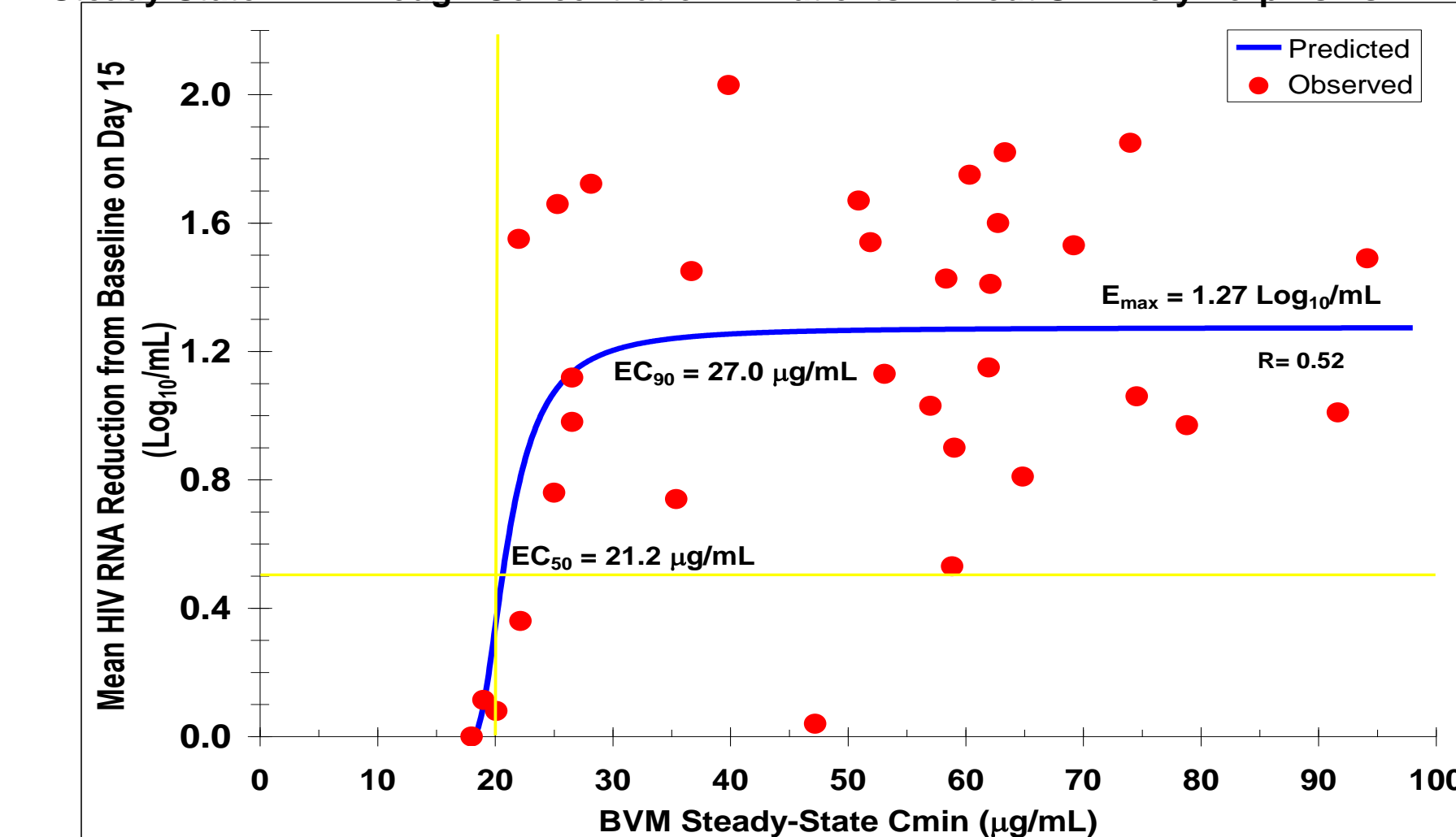
Figure 1. Scatter Plots of Individual Patient Data of HIV RNA Reduction from Baseline vs. BVM Steady-State Trough Concentration



Solid symbols are patients without SP1 polymorphisms, open symbols are patients with or unknown polymorphisms.

## Results

Figure 2. Plots of Sigmoidal E<sub>max</sub> Modeling of HIV RNA Reduction from Baseline vs. Steady-State BVM Trough Concentration in Patients without SP1 Polymorphisms



Excluding 1 patient in Part C who had an increased viral load, and 1 patient in Part A who did not achieve C<sub>min</sub> of 18 µg/mL.

## Summary

- Almost all of the responders (i.e., Day 15 viral load reduction from baseline greater than 0.5 Log<sub>10</sub> copies/mL) did not have polymorphisms in the SP1 region of Gag and all responders had steady-state BVM C<sub>min</sub> >20 µg/mL (Figure 1).

- The mean Day 15 viral load reduction from baseline was 1.13 and 0.38 Log<sub>10</sub> in patients without and with polymorphisms in the SP1 region of Gag, respectively, regardless of dose level (Table 2).

- PK-PD correlation between BVM steady-state C<sub>min</sub> and viral load reduction response was significantly improved by considering a threshold steady-state C<sub>min</sub> of 18 µg/mL to be achieved.

- The PK-PD modeling indicates that the maximal anti-HIV effect of BVM was observed over the dose range evaluated, with an estimate for E<sub>max</sub> of 1.27 Log<sub>10</sub>. The 50% effective BVM trough concentration (EC<sub>50</sub>) was estimated to be 21.2 µg/mL (Figure 2).

- The EC<sub>50</sub> of 21.2 µg/mL was achieved in 41 out of 42 responders and in all except one patient receiving the solution doses of BVM (Figure 1).

## Conclusion

This PK-PD Analysis shows that:

- Naïve or experienced HIV-infected patients without polymorphisms in the SP1 region of Gag, specifically amino acid residue 369-371, are more likely to respond to BVM treatment.

- Anti-HIV response to BVM treatment was observed when plasma BVM steady-state trough concentrations were greater than 20 µg/mL, which was achievable with once daily solution doses of 250 – 400 mg BVM.

- Functional monotherapy of BVM 250 – 400 mg QD produced maximal antiviral response of 1.27 Log<sub>10</sub> reduction in HIV viral load on Day 15 in naïve and experience patients without polymorphisms in Gag.