Safety, Pharmacokinetics and Outcomes of PAR-101 in Healthy Subjects and Patients with *Clostridium difficile*-Associated Diarrhea (CDAD)

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Abstract

BACKGROUND PAR-101 is in clinical development for the treatment of *Clostridium difficile*-associated diarrhea (CDAD).

METHODS Phase 1B and 2A clinical trials assessed the safety, pharmacokinetics, and efficacy of PAR-101 after 10 days of daily administration. The studies evaluated tolerability/safety based on clinical and laboratory outcomes. Serial blood, urine (1B only), and fecal samples were collected for pharmacokinetic analysis. The Phase 1B double-blinded, placebo-controlled trial enrolled 24 healthy volunteers at 150, 300, and 450 mg/day po. The Phase 2A was an open-label, dose ranging, clinical evaluation in 45 evaluable subjects with mild-moderate CDAD. The doses evaluated were 50, 100, and 200 mg q12h po. Clinical evaluation included relief of symptoms, time to resolution of diarrhea, and recurrence.

RESULTS In both trials, PAR-101 was well tolerated by all subjects, and plasma concentrations were typically ≤ 5 ng/mL (0.005 µg/mL) across the dose range, while fecal concentrations exceeded 10,000 times the MIC_{90} at the top dose. Phase 1B urine levels were below 5 ng/mL (0.005 µg/mL). In the Phase 2A, clinical response was very promising; two subjects in each of the two lower dosing groups were judged to be treatment failure (41/45 cured overall); no failures were seen in the high dose group (0/16 failures at 200 mg q12h). Of 41 subjects completing therapy, 2 (5%) had recurrence of symptoms within the 6 week follow-up.

CONCLUSIONS The clinical response, tolerability, and systemic exposure data obtained support the further clinical development of PAR-101 as an oral therapy for *C. difficile* infection.

Introduction

Clostridium difficile-associated diarrhea (CDAD) is a significant problem in hospitals, long-term care facilities, and in the community. *Clostridium difficile* is the most common cause of nosocomial diarrhea in developed countries. (3, 5, 6) The organism accounts for approximately 20% of cases of antibiotic-associated diarrhea and the majority of cases of antibiotic-associated colitis. (1, 2, 4, 10) The rising incidence of CDAD has been attributed to the frequent prescription of broad-spectrum antibiotics to hospitalized subjects. (9)

The two most commonly utilized specific therapies are vancomycin and metronidazole, though vancomycin is the only drug approved by the FDA for this indication. Although both agents are effective in treating the infection, increasing rates of treatment failures and recurrence of diarrhea in approximately 20% of subjects that initially respond are deficiencies of standard therapies. (7, 8)

PAR-101 (formerly OPT-80) is a fermentation product primarily composed of an 18-membered macrocycle. It has a narrow spectrum of activity, with strong activity against *Clostridium difficile*. A typical MIC_{90} versus this organism is 0.125 µg/mL, as compared to 0.5 and 2 µg/mL for metronidazole and vancomycin, respectively. PAR-101 is bactericidal with a low propensity to generate resistance, has no cross-resistance to existing antimicrobials, and has a prolonged post-antibiotic effect.

PAR-101 has a promising preclinical safety profile. It is minimally absorbed, and showed no adverse effects in rats at single oral doses up to 1000 mg/kg, or in rats or monkeys at repeated doses of up to 90 mg/kg/day for 28 days.

The previous Phase 1A trial, a single-dose dose-escalating study, showed that PAR-101 is well tolerated after single oral doses up to 450 mg. No medication-related adverse events were reported. Plasma concentrations of PAR-101 were generally below the limit of quantitation (5 ng/mL) following oral administration, while high fecal concentrations were observed. In this report, we present the safety, pharmacokinetics, and outcomes of PAR-101 in healthy subjects and CDAD patients following 10 days of study drug administration.

Methods

PHASE 1B-MD

SYNOPSIS

This was an oral, multiple-dose, double-blind, randomized, placebo-controlled, dose escalation study conducted at the University of Miami Division of Clinical Pharmacology, Miami, Florida. Richard Preston, M.D. served as the Principal Investigator for this trial. The tolerability and pharmacokinetics of multiple oral doses of PAR-101 were evaluated in a total of 24 healthy volunteer subjects. The oral doses of PAR-101 evaluated (in 3 groups of 8 subjects each, with 6 active and 2 placebo) were 150, 300, and 450 mg (in powder-filled capsules containing 50 mg of study drug) administered daily after a morning breakfast for 10 consecutive days. Subjects were dosed and monitored on a combined inpatient/outpatient basis. Subjects were admitted to the research unit on Day 0 and again on Day 9 of the 10-day dosing period, and stayed for up to 48 hours after each admission. Subjects were discharged on Day 2 and Day 11 after completing the scheduled events and procedures. During the outpatient period, subjects reported daily to the research unit for dosing and stayed for 3 hours under observation.

Serial blood, urine, and fecal samples were collected at various time points/intervals during the multiple dosing periods. Plasma, urine, and fecal concentrations of PAR-101 were determined for pharmacokinetic analysis. A follow-up examination was scheduled on Day 17 of each study period before subjects exited from the study. Study subjects were closely monitored for the occurrence of any adverse experiences or abnormal laboratory test findings throughout the treatment periods and at the study follow-up.

PHASE 2A

SYNOPSIS

This was a dose-finding study to select a safe and effective dose of PAR-101. Subjects were randomized to receive either 100 (50 mg every 12 hours), 200 (100 mg every 12 hours), or 400 (200 mg every 12 hours) mg/day for 10 days followed by clinical evaluation. Subjects recorded all symptoms on daily diary cards. Particular attention was to be given to stool frequency and consistency, the presence of blood in the stool, and abdominal discomfort. Laboratory assessments were performed at Screening for entry and at End of Treatment (Day 10-12) or withdrawal (whichever was sooner). Clinical observation and diary card evaluation were performed at End of Treatment (Day 10-12). Patient interviews were conducted on treatment Days 2 through 9, Day 17, and Day 52. For entry inclusion criteria, an assay for *Clostridium difficile* toxin was performed. For subjects that failed to respond to PAR-101 treatment, and in the event of clinical recurrence, both *C. difficile* toxin assay and culture were performed. Clinical, laboratory, and microbiological assessments were also performed at exit for subjects that failed to respond to treatment. Pharmacokinetic plasma samples were taken 0.5 hr prior to dosing and 2 hr after dosing on the first and last days of dosing.

KEY INCLUSION CRITERIA

Subjects were patients with *C.difficile*-associated diarrhea as defined by:
- **Diarrhea** *(a change in bowel habits, with three or more unformed bowel movements in 24 hours, or more than six loose or watery stools within 36 hours)*
- **Presence of either toxin A or B of *C. difficile* in the stool**

KEY EXCLUSION CRITERIA

Subjects could *not* have:
- Severe or life-threatening CDAD
- Life-threatening or serious disease unrelated to CDAD
- Concurrent use of: vancomycin, metronidazole, bacitracin, or related drugs *(if the Investigator felt the clinical imperative to begin treatment before knowing the laboratory result for stool toxin, up to 24 hours, but no more than three doses, of treatment with metronidazole and/or vancomycin was to be allowed)*; any drugs used for the treatment of CDAD; or other antibiotics
- History of ulcerative colitis or Crohn's disease
- Multiple recurrences *(defined as more than one recurrence)* of CDAD within the past three months *(subjects with a single recurrence of CDAD were permitted to enroll)*

ENDPOINTS

At the end of therapy, the investigator determined if the subject had been cured or failed. In addition, the time to resolution of diarrhea (defined as resolution to <3 loose or watery stools per day) and the complete relief of symptoms of CDAD by day 10 of therapy (complete relief was resolution to ≤3 total stools per day, whether loose or firm; and absence of fever, elevated white blood cells, or abdominal pain) were tracked as primary endpoints, and recurrence within 6 weeks following therapy (recurrence of diarrhea, defined as 3 or more loose/watery stools per day with a positive toxin test) was tracked as a secondary endpoint.

ANALYSIS

Safety Population: The safety population was to include all randomized subjects who received at least one dose of study medication and had safety information available.

Efficacy Population: Clinical success or failure was determined in subjects treated per protocol. The population analyzed for time to resolution of diarrhea and complete relief of symptoms was the modified intent to treat population (mITT), consisting of all randomized subjects who received at least one dose of study medication, had a history of diarrhea, and had 3 or more loose stools in 24 hours and a positive *C. difficile* toxin at baseline.

Time to resolution of diarrhea: Defined as time (in days) from the first dose of study medication to the resolution of diarrhea; time to resolution of diarrhea was compared among the three treatment groups. The cessation day of diarrhea was defined as the first day that <3 unformed stools (watery or loose) within a 24 hour period occurred and was sustained for the duration of treatment up to study Day 10. Resolution of diarrhea was assessed during a 10 to 12 day period utilizing the subject diary data.

Complete relief of symptoms of CDAD: Complete relief of symptoms of CDAD was defined as resolution to ≤3 bowel movements per day (as recorded on the patient diary) without other associated signs/symptoms such as fever (≥37.7°C), abdominal pain (no response on diary) and elevated WBC (normal laboratory range of WBC) by Day 10 of the study. If any variable was missing, this outcome was considered unknown.

Clinical recurrence rate: Clinical recurrence was defined as ≥3 unformed stools (loose or watery) AND a positive stool for *C. difficile* toxin A or B within six weeks posttreatment.

Results

ENROLLMENT AND DEMOGRAPHICS

The following sections summarize the enrollment and demographic characteristics of the study populations in the Phase 1B-MD and 2A trials. A total of 24 healthy subjects were enrolled for the Phase 1B-MD study. Alternate male and female subjects were enrolled to provide an even split between the sexes. Subjects ranged in age from 38 – 62 years (average 51.6 ± 7.5 yr), in weight from 55.5 – 90 kg (average 71.5 ± 9.2 kg), and in height 147 – 183 cm (average 164.8 ± 10.8 cm.)

In the Phase 2B study, a total of 49 subjects were enrolled. One subject withdrew consent and was dropped from the study prior to receiving any study drug, and was not evaluable for either safety or efficacy. One subject (400 mg dosing group) had >6 bowel movements in 36 hours, but <3 bowel movements in the prior 24 hours, and could not be evaluated for time to resolution of diarrhea but was evaluable for clinical response and safety analyses. Three subjects were discontinued after 1 or 2 doses due to removal of consent (1 subject, 100 mg dosing group), requirement for additional antibiotics for pneumonia (1 subject, 100 mg dosing group), or inability to take study medication (1 subject, 200 mg dosing group). Subject demographics are listed in Table 1.

Table 1. Summary demographics for the Phase 2A study; demographics for the 48 subjects in the population evaluable for safety are shown

PAR-101:	100 mg/day (N=16)		200 mg/day (N=16)		400 mg/day (N=16)		All Subjects	
Gender								
Female	10	(62.5%)	11	(68.8%)	9	(56.3%)	30	(62.5%)
Male	6	(37.5%)	5	(31.3%)	7	(43.8%)	18	(37.5%)
Race								
Caucasian	14	(87.5%)	15	(93.8%)	14	(87.5%)	43	(89.6%)
Black	1	(6.3%)	1	(6.3%)	0	(0.0%)	2	(4.2%)
Asian	0	(0.0%)	0	(0.0%)	1	(6.3%)	1	(2.1%)
Hispanic	0	(0.0%)	0	(0.0%)	0	(0.0%)	0	(0.0%)
Other[a]	1	(6.3%)	0	(0.0%)	1	(6.3%)	2	(4.2%)
Age (yrs)								
Mean±SD	56.3 ± 17.78		53.1 ± 22.97		55.3 ± 17.69		54.9 ± 19.26	
Median	54.5		55.5		56.0		56.0	
Range	28.0 - 89.0		18.0 - 88.0		18.0 - 90.0		18.0 - 90.0	
Weight (kg)								
Mean ± SD	69.2 ± 14.00		68.4 ± 11.46		67.5 ± 13.56		68.4 ± 12.82	
Median	69.3		66.0		65.2		66.0	
Range	38.0 - 89.0		52.0 - 96.0		40.0 - 88.2		38.0 - 96.0	
Height (cm)								
Mean ± SD	163.8 ± 15.52		166.4 ± 9.48		166.2 ± 13.18		165.5 ± 12.80	
Median	162.1		170.0		163.8		165.0	
Range	122.0 - 187.5		150.0 - 178.0		142.0 - 193.0		122.0 - 193.0	
Calculated BMI[b]								
Mean ± SD	25.8 ± 3.89		24.9 ± 4.50		24.3 ± 2.52		25.0 ± 3.68	
Median	25.0		24.0		24.5		25.0	
Range	17.0 - 34.0		17.0 - 32.0		20.0 - 28.0		17.0 - 34.0	

Note: values represent number of subjects unless otherwise indicated

[a] *Other includes: East Indian, Indian;* [b] *Calculated body mass index is defined as (weight in kg)/(height in meters)²*

EFFICACY

In the clinical evaluation of treatment success or failure at the end of therapy, two subjects in the low dosing group (2/14), two subjects in the mid dosing group (2/15), and no subjects in the top dosing group (0/16) were considered treatment failures by the investigator. Among the subjects (n=41) that were treatment successes, CDAD recurred in one subject (1/12) in the 100 mg/day dosing group and one subject (1/16) in the top dosing group, for a recurrence rate of 2/41 (5%) overall. Both recurrences occurred approximately one month following the end of therapy.

Table 2. Rates of clinical cure and recurrence in the population treated per protocol

PAR-101:	100 mg/day N	%	200 mg/day N	%	400 mg/day N	%
Total	14	100	15	100	16	100
Treatment success	12	86	13	87	16	100
Treatment failure	2	14	2	13	0	0
Clinical recurrence[a]	1	8.3	0	0	1	6.3

[a] *Recurrence of toxin-posivite diarrhea within 6 weeks post-treatment, evaluated in subjects that were clinical successes*

The time to resolution of diarrhea was defined as the time for the patient to resolve to less than 3 unformed stools per day, according to the patient's diary card. In the mITT population, the median time to relief was 5.5 days, 3.5 days, and 3.0 days for the PAR-101 100 mg/day, 200 mg/day and 400 mg/day treatment groups, respectively. The mean time to resolution of diarrhea in days was 6.3 ± 3.66 days in 100 mg/day-treated subjects, 4.8 ± 3.56 days in 200 mg/day-treated subjects, and 3.6 ± 2.03 in 400 mg/day-treated subjects. There was no statistically significant difference in time to resolution of diarrhea between the 100 mg/day and 200 mg/day treatment groups, and between the 200 mg/day and 400 mg/day treatment groups; however, the difference between the 100 mg/day and 400 mg/day treatment groups approached statistical significance (p=0.0506 Kaplan Meier estimate and p=0.0503 Kruskal-Wallis test).

Table 3. Time to Resolution of Diarrhea (mITT population), defined as time to resolve to <3 unformed bowel movements per day (according to the patient's diary card)

PAR-101:	100 mg/day	200 mg/day	400 mg/day	P-Value
N	16	16	15	-
N (Resolved Diarrhea)	10	12	14	-
N (Censored: Did not resolve)[a]	4	3	1	-
N (Censored: Dropped from study)	2	1	0	-
N (Censored: Total)	6	4	1	-
Median Time (Days)[b]	5.5	3.5	3.0	-
P-Value[c]	-	-	-	0.1912
PAR-101 100-PAR-101 200[c]	-	-	-	0.2901
PAR-101 100-PAR-101 400[c]	-	-	-	0.0506
PAR-101 200-PAR-101 400[c]	-	-	-	0.6143

[a] *Subjects whose diarrhea was not resolved to <3 loose stools/day by day 10;* [b] *Kaplan-Meier estimates;*
[c] *P-value obtained from generalized Wilcoxon Test*

Complete relief of symptoms of CDAD by the end of treatment, defined as ≤3 total bowel movements per day (whether formed or unformed, as recorded on the patient's diary card), and no fever, elevated WBC count, or abdominal pain (according to response on patient diary card) by the 10th day of the study, is shown in Table 4. Complete relief was achieved by 37.5% of the 100 mg/day treatment group, 50.0% of the 400 mg/day treatment group, and 86.7% of the 400 mg/day treatment group. It is worth noting that most subjects that did not have complete relief by day 10 were nevertheless treatment successes, as they had resolution of symptoms by Day 17 and required no further treatment. Three subjects that dropped from the study (one for removal of consent, one for the requirement of exclusionary antibiotics, and one for the inability to take oral medications) are also listed as having no complete relief.

Table 4. Complete Relief of Symptoms of CDAD by end of therapy in the mITT population, *defined as resolution to ≤3 total bowel movements/day (formed or unformed, as noted on the patient's diary card) without other associated signs/symptoms such as fever, abdominal pain, and elevated WBC by Day 10 of the study*

PAR-101:	100 mg/day N	%	200 mg/day N	%	400 mg/day N	%
Complete relief	**6**	**(37.5)**	**8**	**(50.0)**	**13**	**(86.7)**
No complete relief						
Required further treatment	2	(12.5)	2	(12.5)	-	-
Required no further treatment	5	(31.3)	3	(18.8)	2	(13.3)
Dropped from study	2	(12.5)	1	(6.3)	-	-
TOTAL:	**9**	**(56.3)**	**6**	**(37.5)**	**2**	**(13.3)**
Unknown	**1**	**(6.3)**	**2**	**(12.5)**	-	-

Only two subjects (one subject in the 100 mg/day treatment group and one subject in the 400 mg/day treatment group) experienced clinical recurrence.

SAFETY

In the Phase 1B-MD study, OPT-80 was well tolerated by all subjects at all doses. Fourteen adverse events were reported, seven in the 150 mg group, two in the 450 mg group, and five in the placebo group. The adverse events are summarized as follows: headache (2), dizziness (1), weakness (1), fatigue (1), nasal congestion (1), difficulty swallowing (1), pharyngitis (1), conjunctivitis (1), upper respiratory infection (2), rash (1), and pruritis (1). No subjects receiving PAR-101 had adverse events considered to be drug-related.

In the phase 2A study, as shown in Table 5, 4/16 (25.0%) subjects in the 100 mg/day treatment group, 4/16 (25.0%) subjects in the 200 mg/day treatment group, and 1/16 (6.3%) subjects in the 400 mg/day treatment group reported at least one adverse event during the study. The highest frequency of adverse events was reported in the infections and infestations body system in the 100 mg/day treatment group (3/16; 18.8% subjects). There were 2/16 (12.5%) subjects that reported vascular disorders in the 100 mg/day treatment group, and in the 200 mg/day treatment group there were 2/16 (12.5%) subjects that reported gastrointestinal disorders and 2/16 (12.5%) that reported infections or infestations.

Table 5. Incidence of adverse events in the safety population of the 2A study, summarized by system organ class and preferred term (% are the proportions of subjects within each category)

PAR-101 (N=16):	100 mg/day N	%	200 mg/day N	%	400 mg/day N	%
Total subjects with adverse events	4	(25.0)	4	(25.0)	1	(6.3)
Cardiac disorders	1	(6.3)	-	-	-	-
Cardiac failure congestive	1	(6.3)	-	-	-	-
Gastrointestinal disorders	-	-	2	(12.5)	-	-
Gastrointestinal haemorrhage	-	-	1	(6.3)	-	-
Pancreatitis chronic	-	-	1	(6.3)	-	-
General disorders and administration site conditions	1	(6.3)	1	(6.3)	-	-
Chest pain	1	(6.3)	1	(6.3)	-	-
Infections and infestations	3	(18.8)	2	(12.5)	-	-
Bronchitis	1	(6.3)	-	-	-	-
Infection	1	(6.3)	-	-	-	-
Pneumonia	1	(6.3)	-	-	-	-
Staphylococcal sepsis	-	-	1	(6.3)	-	-
Urinary tract infection	1	(6.3)	1	(6.3)	-	-
Injury, poisoning and procedural complications	-	-	1	(6.3)	-	-
Fall	-	-	1	(6.3)	-	-
Metabolism and nutrition disorders	-	-	-	-	1	(6.3)
Fluid overload	-	-	-	-	1	(6.3)
Musculoskeletal and connective tissue disorders	1	(6.3)	-	-	-	-
Pain in extremity	1	(6.3)	-	-	-	-
Nervous system disorders	-	-	1	(6.3)	-	-
Cerebral haemorrhage	-	-	1	(6.3)	-	-
Renal and urinary disorders	1	(6.3)	-	-	-	-
Nephrolithiasis	1	(6.3)	-	-	-	-
Respiratory, thoracic and mediastinal disorders	1	(6.3)	-	-	-	-
Dyspnoea	1	(6.3)	-	-	-	-
Vascular disorders	2	(12.5)	-	-	-	-
Hypotension	2	(12.5)	-	-	-	-

Five subjects were reported as having serious adverse events (SAEs) during the study (Table 6). In the 100 mg/day treatment group, one subject had diarrhea of moderate severity and another subject had severe exacerbation of congestive heart failure (CHF). In the 200 mg/day treatment group, one subject had severe staphylococcal sepsis and a severe cerebral hemorrhage, another subject had a gastrointestinal hemorrhage of moderate severity, and a third subject had chest pain of moderate severity. No subject in the PAR-101 400 mg treatment group had an SAE. All SAEs were considered to be unrelated to study drug.

Table 6. Incidence of serious adverse events in the safety population of the PAR-101 2A study

	Gender, Age (yr), Race	# of Therapy Days[a]	Adverse Event (preferred term)	Study Day[b], # of AE Days	Severity	Relationship to Drug[c]	Outcome
100 mg/day							
subject 314	M, 34, C	10	Diarrhea	33, 3	Moderate	Not Related	Recovered w/o Sequelae
subject 400	M, 52, B	10	Cardiac Failure Congestive	39, 12	Severe	Not Related	Recovered w/ Sequelae
200 mg/day							
subject 200	F, 85, C	10	Staphylococcal Sepsis	10, 7	Severe	Not Related	Not Yet Recovered[d]
subject 200	-	-	Cerebral Haemorrhage	10, 7	Severe	Not Related	Not Yet Recovered[d]
subject 208	F, 71, C	10	Gastrointestinal Haemorrhage	15, 14	Moderate	Not Related	Recovered w/o Sequelae
subject 304	F, 59, C	11	Chest Pain	23, 6	Moderate	Not Related	Recovered w/o Sequelae

[a] *Date of last dose of study medication minus date of first dose of study medication plus one;* [b] *Study day is calculated as follows: date of onset minus date of first date of study medication plus one;* [c] *Based on Investigator's assessment;* [d] *Subject died; C=Caucasian; B=Black*

PHARMACOKINETICS

PLASMA CONCENTRATION DATA

In the Phase 1B-MD study, after multiple dose oral administrations, plasma concentrations of PAR-101 were mostly below the limit of quantification across the dose range.
- Detectable plasma concentrations were found only in 12 samples from 6 subjects
- Of the 12 detectable concentrations, only 2 were significantly above the LLOQ, while others barely exceeded the LLOQ of 5 ng/mL
- These two concentrations (11.1 and 48.0 ng/mL) were observed in Subject 021 on Day 1, hour 1 and just prior to the tenth dose on Day 10, respectively
- It is to be noted that the 150 mg dose produced no detectable concentrations
- Due to low PAR-101 plasma levels across the dose range, there were insufficient plasma data points above LLOQ for pharmacokinetic analysis

In the Phase 2A study, after multiple dose oral administrations, plasma concentrations of PAR-101 were mostly below the limit of quantification but with a dose dependent increase in the number of samples, and number of subjects, with measurable plasma concentrations.
- Detectable plasma concentrations were found in 2/15 (13.3%) subjects in the PAR-101 100 mg/day treatment group, 9/16 (56.3%) subjects in the PAR-101 200 mg/day treatment group, and 13/17 (76.5%) subjects in the PAR-101 400 mg/day treatment group
- Observable PAR-101 concentrations ranged from 9.45 to 12.3 ng/mL in the PAR-101 100 mg/day treatment group, 5.12 to 93.7 ng/mL in the PAR-101 200 mg/day treatment group, and 5.32 to 84.9 ng/mL in the PAR-101 400 mg/day treatment group
- Of the detectable concentrations of PAR-101 in all treatment groups, the majority (35/41; 85.4%) were under 21 ng/mL
- Concentrations of PAR-101 over 50 ng/mL were observed in only two subjects, one each in the 200 mg/day and 400 mg/day dosing groups

URINARY EXCRETION DATA OF PAR-101

Levels of PAR-101 in the urine in the Phase 1B-MD study were all below the limit of quantification (LLOQ = 5 ng/mL).

FECAL CONCENTRATION DATA OF PAR-101

Table 7 shows fecal concentrations from the 1B-MD study, normalized to the 150 mg dose; fecal PAR-101 averaged 916.0 µg/g (138.4 - 1768.9 µg/g).

For the Phase 2A study, in the PAR-101 100 mg/day treatment group (n=11 samples sufficient), fecal PAR-101 averaged 255.6 µg/g (range: 81.9 - 558.3 µg/g) at the end of treatment. In the PAR-101 200 mg/day treatment group (n=9 samples sufficient), fecal PAR-101 averaged 441.7 µg/g (range: 11.7 - 786.7 µg/g). In the PAR-101 400 mg/day treatment group (n=13 samples sufficient), fecal PAR-101 averaged 1433.3 µg/g (range: 389.0 - 3974.8 µg/g).

Table 7. Fecal concentrations of PAR-101 in the Phase 1B-MD study, normalized to a 150 mg dose

	Dose (mg)	[PAR-101] (µg/g)	Normalized [PAR-101] (µg/g)
Range:	150-450	415.1 - 5306.8	138.4 – 1768.9
Mean:	-	-	916.0
SD:	-	-	450.2

Table 8. Fecal concentrations of PAR-101 at the end of treatment in the Phase 2A study

Dose (mg/day)	Dose (mg)	Range [PAR-101] (µg/g)	Average [PAR-101] (µg/g)
100	11	81.9 - 558.3	255.6
200	9	11.7 - 786.7	441.7
400	13	389.0 - 3974.8	1433.3

Conclusion

In summary, the present studies show that PAR-101 is well-tolerated after multiple oral doses up to 450 mg, achieves high levels at the site of action, and shows promising results in the treatment of *C. difficile*-associated diarrhea.
- There were no treatment-emergent adverse events felt to be possibly drug related in either study.
- After multiple dose oral administrations, low PAR-101 levels were detected in plasma, most of which fell below the limit of quantification. Consequential to low plasma concentrations, no intact PAR-101 was detected in the collected urine of the 1B-MD study.
- By contrast, fecal levels in both studies were extremely high, exceeding 10,000 times the MIC_{90} (0.125 µg/mL) versus *C. difficile*.
- Among 45 subjects treated with a full course of therapy, only four subjects were considered failures prior to or at the end of 10 days of therapy, two subjects in the 50 mg q12h and two subjects in the 100 mg q12h dose groups. No failures (0/16) were noted in the 200 mg q12h dose.
- Recurrence was observed in only two subjects following successful treatment. Both recurred approximately one month after the end of therapy.
- Although not statistically significant, the median time-to-cessation of diarrhea showed a trend that suggested higher doses may be more efficacious. Time-to-cessation of diarrhea was determined to be 5.5 days for the 50 mg q12h dose group, 3.5 days for the 100 mg q12h dose group, and 3.0 days for the 200 mg q12h dose group.

REFERENCES

1. Bartlett, J. G. 1992. Antibiotic-associated diarrhea. *Clin Infect Dis* 15:573-81.
2. Fekety, R., and A. B. Shah. 1993. Diagnosis and treatment of *Clostridium difficile* colitis. *Jama* 269:71-5.
3. Guerrant, R. L., J. M. Hughes, N. L. Lima, and J. Crane. 1990. Diarrhea in developed and developing countries: magnitude, special settings, and etiologies. *Rev Infect Dis* 12 Suppl 1:S41-50.
4. Kelly, C. P., C. Pothoulakis, and J. T. LaMont. 1994. *Clostridium difficile* colitis. *N Engl J Med* 330:257-62.
5. McFarland, L. V. 1995. Epidemiology of infectious and iatrogenic nosocomial diarrhea in a cohort of general medicine patients. *Am J Infect Control* 23:295-305.
6. Miller, M. A., M. Hyland, M. Ofner-Agostini, M. Gourdeau, and M. Ishak. 2002. Morbidity, mortality, and healthcare burden of nosocomial *Clostridium difficile*-associated diarrhea in Canadian hospitals. *Infect Control Hosp Epidemiol* 23:137-40.
7. Musher, D. M., S. Aslam, N. Logan, S. Nallacheru, I. Bhaila, F. Borchert, and R. J. Hamill. 2005. Relatively poor outcome after treatment of *Clostridium difficile* colitis with metronidazole. *Clin Infect Dis* 40:1586-90.
8. Pepin, J., M. E. Alary, L. Valiquette, E. Raiche, J. Ruel, K. Fulop, D. Godin, and C. Bourassa. 2005. Increasing risk of relapse after treatment of *Clostridium difficile* colitis in Quebec, Canada. *Clin Infect Dis* 40:1591-7.
9. Wilcox, M. H. 1996. Cleaning up *Clostridium difficile* infection. *Lancet* 348:767-8.
10. Wistrom, J., S. R. Norrby, E. B. Myhre, S. Eriksson, G. Granstrom, L. Lagergren, G. Englund, C. E. Nord, and B. Svenungsson. 2001. Frequency of antibiotic-associated diarrhea in 2462 antibiotic-treated hospitalized patients: a prospective study. *J Antimicrob Chemother* 47:43-50.