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48-WEEK ASSESSMENT OF HIGH STRENGTH T-20 IN MULTI-CLASS EXPERIENCED PATIENTS

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Introduction

T-20 is a 36-amino acid peptide that inhibits the gp41-mediated fusion of HIV-1 with the cell membranes of CD4+ lymphocytes. Based on this novel mechanism of action, T-20 offers an attractive new therapy in the management of HIV infection in treatment-experienced patients with drug-resistant HIV.

Phase I/II, dose-ranging studies identified a T-20 dose of 100 mg (90 mg deliverable) twice-daily for further development, but the initial 50 mg/mL T-20 carbonate (CO_3) formulation required two injections twice-daily to deliver this dose. High strength (100 mg/mL) CO_3 and TRIS formulations were developed to reduce the number of daily injections required and improve convenience for patients. The study presented here assessed the safety, tolerability, pharmacokinetics and antiviral activity of the T-20 formulations in treatment-experienced patients over a 48-week period.

Objectives

- To compare the steady-state pharmacokinetics and tolerability of 50 mg/mL CO_3 formulation with high strength (100 mg/mL) T-20 formulations
- To assess the safety, tolerability and antiviral activity of high strength T-20 formulations through 48 weeks of treatment.

Study design

- Sequential, 28-day, steady-state, cross-over phase comparing pharmacokinetics and tolerability of the original 50 mg/mL CO_3 formulation of T-20 with high strength (100 mg/mL) CO_3 and TRIS formulations
- 46 triple-class, treatment-experienced patients were assigned to one of three treatment cohorts (Table 1). All patients received an optimal ARV regimen in addition to T-20
- Following the cross-over phase the safety, tolerability and antiviral activity of the high strength formulations of T-20 were assessed through a further 44 weeks of therapy
- The study was not designed or statistically powered for hypothesis testing of differences.

Table 1. Study design

Cross-over phase			
	Cohort I (N=22)	**Cohort II (N=12)**	**Cohort III (N=12)**
0–14 days	100 mg/mL CO_3 100 mg* BID	100 mg/mL CO_3 75 mg** BID	100 mg/mL TRIS 100 mg* BID
15–28 days	50 mg/mL CO_3 Two injections BID		
Continuation phase			
29 days–48 weeks	100 mg/mL CO_3 100 mg* BID	100 mg/mL CO_3 75 mg** BID	100 mg/mL TRIS 100 mg* BID

*90 mg deliverable
**67.5 mg deliverable

Results

Forty-six patients were enrolled in the study, most of whom were men and of Caucasian origin with high baseline viral load and low CD4 cell counts (Table 2).

On average patients in Cohort I had a somewhat lower baseline viral load and higher CD4 cell count at baseline than patients in Cohorts II and III.

Table 2. Patient characteristics and baseline HIV-1 RNA and CD4+ cell counts

	Cohort I 100 mg BID CO_3	**Cohort II 75 mg BID CO_3**	**Cohort III 100 mg BID TRIS**	**All Cohorts**
Gender, N (%)				
Male	22 (100)	11 (92)	11 (92)	44 (96)
Female	0 (0)	1 (8)	1 (8)	2 (4)
Ethnic origin, N (%)				
Caucasian	18 (82)	11 (92)	9 (75)	38 (83)
Black	2 (9)	1 (8)	3 (25)	6 (13)
Other	2 (9)	0 (0)	0 (0)	2 (4)
Age, years (SE)	44 (1.7)	42 (2.3)	39 (1.6)	43 (1.1)
Median plasma HIV-1 RNA, log_{10}copies/ml	5.12	5.44	5.50	5.37
Median CD4+ cell count, cells/mm^3	98	12	23	24
Mean number of prior ARV agents	12.5	12.0	11.5	12.0
Mean duration of ARV therapy, yrs	8.3	8.5	7.5	7.8
Total primary mutations, %				
0–4 mutations	23	8	42	24
5–9 mutations	23	42	33	30
≥10 mutations	55	50	25	46

Three subjects (6.5%) discontinued T-20 before Week 48; one each for an adverse event (abdominal distension), patient request, and lost to follow-up.

Pharmacokinetic comparison of formulations

Plasma concentration-time profiles were collected in a sub-set of patients to estimate pharmacokinetic parameters for each treatment group (Table 3).

Table 3. Mean (CV%) pharmacokinetic parameters for T-20 following subcutaneous administration of 50 mg/mL CO_3,100 mg/mL CO_3 and 100 mg/mL TRIS formulations

Cohort I, 100mg* BID (N=11)	**Formulation**	
Pharmacokinetic parameter	**100 mg/mL CO_3 (Days 1–14)**	**50 mg/mL CO_3 (Cross-over phase – days 15–28)**
C_{max} (µg/ml)	5.00 (34)	4.77 (23)
T_{max} (h)	4.07	4.00
AUC_{12h} (µg.h/mL)	48.7 (39)	46.2 (26)
CL/F (L/h)	2.39 (42)	2.33 (30)
Cohort II, 75 mg BID (N=8)**	**Formulation**	
Pharmacokinetic parameter	**100 mg/mL CO_3 (Days 1–14)**	**50 mg/mL CO_3 (Cross-over phase – days 15–28)**
C_{max} (µg/ml)	3.70 (37)	3.85 (27)
T_{max} (h)	4.13	5.13
AUC_{12h} (µg.h/mL)	34.4 (45)	37.0 (37)
CL/F (L/h)	2.77 (58)	2.43 (53)
Cohort III, 100 mg* BID (N=7)	**Formulation**	
Pharmacokinetic parameter	**100 mg/mL TRIS (Days 1–14)**	**50 mg/mL CO_3 (Cross-over phase – days 15–28)**
C_{max} (µg/ml)	3.51 (28)	5.17 (30)
T_{max} (h)	4.00	4.00
AUC_{12h} (µg.h/mL)	35.0 (30)	44.7 (27)
CL/F (L/h)	3.15 (38)	2.45 (38)

*90 mg deliverable **67.5mg deliverable

- The 100 mg/mL CO_3 formulation was bioequivalent by ANOVA analysis to the 50 mg/mL CO_3 formulation, with comparable values for C_{max}, T_{max}, AUC_{12h} and CL/F
- The 100 mg/mL TRIS and 50 mg/mL CO_3 formulations were not bioequivalent by ANOVA analyses.

Antiviral and immunological activity

Plasma viral load (Roche Amplicor) and CD4 cell counts were monitored over the 48 weeks of the study (Table 4). Median change in log_{10} plasma HIV-RNA and CD4 cell counts were based upon observed treatment analyses, responder analyses of proportion of patients with viral load ≤400 and ≤50 copies/mL were based upon intent-to-treat analyses.

Table 4. Antiviral activity of high strength CO_3 and TRIS T-20 formulations

	Week	**Cohort I 100 mg BID CO_3**	**Cohort II 75 mg BID CO_3**	**Cohort III 100 mg BID TRIS**
Median change in log_{10} plasma HIV-1 RNA*	16	-2.38	-2.75	-0.54
	24	-2.64	-3.13	-0.81
	48	-2.97	-3.48	-0.87
Number (%) of subjects with plasma HIV-RNA ≤400 copies/mL	16	8/21 (38.1)	6/12 (50.0)	2/12 (16.7)
	24	10/22 (45.5)	8/12 (66.7)	2/12 (16.7)
	48	13/22 (59.1)	8/12 (66.7)	2/12 (16.7)
Number (%) of subjects with plasma HIV-RNA ≤50 copies/mL	16	2/22 (9.1)	2/12 (16.7)	1/12 (8.3)
	24	5/22 (22.7)	3/12 (25.0)	2/12 (16.7)
	48	9/22 (40.9)	5/12 (41.7)	2/12 (16.7)
Median increase in CD4+ cell count (cells/mm^3)*	16	84	88	100
	24	88	103	85
	48	111	175	79

*compared with baseline

Safety and tolerability

Injection site reactions (ISRs) were the most frequent occurrence associated with subcutaneous injection of T-20 with all patient cohorts experiencing at least one event. However, no patient discontinued treatment due to ISRs (Table 5).

Table 5. Signs and symptoms of injection site reactions (ISRs)

	Cohort I 100 mg BID CO_3	**Cohort II 75 mg BID CO_3**	**Cohort III 100 mg BID TRIS**	**All Cohorts**
Signs/symptoms of ISRs, n (%)				
Induration	22 (100)	12 (100)	12 (100)	46 (100)
Pain/discomfort	20 (90.9)	10 (83.3)	12 (100)	42 (91.3)
Erythema	18 (81.8)	10 (83.3)	12 (100)	40 (87.0)
Pruritus	15 (68.2)	7 (58.3)	11 (91.7)	33 (71.7)
Study discontinuations due to ISR	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**

Adverse events were relatively common and consistent with the stage of HIV disease of the study participants (Table 6). However, there was no consistent pattern or dose-dependent increase in the incidence of adverse events.

Table 6. Most Frequent (≥5% Subjects in Any Cohort) Treatment-Emergent Adverse Events and Serious Adverse Events

	Cohort I 100 mg BID CO_3 (N=22)		**Cohort II 75 mg BID CO_3 (N=12)**		**Cohort III 100 mg BID TRIS (N=12)**		**All Cohorts (N=46)**	
	N	%	N	%	N	%	N	%
At least one adverse event	**22**	**100**	**12**	**100**	**12**	**100**	**46**	**100**
Diarrhea NOS/Diarrhea aggravated/Loose stools	10	45.5	11	91.7	6	50.0	27	58.7
Nausea/Nausea aggravated	11	50.0	3	25.0	4	33.3	18	39.1
Fatigue/Fatigue aggravated	4	18.2	5	41.7	6	50.0	15	32.6
Lymphadenopathy	6	27.3	4	33.3	5	41.7	15	32.6
Nasopharyngitis	9	40.9	3	25.0	3	25.0	15	32.6
Headache NOS	6	27.3	4	33.3	2	16.7	12	26.1
Insomnia NEC/Insomnia exacerbated	6	27.3	4	33.3	2	16.7	12	26.1
Peripheral neuropathy	5	22.7	3	25.0	1	8.3	9	19.6
Pyrexia	5	22.7	2	16.7	2	16.7	9	19.6
Weight decreased	5	22.7	1	8.3	3	25.0	9	19.6
Myalgia/muscle cramps	5	22.7	2	16.7	0	0.0	7	15.2
Abdominal distension	6	27.3	0	0.0	0	0.0	6	13.0
Serious Adverse Events	**7**	**25.9**	**5**	**41.6**	**7**	**58.3**	**19**	**41.3**

Conclusions

- The high strength 100 mg/mL CO_3 but not TRIS, formulation of T-20 was bioequivalent to the initial 50 mg/mL CO_3 formulation
- As part of a varied ARV regimen, the 100 mg/mL CO_3 formulation dosed at 75 mg BID and 100 mg BID displayed greater antiviral activity over 48 weeks of treatment than the 100 mg/mL TRIS formulation dosed at 100 mg BID
- All T-20 formulations were well tolerated in this very heavily treatment-experienced HIV-1 infected population with only one patient discontinuing for an adverse event
- The pharmacokinetics, safety profile and antiviral activity for T-20 support use as a 100 mg/mL CO_3 formulation administered as two daily injections.

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