P-E1 # 1479

Board # 338

Reduction of sCD163, SP and PD1+ Th Cells Levels in a Phase 1B trial of the NK1R Antagonist Aprepitant

P. TEBAS[1], **S. SPITSIN**[2], **F. TULUC**[2], **J.S. BARRETT**[2], **O. ELCI**[2], **J. KORELITZ**[3], **W. WAGNER**[1], **D. KIM**[1], **R. CATALANO**[3], **S.D. DOUGLAS**[2]

[1]University of Pennsylvania Division of Infectious Diseases, Philadelphia, United States, [2]Dept Pediatrics Univ of Pennsylvania and Children's Hospital of Philadelphia Research Institute, Philadelphia, [3]Westat, Rockville, United States

Introduction

- Substance P (SP) is an undecapeptide produced in neurons and immune cells and involved in nociception and inflammatory responses.
- The effects of SP are mediated by the neurokinin 1 receptor (NK1R). Increased plasma levels of SP are present in HIV-infected individuals.
- NK1R antagonists have anti-HIV effects in monocyte-derived macrophages *in vitro*, by decreasing the expression of CCR5.
- Aprepitant is an NK1R antagonist approved by FDA as an antiemetic.
- Increased plasma levels of sCD163 shed from monocytes and/or macrophages are associated with HIV disease progression.
- We conducted a randomized, placebo-controlled, double-blind study to determine the safety and antiviral activity of 375 mg of aprepitant by comparing the change in HIV RNA viral load after 2 weeks of aprepitant monotherapy in patients with HIV infection not receiving any other antiretroviral treatment.

Methods

Study Objectives

Primary

- To assess the safety and tolerability of 375 mg aprepitant for 2 weeks.
- To assess the response of plasma HIV-1 RNA to a 375 mg dose of aprepitant compared with baseline.

Secondary

- To evaluate aprepitant effect on immunogical, virological, and metabolic parameters.
- To evaluate the pharmacokinetic and pharmacodynamic relationships between viral load and aprepitant plasma levels.

Endpoints

- Primary endpoints were Grade 2-4 adverse events (AE), change in viral load, plasma SP levels, cellular inflammatory markers and plasma sCD163 levels.

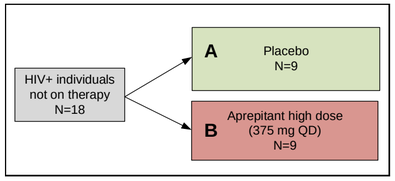
Study Subjects

- HIV infected males and females ≥ 18 years old who have early infection, and CD4 cell counts ≥ 350 cells/mm^3 and plasma viral load ≥ 2,000 copies/ml.
- Subjects were stratified by viral load (< vs. ≥20,000 copies/ml).

Study Design

- Randomized, placebo-controlled, double-blind study .
- Subjects randomized 1:1 to receive 375 mg of aprepitant (Emend®) or placebo for 14 days and then followed off drug for 42 days

Figure 1. Study design



Results

Table 1. Patient characteristics

Characteristic	Treatment Group 375 mg	Placebo
Number of subjects	**9**	**9**
Gender		
Male	**6 (67%)**	**7 (78%)**
Female	**3 (33%)**	**2 (22%)**
Age (years)		
Median	**32.4**	**41.8**
Range	**(19 - 56)**	**(25 - 52)**
Ethnicity		
Hispanic	**1 (11%)**	**1 (11%)**
Non–Hispanic	**8 (89%)**	**8 (89%)**
Race		
White	**0 (0%)**	**1 (11%)**
Black	**9 (100%)**	**7 (78%)**
Other	**0 (0%)**	**1 (11%)**
Viral load at screening (copies/mL)		
< 20,000	**7 (78%)**	**6 (67%)**
≥ 20,000	**2 (22%)**	**3 (33%)**

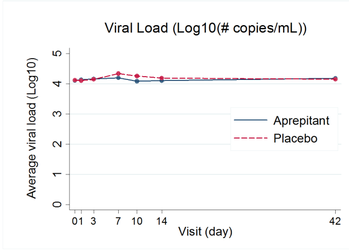
- Eighteen subjects were randomized (9 to aprepitant, and 9 to placebo).
- 72% male; 89% black; 36.9 years of age.
- Mean viral load (copies/ml) at baseline for aprepitant was 22,466 and 19,414 for mL for placebo.

Results (Cont)

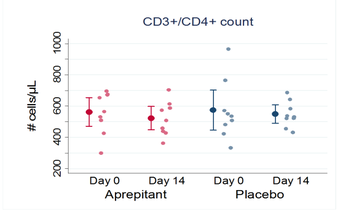
- There were no significant changes in plasma viremia during the dosing period: mean (SD) change in log10 viral load at day 14 was -0.02 (0.15) in the aprepitant arm and 0.07 (0.24) in the placebo (p=NS).
- There were no significant changes in cellular inflammatory markers CD4+ or CD8+ CD38+/HLA-DR+ cells or in in the frequency of CD4+/CCR5+ cells.

Viral load and CD4 effects

Viral Load
(Log$_{10}$ copies/ml)



CD4 + Count



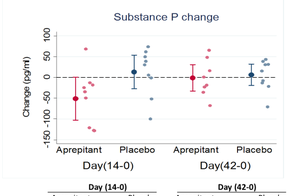
	Aprepitant Day 0	Aprepitant Day 14	Placebo Day 0	Placebo Day 14
Mean (SD)	562.4 (130.1)	523.2 (106.3)	574.1 (181.9)	549.4 (84.0)
Median (Min-Max)	543 (309-705)	486 (372-713)	533 (342-943)	537 (441-697)

Substance P, CD4+/PD1+ and soluble CD163

Aprepitant was associated with significant decreases in

- percentages of CD4+ T cells expressing PD-1 (30% to 21%, p=0.04).
- plasma SP (-48.2, -10%, p=0.05).
- sCD163 (-503 ng/ml, -22%, p=0.02), with no significant changes in the placebo arm.

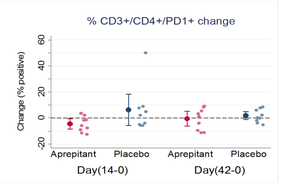
Substance P



	Day (14-0) Aprepitant	Day (14-0) Placebo	Day (42-0) Aprepitant	Day (42-0) Placebo
Mean Change	-48.2	12.9	-1.13	6.00
Median Change	**-34.0** ← p=0.05 →	**30.0**	**- 6.00** ← p=0.70 →	**15.00**
P value *	0.05	0.55	0.99	0.44

* P value for testing within subject median change

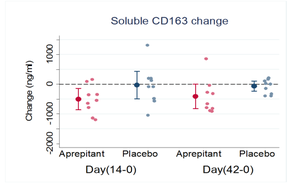
CD4+ / PD1+
(% Positive)



	Day (14-0) Aprepitant	Day (14-0) Placebo	Day (42-0) Aprepitant	Day (42-0) Placebo
Mean Change	-4.48	6.34	-0.53	1.94
Median Change	**-4.80** ← p=0.04 →	**3.60**	**2.20** ← p=0.72 →	**1.80**
P value *	0.04	0.26	0.91	0.21

* P value for testing within subject median change

Soluble CD163
(ng/ml)



	Day (14-0) Aprepitant	Day (14-0) Placebo	Day (42-0) Aprepitant	Day (42-0) Placebo
Mean Change	-502.8	-30.8	-409.1	-64.2
Median Change	**-563.0** ← p=0.10 →	**-20.0**	**-594.0** ← p=0.06 →	**46.0**
P value *	0.02	0.77	0.09	0.59

* P value for testing within subject median change

Tolerability and lipid effects

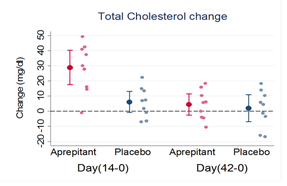
- There were no serious adverse events.
- Adverse events were equally frequent in both arms, mild and self-limited in nature.
- The use of aprepitant was associated with moderate increases in total and LDL cholesterol (+ 29 mg/dl, p=0.01; + 24 mg/dl p=0.02 respectively), and increases in HDL cholesterol (+ 4 mg/dl, p=0.02).

Adverse Events

Number (%) of Subjects with Adverse Events by Body System

	Treatment Group 375 mg (n=9)		Placebo (n=9)		Total (n=18)	
Body System	n	(%)	n	(%)	n	(%)
Neurological	1	(11.1)	4	(44.4)	5	(27.8)
Systemic	2	(22.2)	5	(55.5)	7	(38.9)
Gastrointestinal	3	(33.3)	4	(44.4)	7	(38.9)
Respiratory	0	(0.0)	4	(44.4)	4	(22.2)
Skin/Dermatological	2	(22.2)	0	(0.0)	2	(11.1)
Musculoskeletal	0	(0.0)	1	(11.1)	1	(5.6)
Urinary	1	(11.1)	0	(0.0)	1	(5.6)
Genitourinary	0	(0.0)	1	(11.1)	1	(5.6)

Laboratory Tests
Total Cholesterol (mg/dl)



	Day (14-0) Aprepitant	Day (14-0) Placebo	Day (42-0) Aprepitant	Day (42-0) Placebo
Mean Change	28.9	6.1	4.4	2.0
Median Change	**31.0** ← p=0.01 →	**8.0**	**6.0** ← p=0.72 →	**3.0**
P value *	0.01	0.09	0.21	0.59

* P value for testing within subject median change

Conclusions

- Aprepitant was safe and well tolerated.
- At the dose used in this proof of concept Phase 1B study, aprepitant did not show significant antiviral activity.
- Aprepitant was associated with
  - Decreased levels of Substance P.
  - Decreased levels of Soluble CD163.
  - Decreased levels of CD4 + / PD1 + cells.
- Blockade of NK-1 receptor pathway may have a role in modulating monocyte activity.
- Prospective studies using aprepitant in virologically suppressed patients on ART are warranted to evaluate its potential anti-inflammatory properties.

Pablo Tebas, MD Univ. of Pennsylvania
E-mail: pablo.tebas@uphs.upenn.edu

Research support: NIH grant **UO1-MH-090325**