Atazanavir: A Once-Daily Protease Inhibitor With a Superior Lipid Profile – Results of Clinical Trials at Week 48

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ABSTRACT

Background: Atazanavir is a once daily protease inhibitor (PI) that rapidly and durably suppresses HIV RNA and durably increases CD4 cell count. Current PIs cause prompt, marked and sustained elevations in lipids. No elevations in lipids have been observed with atazanavir treatment through week 48. **Methods:** In addition to evaluating safety and efficacy, clinical trials AI424-007 and AI424-008 carried out in treatment-naïve subjects, have evaluated changes in lipid profiles of atazanavir administered once daily and nelfinavir administered twice or three times daily, both with 2 nucleoside reverse transcriptase inhibitors (NRTIs). **Results:** Changes in lipid profile from baseline at week 48 are shown in the table. The atazanavir dose of 400 mg once daily is the dose currently used in Phase III clinical trials. Available lipid results beyond week 48 will be presented.

	Mean Change, % (n) From Baseline		
	Total Cholesterol	Fasting LDL	Fasting Triglycerides
Trial AI424-007 at week 48 (n)			
Atazanavir 400 mg qd (101)	7* (81)	–7* (35)	2* (44)
Nelfinavir 750 mg tid (100)	28 (82)	31 (39)	42 (46)
Trial AI424-008 at week 48 (n)			
Atazanavir 400 mg qd (178)	5* (153)	5* (87)	7* (85)
Nelfinavir 1,250 mg bid (91)	25 (76)	23 (41)	50 (50)

*P<0.05, atazanavir vs nelfinavir

Conclusion: Results of these 2 studies in treatment-naïve subjects at week 48 confirm that the prompt, marked, and sustained elevations in lipids seen with current PIs are not seen with atazanavir. This suggests that atazanavir may reduce the risk of cardiovascular events in this population.

BACKGROUND

Atazanavir

- A once-daily PI with a low pill burden (2 capsules/day)
- C_{min} (trough) exceeds IC_{90} (8–12 nM) for >24 hours at 400 mg; provides forgiveness for missed dose
- No clinically relevant lipid elevations
  - In treatment-naïve and treatment-experienced subjects
  - Current PIs are associated with prompt, marked, and sustained elevations in lipids
- Favorable resistance profile in vitro
- Safe, well tolerated, effective
  - Rapidly, durably suppresses HIV RNA; durably increases CD4
  - Fewer GI side effects vs nelfinavir

OBJECTIVES

BMS-007

- Safety
- Tolerability
- Efficacy
  - Primary objectives
    - Magnitude, durability of change in HIV RNA
  - Secondary objectives
    - Proportions of subjects with HIV RNA ≤400 c/mL
    - Magnitude, durability of changes in CD4 cell count
    - Optimal dosage of atazanavir for Phase III

BMS-008

- Safety
- Tolerability
- Efficacy
  - Primary objectives
    - Magnitude, durability of change in HIV RNA
  - Secondary objectives
    - Proportions of subjects with HIV RNA ≤400 c/mL ≤50 c/mL
    - Magnitude, durability of changes in CD4 cell count

METHODS

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Study Design

Screening: HIV RNA ≥2,000 c/mL, ≤200,000 c/mL; CD4 ≥100 cells/mm^3

Enrollment

1:1:1:1 Randomization

Group I n=83	Group II n=78	Group III n=76	Group IV n=80
Atazanavir 200 mg qd	Atazanavir 400 mg qd	Atazanavir 500 mg qd	Nelfinavir 750 mg tid
2-week monotherapy	2-week monotherapy	2-week monotherapy	2-week monotherapy
46-week triple therapy	46-week triple therapy	46-week triple therapy	46-week triple therapy
Subjects ≥50 kg	**Subjects ≥50 kg**	**Subjects ≥50 kg**	**Subjects ≥50 kg**
ddI 400 mg qd	ddI 400 mg qd	ddI 400 mg qd	ddI 400 mg qd
d4T 40 mg bid	d4T 40 mg bid	d4T 40 mg bid	d4T 40 mg bid

- Multinational, 2-staged, active controlled, blinded (by atazanavir dose), randomized
- Inclusion
  - Males and females ≥18 years of age
  - CD4 ≥100 cells/mm^3
- Exclusion
  - Prior antiretroviral therapy except ≤7days NRTI
  - Prior NRTI therapy within 30 days of enrollment
  - Newly diagnosed opportunistic infection

BMS-008

Study Design

Screening: HIV RNA ≥2,000 c/mL; CD4 ≥100 cells/mm^3

Enrollment

2:2:1 Randomization

Group I n=181	Group II n=195	Group III n=91
Atazanavir 400 mg qd	Atazanavir 600 mg qd	Nelfinavir 1,250 mg qd
48-week triple therapy	48-week triple therapy	48-week triple therapy
Subjects ≥60 kg	**Subjects ≥60 kg**	**Subjects ≥60 kg**
3TC 150 mg bid	3TC 150 mg bid	3TC 150 mg bid
d4T 40 mg bid	d4T 40 mg bid	d4T 40 mg bid

- Multinational, active-controlled, blinded (by atazanavir dose), randomized
- Inclusion
  - Males and females ≥18 years of age
  - CD4 ≥100 cells/mm^3 (or ≥75 cells/mm^3 with no prior AIDS-defining diagnosis)
- Exclusion
  - Prior antiretroviral therapy
- Amplicor HIV-1 Monitor™ Ultra Sensitive test (PCR, Version 1.5); ambient shipment

RESULTS

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Baseline Characteristics*

Characteristic	Atazanavir 200 mg n=104	Atazanavir 400 mg n=103	Atazanavir 500 mg n=110	Nelfinavir n=103
Median age, yr	34	34	34	34
Male/Female, %	70/30	61/39	61/39	65/35
White, n (%)	63 (61)	58 (56)	58 (53)	58 (56)
AIDS diagnosis, n (%)	6 (6)	5 (5)	4 (4)	4 (4)
HIV RNA, median, $\log_{10}$ c/mL	4.60	4.66	4.76	4.77
CD4, median, cells/mm^3	305	305	268	343

*Stage II randomized subjects

Subject Disposition at 48 Weeks*

Characteristic	Atazanavir 200 mg n=104	Atazanavir 400 mg n=103	Atazanavir 500 mg n=110	Nelfinavir n=103
Treated	102 (98)	101 (98)	107 (97)	100 (97)
Discontinued	17 (16)	15 (15)	16 (15)	16 (16)
Adverse event (AE)	5 (5)	6 (6)	10 (9)	7 (7)
AE, study drug-related	3 (1)†	4 (4)†	7 (6)†	6 (6)†

AE=adverse event
*Stages I and II randomized subjects; Number of subjects (%)
†200 mg: Lactic acidosis, lipodystrophy, hyperbilirubinemia
400 mg: Nausea, hepatitis with jaundice, rash, lipodystrophy
500 mg: Nausea, rash, hyperbilirubinemia, jaundice, increased amylase, lipase, ALT
Nelfinavir: Hepatitis, allergy, liver enzyme increase, lipodystrophy, diarrhea, neutropenia

Clinical Adverse Events n (%) at 48 Weeks*

Characteristic	Atazanavir 200 mg n=102	Atazanavir 400 mg n=101	Atazanavir 500 mg n=107	Nelfinavir n=100
Diarrhea	23 (23)†	25 (25)†	32 (30)†	61 (61)
Nausea	25 (25)	35 (35)	32 (30)	18 (18)
Pain, abdomen	25 (25)	31 (31)	24 (22)	23 (23)
Infection	47 (46)	53 (52)	64 (60)	53 (53)

*Grades 1–4; Reported with a frequency of ≥30% in any treatment group; Stages I and II
†P<0.05, atazanavir vs nelfinavir

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Baseline Characteristics

Characteristic	Atazanavir 400 mg n=181	Atazanavir 600 mg n=195	Nelfinavir n=91
Median age, yr	33	34	34
Male/Female, %	61/39	64/36	63/37
White, %	55	53	57
AIDS diagnosis, n (%)	18 (10)	24 (12)	9 (10)
HIV RNA, median, $\log_{10}$ c/mL	4.77	4.70	4.71
CD4, median, cells/mm^3	260	283	273

Subject Disposition at 48 Weeks*

Characteristic	Atazanavir 400 mg n=181	Atazanavir 600 mg n=195	Nelfinavir n=91
Treated	178 (98)	195 (100)	91 (100)
Discontinued	29 (16)	32 (16)	17 (19)
Adverse event (AE)	9 (5)	14 (7)	4 (4)
AE related to study drug	4 (2)	13 (7)	4 (4)

*Number of subjects (%)

Clinical Adverse Events* at 48 Weeks

Characteristic	Atazanavir 400 mg n=178	Atazanavir 600 mg n=195	Nelfinavir n=91
Diarrhea	36 (20)†	29 (15)†	51 (56)
Infection	75 (42)	107 (55)	44 (48)
Headache	45 (25)	52 (27)	24 (26)
Rash	39 (22)	34 (17)	17 (19)
Nausea	38 (21)	35 (18)	16 (18)
Pain (abdomen)	33 (19)	43 (22)	12 (13)
Peripheral neurological symptoms	32 (18)	42 (22)	19 (21)
Jaundice	20 (11)	39 (20)	—

*Grade 1–4; reported with frequency of >20% in any treatment group; number of subjects (%)
†P<0.0001, atazanavir 400 mg and 600 mg vs nelfinavir

RESULTS

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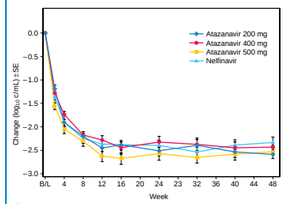
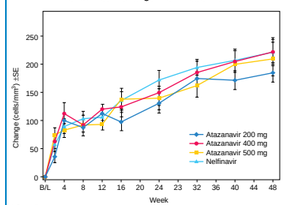
HIV RNA: Mean Change From Baseline*



* Stage II on treatment

Number of subjects			
ATV 200	83	73	67
ATV 400	78	72	64
ATV 500	79	68	60
NFV	82	74	65

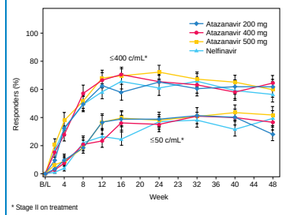
CD4: Mean Change From Baseline*



* Stage II on treatment

Number of subjects			
ATV 200	83	72	65
ATV 400	78	71	63
ATV 500	79	69	60
NFV	82	73	65

Treatment Response, Intent to Treat NC=F*



* Stage II on treatment

Number of subjects			
ATV 200	83		
ATV 400	78		
ATV 500	79		
NFV	82		

NC=F, noncompleter=failure

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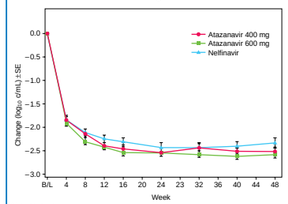
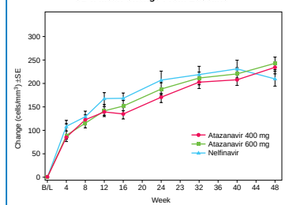
HIV RNA: Mean Change From Baseline*



* Intent to treat

Number of subjects		
ATV 400	181	
ATV 600	195	
NFV	91	

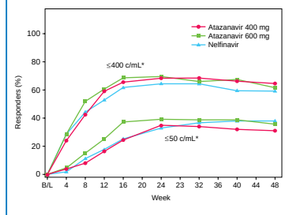
CD4: Mean Change From Baseline*



* All observed values (LOCF)

Number of subjects			
ATV 400	181	169	153
ATV 600	195	179	166
NFV	91	83	78

Treatment Response, Intent to Treat NC=F



* Number of subjects

ATV 400	181	
ATV 600	195	
NFV	91	

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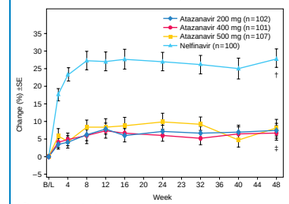
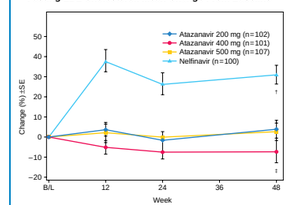
Total Cholesterol: Mean Change From Baseline*



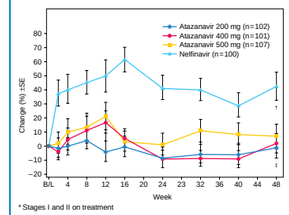
* Stages I and II on treatment
† P<0.0001, nelfinavir at 48 weeks vs nelfinavir baseline
‡ P<0.05, atazanavir vs nelfinavir

Fasting LDL Cholesterol: Mean Change From Baseline*



* Stages I and II on treatment
† P<0.0001, nelfinavir at 48 weeks vs nelfinavir baseline
‡ P<0.05, atazanavir vs nelfinavir

Fasting Triglycerides: Mean Change From Baseline*



* Stages I and II on treatment
† P<0.0001, nelfinavir at 48 weeks vs nelfinavir baseline
‡ P<0.05, atazanavir vs nelfinavir

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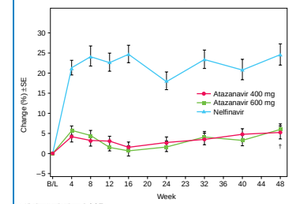
Total Cholesterol: Mean Change From Baseline*

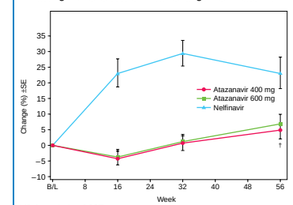


* All observed values (LOCF)

Number of subjects			
ATV 400	178	169	153
ATV 600	195	176	166
NFV	91	81	76

†P<0.0001, atazanavir 400 and 600 mg vs nelfinavir

Fasting LDL Cholesterol: Mean Change From Baseline*

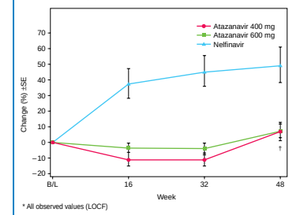


* All observed values (LOCF)

Number of subjects			
ATV 400	136	102	87
ATV 600	164	122	97
NFV	75	52	41

†P<0.001, atazanavir 400 and 600 mg vs nelfinavir

Fasting Triglycerides: Mean Change From Baseline*



* All observed values (LOCF)

Number of subjects			
ATV 400	139	109	85
ATV 600	167	131	99
NFV	77	61	50

†P<0.001, atazanavir 400 and 600 mg vs nelfinavir

BMS-007/-008

Summary: Frequency and Severity of Hyperlipidemia Using ATP III Classification at 48 Weeks

Total cholesterol (mg/dL)	-007 Atazanavir 400 mg qd n=101	-007 Nelfinavir 750 mg tid n=100	-008 Atazanavir 400 mg qd n=178	-008 Nelfinavir 1250 mg bid n=91
<200	65 (80)*	33 (40)	115 (75)	37 (49)
200 to <240	12 (15)	33 (40)	30 (20)	19 (25)
240 to <300	4 (5)	15 (18)	7 (5)	15 (20)
≥300	—	1 (1)	1 (<1)	5 (7)
Fasting LDL cholesterol (mg/dL)				
<100	18 (51)	5 (13)	42 (48)†	15 (37)
100 to <130	9 (26)	18 (46)	25 (29)	11 (27)
130 to <160	6 (17)	9 (23)	15 (17)	9 (22)
% With desirable LDL cholesterol	**93**	**82**	**93**	**86**
160 to <190	2 (6)	5 (13)	5 (6)	4 (10)
≥190	—	2 (5)	—	2 (5)
% Meeting ATP III, ACTG criteria for lipid-lowering therapy (LDL ≥160 mg/dL) based upon 0 to 1 cardiovascular risks	**6**	**18**	**6**	**15**

*Values are number of subjects (%)
†Values at 56 weeks

CONCLUSIONS

BMS-007

- Atazanavir once daily is safe, well tolerated, and effective. Dose for Phase III=400 mg qd
- Atazanavir once daily rapidly and durably suppresses HIV RNA and durably increases CD4 in treatment-naïve subjects
- Atazanavir+ddI+d4T=potential qd regimen
- Substantial proportions of subjects achieve HIV RNA responses at ≤400 and ≤50 c/mL
- Atazanavir has a superior lipid profile
  - To date, no significant elevations in blood lipids, compared with prompt, marked, and sustained elevations with nelfinavir
- Rate of diarrhea significantly lower vs nelfinavir
- Fewer subjects met ATP-III ACTG criteria for lipid-lowering therapy with atazanavir vs nelfinavir

BMS-008

- Atazanavir is safe, well tolerated, and effective
- Atazanavir once daily has efficacy comparable or superior to nelfinavir twice daily
  - Rapidly and durably suppresses HIV RNA (~2.5 $\log_{10}$ c/mL)
  - Analyses at all time points after week 8 (for HIV RNA ≤400 c/mL) favor atazanavir. At 48 weeks, atazanavir is statistically superior to nelfinavir in on-treatment analysis for both 400 and 600 mg (P<0.05, on-treatment completers analysis, data not shown)
  - Durably increases CD4 (~240 cells/mm^3)
- Atazanavir does not elevate lipids as assessed by percent change from baseline in total cholesterol and fasting LDL cholesterol and fasting triglycerides
- With nelfinavir, increases in lipids were prompt, marked, and sustained
  - Fasting LDL cholesterol increased 23% from baseline for nelfinavir vs 5% for atazanavir 400 mg once daily (P<0.001)
- Lipid benefits of this magnitude may be associated with a reduction in the risk of cardiovascular events
- Fewer subjects met ATP-III ACTG criteria for lipid-lowering therapy with atazanavir vs nelfinavir