PRINCE

ONE

Pediatric Atazanavir International Clinical Evaluation

48 Week Safety and Efficacy of once daily atazanavir powder and ritonavir liquid in HIV-1-infected antiretroviral-naïve and experienced infants and children 3 months to 6 years of age

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PRINCE 1: Study Design

- **Phase IIIb, prospective, international, multi-center, non-randomized, 2-stage study**
  - Stage 1: Subjects treated for 48 weeks or until reaching 6 years or weight ≥ 25 kg
  - Stage 2: > 48 weeks **or** if reaching ≥ 6 years or weight ≥ 25 kg and switch to ATV capsules.
- **Population: 3 months to < 6 yrs old, weight 5 - <25kg in stage 1**
  - ARV Naïve or Experienced
  - Screening HIV RNA-1 ≥ 1000c/mL
  - Exclusion: HBV or HCV co-infection; Cardiac conduction disorders
- **Sample Size**: **56**
- **Treatment**: **ATV powder + RTV liquid + dual NRTI** (locally approved; based on screening resistance test; No TDF)

ATV powder /RTV Dosing Table*			
Body weight (kg)	ATV Dose (mg)	RTV Dose (mg)	
5 to < 10	150	80*	+ local approved NRTI backbone (TDF is prohibited)
10 to < 15	200	80	
15 to < 25	250	80	

- **Assessments**: Safety, Efficacy, Intensive PK and PK/PD
- **Independent Data Monitoring Committee**

*Ying Hong et al: Model-based Analysis to Propose Atazanavir Doses for HIV-Infected Pediatric Patients; American Conference on Pharmacometrics 2009 Annual Meeting

PRINCE 1: Study Objectives

Primary Objective

- **Safety** of ATV powder formulation with RTV-based regimens in pediatric subjects dosed through 48 weeks, including deaths, SAEs and discontinuation due to AEs

Secondary Objectives

- **Efficacy** as measured by proportion of subjects with virologic response
  - HIV RNA < 50 copies/mL and < 400 copies/mL through Week 48
- **Pharmacokinetic** profile of ATV powder formulation with RTV in pediatric subjects in terms of ATV C_{max}, C_{min} and AUC
  - Intensive PK on all 3 weight bands: 5 < 10kg / 10 < 15kg / 15 < 25kg

Exploratory Objective

- **PK/PD:** Relationship of ATV PK parameters with efficacy and safety endpoints in pediatric subjects (to be conducted at later stage)

Baseline Characteristics

	5-<10kg N=21	10-<15kg N=19	15-<25kg N=16	TOTAL N=56
Age in months, median (min-max)	6 (3-15)	35 (21-54)	55 (34-65)	28.5 (3-65)
Female, n (%)	10 (47.6)	12 (63.2)	6 (37.5)	28 (50)
Region (%)				
Africa	17 (81)	13 (68.4)	8 (50)	38 (67.9)
Asia	0	1 (5.3)	0	1 (1.8)
North America	2 (9.5)	3 (15.8)	4 (25)	9 (16.1)
South America	2 (9.5)	2 (10.5)	4 (25)	8 (14.3)
HIV RNA $\log_{10}$ c/mL, median (min-max)	5 (2.8-5)	5 (4-5)	4.28 (3.1-5)	5 (2.8-5)
HIV RNA > 100,000 c/mL, n (%)	18 (85.7)	10 (52.6)	4 (25)	32 (57.1)
CD4 cells/mm^3, median (min-max)	1814.5 (84-3451)	1002 (46-2172)	668.5 (106-1019)	1004 (46-3451)
CD4 percent categories (%)				
<15	2 (9.5)	2 (10.5)	1 (6.3)	5 (8.9)
15-<25	7 (33.3)	6 (31.6)	4 (25)	17 (30.4)
>=25	7 (33.3)	6 (31.6)	6 (37.5)	19 (33.9)
Not reported	5 (23.8)	5 (26.3)	5 (31.3)	15 (26.8)
ARV experienced	8 (38.1)	7 (36.8)	7 (43.8)	22 (39.3)

Week 48 Subject Disposition

	5-<10kg N=21	10-<15kg N=19	15-<25kg N=16	TOTAL N=56
Treated	21	19	16	56
Completed Stage 1 period (%)	17 (81)	14 (73.7)	15 (93.8)	46 (82.1)
Discontinued before week 48	4 (19)	4 (21.1)	1 (6.3)	9 (16.1)
AEs	4 (19)	1 (5.3)	0	5 (8.9)
Withdrew consent	0	0	1 (6.3)	1 (1.8)
Lack of efficacy	0	2 (10.5)	0	2 (3.6)
Poor/noncompliance	0	1 (5.3)	0	1 (1.8)

Week 48 Efficacy Results

	5-<10kg N=21	10-<15kg N=19	15-<25kg N=14*	TOTAL N=54*
HIV RNA < 50 c/mL (%)				
Modified ITT	10 (47.6)	13 (68.4)	10 (71.4)	33 (61.1)
Observed values	10/17 (58.8)	13/15 (86.7)	10/13 (76.9)	33/45 (73.3)
HIV RNA < 400 c/mL (%)				
Modified ITT	14 (66.7)	14 (73.7)	12 (85.7)	40 (74.1)
Observed values	14/17 (82.4)	14/15 (93.3)	12/13 (92.3)	40/45 (88.9)
Mean (median) CD4 cell count change from BL	550 (491)	225 (274)	374 (363)	397 (363)
Mean (median) CD4 % change from BL	6.1% (6%)	7.3% (7.5%)	8.8% (9.5%)	7% (7.5%)

*2 subjects switched to ATV capsules before Week 48

Week 48 Efficacy Results by Prior ARV Use

	ARV Experienced N=20	ARV Naïve N=34	TOTAL N=54*
HIV RNA < 50 c/mL (%)			
Modified ITT	12 (60)	21 (61.8)	33 (61.1)
Observed values	12/16 (75)	21/29 (72.4)	33/45 (73.3)
HIV RNA < 400 c/mL (%)			
Modified ITT	15 (75)	25 (73.5)	40 (74.1)
Observed values	15/16 (93.8)	25/29 (86.2)	40/45 (88.9)
Mean (median) CD4 cell count change from BL	182 (213)	493 (520)	397 (363)
Mean (median) CD4 % change from BL	3.2% (2.5%)	8.8% (9%)	7% (7.5%)

*2 subjects switched to ATV capsules before Week 48

Resistance data

- By Week 48,
  - 14 subjects met the criteria for virologic failure.
  - 6 (43%) were ARV-experienced and 8 (57%) were ARV-naive.
  - 9 had paired genotypic data (data at baseline and on treatment) and 6 had paired phenotypic data.

- None of the subjects acquired phenotypic resistance to ATV, ATV/RTV, or any NRTI or NNRTI.
- One subject developed phenotypic resistance to saquinavir.
- No subjects developed any major PI substitution to ATV or ATV/RTV.

Safety Results

- **No deaths were reported**
- **SAEs: 11 (20%) subjects had on-treatment SAEs**
  - The only SAE reported in ≥ 2 subjects was herpes zoster (2 subjects [4%])
- **AEs leading to discontinuation: 5 (9%)**
  - 4 in the 5 - < 10 kg group (meningitis, pulmonary TB, increased transaminases, and lymphadenitis =1 subject each)
  - 1 in the 10 - < 15 kg group (ECG QT prolonged = also a SAE)
- **Hyperbilirubinemia-related events: 7 (13%)**
  - 3 subjects in the 5 - < 10 kg group and 2 subjects each in the 10 - < 15 kg and 15 - < 25 kg groups. No DC due to HBR
- **Cardiac disorders: 3 (5%):**
  - 2 considered related to the study therapy (ECG QT prolonged in 1 subject in the 10 - < 15 kg group and first degree AV block in 1 subject in the 15 - < 25 kg group)

Safety Results: Other Significant Events

- **Rash of special interest: 8 (14%), all considered unrelated to study therapy**
- **3 CDC Class C AIDS events: all considered unrelated to study therapy**
  - In Stage 1, 2 subjects (4%) on ATV powder had CDC Class C AIDS events (1 in 5 - <10 kg group had pulmonary tuberculosis and 1 in 10 - < 15 kg group had hepatomegaly)
  - In Stage 2, 1 subject in the 5 - < 10 kg group had a mycobacterium abscess infection.
- **2 (4%) had renal toxicity events: all considered unrelated to study therapy:**
  - Proteinuria in 1 subject in the 5 - < 10 kg group and dysuria in 1 subject in the 10 - < 15 kg group).
- **No lipodystrophy-related events.**
- **7 (13%) had potential lactic acidosis syndrome events: all considered unrelated to study therapy: one was a pre-treatment event.**

Safety Results: Most Common Adverse Events (at least 20% in any group) on ATV Powder Through Week 48

	5-<10kg N=21	10-<15kg N=19	15-<25kg N=16	TOTAL N=56
Total subjects with event (%)	**20 (95.2)**	**18 (94.7)**	**14 (87.5)**	**52 (92.9)**
Infections	**18 (85.7)**	**16 (84.2)**	**12 (75)**	**46 (82.1)**
Upper Resp Tract Infection	11 (52.4)	5 (26.3)	4 (25)	20 (35.7)
Nasopharyngitis	4 (19)	3 (15.8)	5 (31.3)	12 (21.4)
Otitis media	6 (28.6)	3 (15.8)	1 (6.3)	10 (17.9)
Gastrointestinal disorders	**13 (61.9)**	**11 (57.9)**	**8 (50)**	**32 (57.1)**
Diarrhoea	11 (52.4)	6 (31.6)	3 (18.8)	20 (35.7)
Vomiting	6 (28.6)	6 (31.6)	4 (25)	16 (28.6)
Respiratory, Thoracic & mediastinal disorders	**11 (52.4)**	**7 (36.8)**	**7 (43.8)**	**25 (44.6)**
Cough	5 (23.8)	5 (26.3)	4 (25)	14 (25)
Skin & subcutaneous	**14 (66.7)**	**4 (21.1)**	**6 (37.5)**	**24 (42.9)**
Eczema	7 (33.3)	2 (10.5)	1 (6.3)	10 (17.9)
Dermatitis Diaper	6 (28.6)	1 (5.3)	0	7 (12.5)
Blood & Lymphatic system disorders	**9 (42.9)**	**5 (26.3)**	**5 (31.3)**	**19 (33.9)**
Neutropenia	5 (23.8)	1 (5.3)	0	6 (10.7)

Toxicity Grade 3 - 4 Laboratory Abnormalities

Lab Test Description (%)	5-<10kg N=21	10-<15kg N=19	15-<25kg N=16	TOTAL N=56
Hematology				
Hemoglobin	2/20 (10)	3/17 (17.6)	0/15 (0)	5/52 (9.6)
Neutrophils (absolute)	3/20 (15)	2/17 (11.8)	0/15 (0)	5/52 (9.6)
Liver Function Tests				
ALT/SGPT	5/20 (25)	0/18 (0)	1/15 (6.7)	6/53 (11.3)
AST/SGOT	1/20 (5)	0/18 (0)	0/15 (0)	1/53 (1.9)
Total Bilirubin	2/20 (10)	0/18 (0)	3/15 (20)	5/53 (9.4)
Serum Chemistries				
Amylase	8/20 (40)	5/8 (27.8)	1/15 (7)	14/53 (26.4)
Lipase	0/20 (0)	1/18 (5.6)	1/15 (6.7)	2/53 (3.8)

Amylase = Most common Grade 3 - 4 laboratory abnormality, but all subjects with Grade 3 - 4 amylase had normal pancreatic amylase.

PRINCE 1

Summary of 48 Week efficacy & safety results:

- ATV powder/RTV + 2 NRTIs was generally safe and well tolerated across all 3 weight bands
- Viral suppression and immunologic efficacy was observed with ATV powder/RTV + 2 NRTIs across all 3 weight bands in treatment-naive and treatment-experienced subjects
- None of the subjects who underwent resistance testing for virologic failure or discontinuation from the study acquired phenotypic resistance to ATV, ATV/RTV, or any NRTI or NNRTI

BMS Pediatric ATV powder program: PRINCE 1&2

- PRINCE 2: ATV powder in 3 months to <11years (n=95); recruiting
- PRINCE 1 & 2 studies combined Dataset Analyses: ~ 150 subjects (PK, safety, efficacy)

Acknowledgements

- **The patients and their families for their participation and commitment during the study**

- **The investigators and co-investigators:**

Brazil: Marinella Della Negra, Roberio Carneiro, Yu Lian, Denise Pacola, Wladimir Queiroz

Chile: Maria Isabel Galaz, Carmen Navarrete, Anamaria Pena Donati, Marcela Rabello, Tamara Viviani Salgado,

Mexico: Alma Perez Rios, Liliana Castro,Karla De La Torre, Rafael Diaz, Martha Espinoza, Julia Gonzalez, Rocio Sandoval, Pedro Martinez Arce, Martin Guerrero, Antonio Luevanos, Monica Mercado, Noris Pavia Ruz, Jorge Gamboa, Dulce Maria Morales, Karla Ojeda, Indiana Torres Escobar, Ana Maria Espinoza, Concepcion Arias Cruz, Blanca Ramos, Cesar Zarate, Aldolfo Palma Chan, Luis Basso

Peru: Francisco Campos, Aguirre, Ildauro, Lenka Kolevic, Carlos Mora

South Africa: Mark Cotton, Emma Kalk, Emma Krzesinski, Susan Purchase, Alison Riddick, Magdel Rossouw, Magdel, Mercia Van Der Linde, Raziya Bobat, , Moherndran Archary, Sajeeda Mawlana, Ashraf Hassen Coovadia, Leigh Martens, Julia Maisel, Faeezah Patel, Francoise Pinillos Saer, Gillian Sorour, Renate Strehlau, Afaaf Liberty, Haseena Cassim, Masebole Masenya, Hillary Mukudu, Avy Violari, Lizelle Keet, A Van Der Vyver, Riana Van Zyl

Thailand: Jintanat Ananworanich, Torsak Bunupuradah, Wasana Prasitsuebsai, Thanyawee Puthanakit, Kulkanya Chokephaibulkit, Thition Narkbunnam, Wanatpreeya Phongsamart, Naphatsara Sawawiboon, Sirinthip Sricharoenchai, Nirun Vanprapar, Orasri Wittawatmongkol

- **The Data Monitoring Committee for providing oversight of safety and efficacy considerations in the study**

- **This BMS-supported study is also known as Study AI424397 and is registered with ClinicalTrials.gov, number NCT01099579.**

- **Professional medical writing and editorial assistance was provided by Emily Cullinan, an employee of Bristol-Myers Squibb**