



# Kaletra™ (ABT-378/ritonavir) in HIV-Infected Children at 60 Weeks

X. Saez-Llorens<sup>1\*</sup>, C. Renz<sup>11</sup>, C. Deetz<sup>11</sup>, P. Jiang<sup>11</sup>, P. Cahn<sup>2</sup>, A. Violari<sup>3</sup>, P. Gomez<sup>4</sup>, E. Handelsman<sup>5</sup>, S. Pelton<sup>6</sup>, O. Ramilo<sup>7</sup>, E. Chadwick<sup>8</sup>, S. Arpad<sup>9</sup>, U. Allen<sup>10</sup>, D. Kempf<sup>11</sup>, R. Bertz<sup>11</sup>, E. Sun<sup>11</sup>

<sup>1</sup>Hosp. del Nino, Panama City, Panama, <sup>2</sup>Fundacion Huesped, Buenos Aires, Argentina, <sup>3</sup>Baragwanath Hosp., Johannesburg, South Africa, <sup>4</sup>Princess Margaret, Nassau, Bahamas, <sup>5</sup>Univ. Hosp. of Brooklyn, Brooklyn, NY, <sup>6</sup>Maxwell Finland Lab, Boston, MA, <sup>7</sup>Univ. of Texas Southwestern Med. Ctr., Dallas, TX, <sup>8</sup>Children's Mem. Hosp., Chicago, IL, <sup>9</sup>St. Luke's Roosevelt Hosp. Ctr., NYC, NY, <sup>10</sup>Hosp. for Sick Children, Toronto, Ontario, and <sup>11</sup>Abbott Laboratories

## BACKGROUND

Kaletra (formerly known as ABT-378/r, lopinavir/ritonavir) is a novel HIV protease inhibitor (PI) that has shown significant antiviral activity and tolerability in clinical trials to date. Lopinavir is co-formulated with ritonavir, an inhibitor of cytochrome P450 3A. It is uniquely sensitive to pharmacokinetic enhancement by ritonavir, resulting in substantially increased lopinavir drug exposure, even at low ritonavir doses. At the dosage selected for phase III clinical trials in adults, 400 mg lopinavir/100 mg ritonavir BID capsules, ritonavir concentrations are below those required for antiviral activity.<sup>1</sup> The efficacy and safety of Kaletra are currently being studied in HIV-infected adult patients, both antiretroviral-naïve and PI-experienced. Study M98-940 is a Phase III, open-label study of cotormulated Kaletra (liquid) at two doses in combination with reverse transcriptase inhibitors in treatment-naïve and -experienced pediatric subjects.

## METHODS

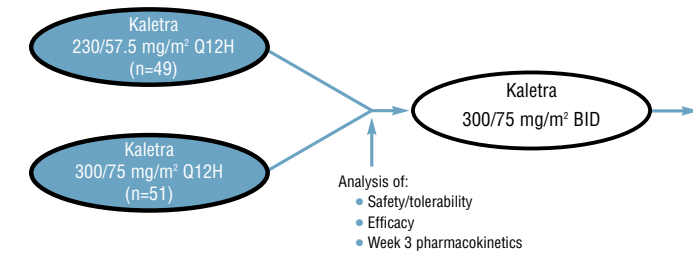
Evaluate the safety, tolerability and antiviral activity of Kaletra (liquid formulation) in HIV-infected children.

### Entry Criteria

- Age: between 3 months and 12 years
- Plasma HIV RNA >400 copies/mL
- No prior NNRTI therapy

### Study Design and Analysis

- One hundred antiretroviral-naïve and -experienced pediatric subjects were randomized to receive one of two dosage levels of Kaletra (230/57.5 mg/m<sup>2</sup> Q12H or 300/75 mg/m<sup>2</sup> Q12H) selected to approximate the adult drug exposure at 400/100 mg BID.
- Subjects were defined as antiretroviral-naïve if they had received ≤3 months of prior antiretroviral therapy or ≤1 week of treatment with 3TC. Subjects were defined as antiretroviral-experienced if they received >3 months of prior antiretroviral therapy or >1 week of treatment with 3TC.
- In addition to Kaletra, naïve subjects received treatment with d4T and 3TC and experienced subjects received treatment with nevirapine and 1 or 2 NRTIs of the investigator's choice.
- All subjects were switched to a dose of Kaletra 300/75 mg/m<sup>2</sup> following an analysis of safety/tolerability, efficacy and Week 3 pharmacokinetics.



## RESULTS

**Table 1. Baseline Characteristics**

	Naïve (n=44)	Experienced (n=56)
<b>HIV RNA (log<sub>10</sub> copies/mL)</b>		
Mean*	4.9	4.5
Range	2.6-7.0	2.7-5.8
<b>CD<sub>4</sub> cell count (cells/mm<sup>3</sup> [%])</b>		
Mean	920 [21.6]*	773 [26.3]*
Range	40-3340 [2-38]	15-2995 [1-48]
<b>Immunologic Categories**</b>		
I. No evidence of suppression	50%	73%
II. Evidence of moderate suppression	39%	14%
III. Severe suppression	11%	13%

\* p<0.05  
\*\* CDC 1994 revised classification system in children under 13 years of age. MMWR 1994;43:4.

### Treatment Experience and Pharmacokinetics

- Of the 56 experienced subjects enrolled, 32 were NRTI experienced and 24 were protease inhibitor and NRTI experienced.
- 88% of the PI experienced subjects had received ritonavir (standard dose) and 29% had received multiple PIs.
- There was no statistically significant effect of age on the pharmacokinetic parameters of lopinavir. From the analysis of covariance (ANCOVA) for age effect p=0.2 for AUC and p=0.7 for C<sub>rough</sub>.

### Subject Disposition

- Of the 100 subjects enrolled in the study, two subjects had discontinued as of Week 60 (Table 2).

### Safety

- There were few adverse events of at least moderate severity and of probable or possible relationship to study drug or grade 3/4 laboratory abnormalities at 60 weeks (Tables 3 and 4).

**Table 2. Subject Disposition at Week 60**

Subjects enrolled	100
Subjects discontinued at/before Week 60	2
Reason for discontinuation:	
* Related to study drugs (pancreatitis)	1
HIV-related event (Burkitt's Lymphoma)	1

\* Pancreatitis: subject had baseline history of elevated amylase.

**Table 3. Laboratory Abnormalities Grade 3 or 4**

Laboratory Parameter	n
Sodium (<130 mEq/L)	3
Neutrophil count (<0.40 x 10 <sup>9</sup> /L)	2
Platelet count (<50 x 10 <sup>9</sup> /L)	4
Total bilirubin (>2.9 x ULN)	3
SGOT (AST) (>10 x ULN)	2
SGPT (ALT) (>10 x ULN)	3
Total cholesterol (>300 mg/dL)	3
Triglyceride (>750 mg/dL)	1
Sodium (>149 mEq/L)	3
Amylase (>2.5 x ULN)	6
Pancreatic Amylase (>2 x ULN)	1

Note: Experienced by 2 or more subjects except Pancreatic Amylase and Triglyceride.

**Table 4. Adverse Events\***

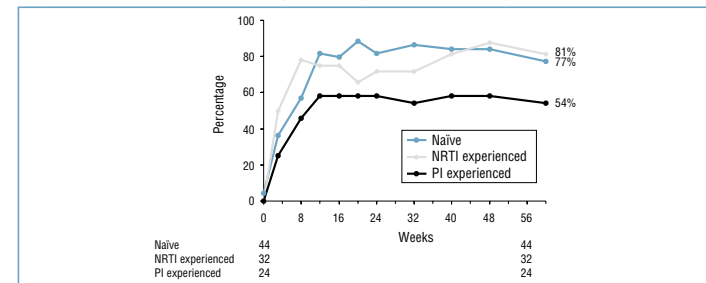
	n		n
<b>Body as a Whole</b>		<b>Metabolic and Nutritional</b>	
Allergic reaction	1	SGPT increased	1
Fever	1	<b>Skin</b>	
Viral infection	1	Dry skin	1
<b>Digestive System</b>		Rash	2
Constipation	1	<b>Special Senses</b>	
Hepatomegaly	1	Taste perversion	1
Pancreatitis	1		
Vomiting	1		

\* Adverse events of at least moderate severity and probable, possible, or unknown relationship to Kaletra.

### Viral Load Suppression to <400 Copies/mL at 60 Weeks

- The proportion of subjects with viral load less than 400 (less than 50) copies at Week 60 was 77% (68%) for naïve subjects and 70% (61%) for experienced subjects by the Intent-to-Treat method of analysis.
- In general, the proportion of subjects below 400 copies was higher in the naïve group than in the PI-experienced group beginning at Week 12 and beyond (Figure 3).

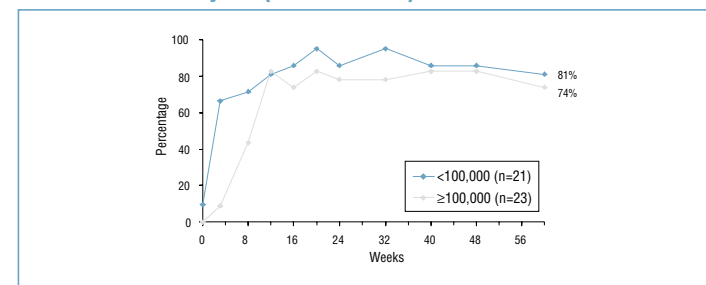
**Figure 3. HIV RNA <400 Copies/mL (Intent-to-Treat)**



**Table 5. Assessment of HIV RNA Levels (log copies/mL)**

	At 24 Weeks		At 48 Weeks		At 60 Weeks	
	<400 at Week 24	>400 at Week 24	<400 at Week 48	>400 at Week 48	<400 at Week 60	>400 at Week 60
Naïve	36/44	-1.85 (n=8)	37/43	-1.60 (n=6)	34/43	-1.81 (n=9)
All experienced	37/55	-0.96 (n=18)	42/55	-0.64 (n=13)	39/55	-0.57 (n=16)

**Figure 4. HIV RNA <400 Copies/mL Stratified by RNA Level at Baseline in Naïve Subjects (Intent-to-Treat)**



### Incidence of Resistance in Experienced Subjects

- Baseline resistance data was available for 20 of 24 subjects in PI-experienced subjects. Of these, 1 of 3 subjects with >10-fold and 10 of 17 subjects with <10-fold reduced baseline susceptibility (by phenotypic assay) to Kaletra had HIV RNA <400 copies/mL at Week 60.

### Incidence of Resistance in Naïve Subjects

- Plasma viral isolates from 10 treatment-naïve subjects with HIV RNA >400 copies/mL at Weeks 24 or 48 were examined for evidence of resistance (Table 6).
- Resistance to Kaletra was defined as any primary or active site mutation.

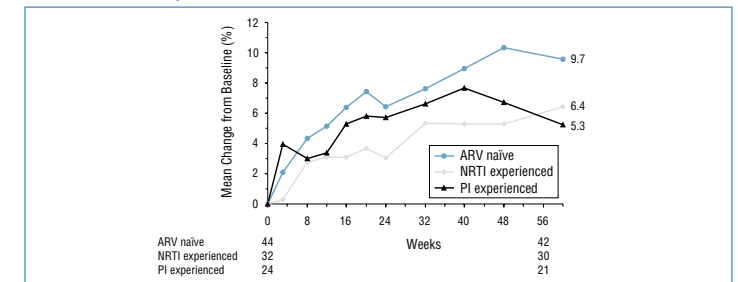
**Table 6. Resistance Through Week 48 for Treatment-Naïve Subjects**

	Kaletra
HIV RNA >400 copies/mL	10
Genotype available	5
Resistance detected in protease	0

### CD<sub>4</sub> Response

- Mean CD<sub>4</sub> cell count increase from baseline was 404 cells for naïve subjects and 238 cells for experienced subjects by Week 60.

**Figure 5. % CD<sub>4</sub> Response**



## CONCLUSIONS

- The liquid formulation of Kaletra was well tolerated by HIV-infected children with only one discontinuation related to study drugs through 60 weeks.
- There were few adverse events of at least moderate severity and of probable or possible relationship to study drugs or grade 3/4 laboratory abnormalities at 60 weeks.
- Kaletra demonstrated excellent antiviral activity with 77% of treatment-naïve subjects and 70% of treatment-experienced subjects <400 copies/mL HIV RNA at Week 60 by an Intent-to-Treat Analysis.

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Genotype and Phenotype testing was performed by ViroLogic, Inc.

## REFERENCE

1. Bertz R, Lam W, Brun S, et al. Multiple-dose pharmacokinetics (PK) of ABT-378/ritonavir (Kaletra) in HIV+ subjects. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, USA, 1999, (abstract 0327).