



# PENTA 15

## **Once-daily abacavir and lamivudine as part of combination antiretroviral therapy to 48 weeks in HIV-1 infected children aged 3 to 36 months**

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on behalf of the PENTA 15 Trial Steering Committee

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# Background

- A once-daily dosing regimen of ABC and 3TC is approved for adults
- Reduce barriers to good adherence for children
  - decrease the frequency medication needs to be taken to once a day
- PENTA 13
  - HIV infected children aged 2-12 years
  - ABC and 3TC once daily non-inferior to twice daily in terms of PK profiles
  - However, only 3 children under 3 years
  - Concerns about higher clearance and lower AUC for 3TC in the younger children



# PENTA 15 Trial Design

- HIV infected children aged 3-36 months
- HIV RNA suppressed, or non-suppressed but low
- Stable or rising CD4%

On combination ART for 12 weeks including  
**ABC 8mg/kg ± 3TC 4mg/kg twice-daily**

Week 0: PK samples collected

Children switched to  
**ABC 16mg/kg ± 3TC 8mg/kg once-daily**

Week 4: PK samples repeated

Children remain on once-daily ABC ± 3TC  
to assess safety and efficacy to week 48



# PENTA 15 Objectives

## Primary objective:

- To compare plasma PK parameters of once-versus twice-daily dosing of ABC and 3TC

## Secondary objectives:

- To compare PK parameters in 3 age groups: 3-12, 12-24 and 24-36 months
- To describe acceptability of and adherence to once- compared to twice-daily dosage regimens



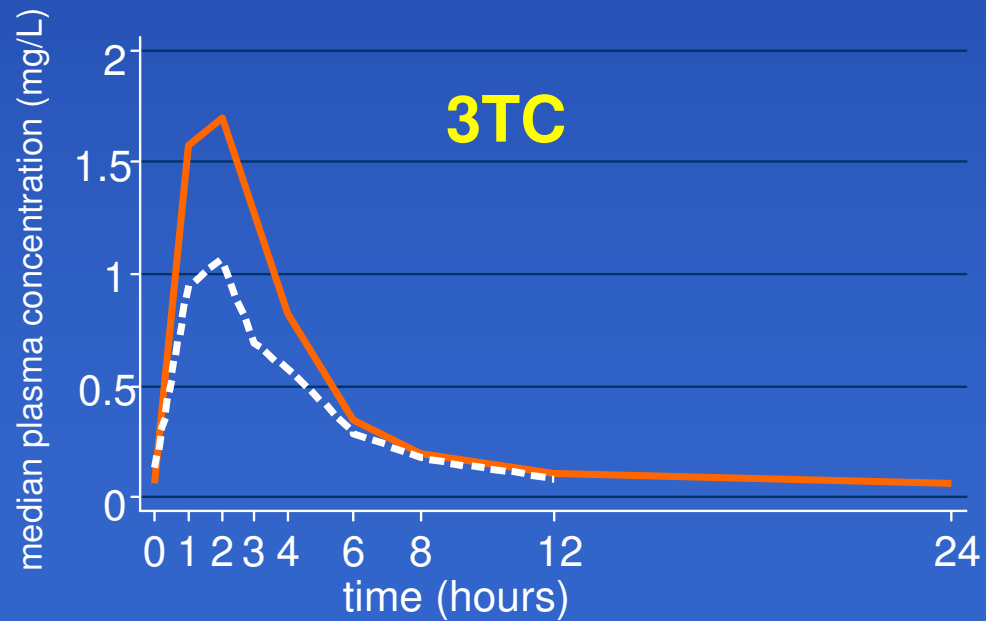
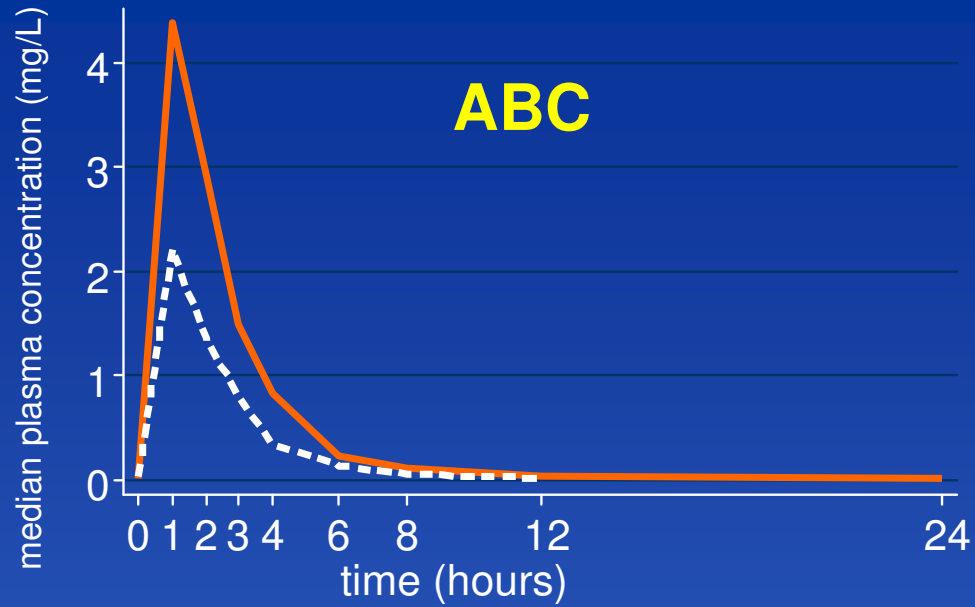
# Baseline Characteristics

<b>Evaluable children</b>	<b>Total=18 (3TC n=17)</b>
<b>Age (months):</b> 3-12 / 12-24 / 24-36	4 / 6 / 8
<b>Gender:</b> male / female	10 / 8
<b>Body weight (kg):</b> median [IQR]	11.3 [10.3-13.0]
<b>Ethnic origin:</b> white / black / mixed	3 / 14 / 1
<b>CDC stage:</b> N / A / B / C	7 / 3 / 1 / 7
<b>ART combination:</b>	
3TC, ABC, NVP (± ZDV or ± D4T)	10
3TC, ABC, LPV/r (± ZDV)	7
FTC, ABC, LPV/r	1



-----  
twice daily

-----  
once daily





# PK Parameters

	<b>N</b>	<b>GM</b> twice daily	<b>GM</b> once daily	<b>GMR</b> once vs twice (90% CI)
<b>ABC</b>				
AUC <sub>0-24</sub> (h*mg/L)	18	10.85	11.57	<b>1.07 (0.92,1.23)</b>
C <sub>max</sub> (mg/L)	17	2.29	4.68	2.04 (1.73,2.42)
<b>3TC</b>				
AUC <sub>0-24</sub> (h*mg/L)	17	9.48	8.66	<b>0.91 (0.79,1.06)</b>
C <sub>max</sub> (mg/L)	16	1.05	1.87	1.78 (1.52,2.09)

Bioequivalence range:  
90% CI within **(0.80,1.25)**



# Age related differences

- No clear age related differences for either drug
- Of importance, unlike PENTA 13, high clearance and low  $AUC_{0-24}$  was not observed for 3TC in this young group of children

		<b>N</b>	<b>GM</b> twice daily	<b>GM</b> once daily
<b>Clearance</b>	<b>PENTA 15</b>	17	0.79	0.86
	<b>PENTA 13</b>	<b>19</b>	<b>0.90</b>	<b>0.80</b>
	2-6 years	10	1.09	0.92
	6-13 years	9	0.73	0.69
<b>AUC<sub>0-24</sub></b>	<b>PENTA 15</b>	17	9.48	8.66
	<b>PENTA 13</b>	<b>19</b>	<b>8.88</b>	<b>9.80</b>
	2-6 years	10	7.60	8.80
	6-13 years	9	10.55	11.04





# Follow-up and ART

- All 18 children followed to 48 weeks
- Only 1 child switched back to twice-daily ABC/3TC
  - at week 16 due to an increased HIV RNA and adherence concerns

week: screening	4	8	13	16	22	26	31	43	53	56	
	<100	<50	=72	=52	<50	=84	=83	<50	<50	<50	=52

- 3 children dropped ZDV from ABC, 3TC, NVP, ZDV
- 5 children switched to once-daily NVP or LPV/r
  - 1 subsequently switched back to twice-daily
- 5 children experienced taking all their ART drugs once-daily



# Efficacy

Week	HIV RNA <400 c/ml	
screening	89%	(16/18)
4	93%	(14/15)
8	93%	(14/15)
12	94%	(16/17)
24	100%	(18/18)
48	89%	(16/18)

And, proportions <50 c/ml remained stable over time

- No indication of decreasing CD4 count or %
- No major mutations associated with resistance were detected to week 12



# Safety

- 5 serious adverse events reported in 4 children (not related to ART)
  - croup
  - scalp laceration
  - bacterial gastroenteritis
  - diarrhoea with persistent vomiting
- Grade 2 adverse events reported
  - 1 diarrhoea with vomiting of medication
  - 1 febrile convulsion
- No new CDC B and C events
- Increased toxicity due to elevated peak levels was not observed



# Carer Adherence and Acceptability

- Adherence - visual analogue scale



- 71% (week 0), 80% (week 4) and 69% (week 12) of carers marked at 100%

- Adherence – missed doses in last 3 days

- Week 0: 1 child missed a 3TC dose yesterday, 1 child missed a ABC, 3TC and LPV/r dose 2 days ago
- Week 4 and 12 no doses missed reported

- Acceptability - week 0

- switching to once daily would make things easier: 15 (83%) a lot, 3 (17%) a little

- Acceptability - week 12

- the switch made things easier: 11 (69%) a lot, 5 (31%) a little



# PENTA 15 Summary

- In HIV-infected children aged 3-36 months
  - Bioequivalent  $AUC_{0-24}$  on once and twice daily ABC
  - Very similar  $AUC_{0-24}$  on once and twice daily 3TC
- no evidence of loss of efficacy and no safety concerns on once-daily in this small group of children



# Discussion

- **ARROW PK substudy (poster P\_11)**
  - 36 children aged 3-12 years on ABC, 35 on 3TC
  - $AUC_{0-24}$  bioequivalent on once and twice daily
- **PENTA 13, PENTA 15 and ARROW show similar AUCs on once and twice daily ABC/3TC**
  - Low concentrations of 3TC were not observed in PENTA 15
  - But, currently limited safety and efficacy data
  - Planned randomisation within ARROW of 1000 children to once vs twice daily
- **Overall, once-daily ABC and 3TC may be an option for children and help to improve adherence**



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