KONCERT

Kaletra (ALUVIA) **ONCE** daily
Randomised **T**rial of PK, safety & efficacy of
QD v BID lopinavir/ritonavir tablets (PENTA 18)

August 2010 - August 2013

Hermione Lyall on behalf of PENTA
(Paediatric European Network for the Treatment of AIDS)

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BACKGROUND

Challenge to simplify adherence to medication

- Adolescents taking more self responsibility
- children who rely on caregivers

Decreasing frequency of dosing

- increase convenience
- enhance adherence

DESIGN AND METHODS

Study hypothesis: QD dosing is as efficacious as BID dosing

Phase II/III randomised, open-label, multi-center, non-inferiority trial

Population: HIV-1 positive, <18 yrs, ≥15kg, on lopinavir/r, and HIV-1 RNA <50c/ml for >24 weeks, no previous rebound on a PI

Primary outcome: Time to confirmed HIV-1 RNA ≥50 copies/ml

Pre-defined non-inferiority margin: 12% for the rebound rate of QD v BID by week 48 (estimated by Kaplan-Meier methods) in the ITT analysis

Secondary outcomes:

- Time to confirmed HIV-1 RNA ≥400 copies/ml
- Change in CD4%
- Grade 3 or 4 clinical & lab adverse events
- New major HIV-1 mutations
- Adherence/acceptability

Within-patient PK sub-study comparison of QD/BID dosing of lopinavir/r

ENROLLMENT

173 children aged <18 years, weight ≥15 kg
Europe (46%), **Thailand** (34%), **South America** (20%)

↓

Week -4 to -2: Screening visit
All children HIV < 50 copies / ml

↓

Week 0: Randomisation (stratified by weight band)
(1:1) to QD or continue BID lopinavir/r
First 53 children baseline full PK - BID

↙ ↘

Week 4
86 children on QD
26 children 2nd full PK - QD

Week 4
87 children on BID

↘ ↙

Follow-up
at week 8, then 12 weekly
If VL ≥ 50c/ml retest to confirm, within 4 weeks

BASELINE CHARACTERISTICS

Median age [range]: 11.0 [3.8, 17.7] yrs (3-7yrs 18%; 8-12yrs 43%; 13<18yrs 39%)

Ethnicity: 35% Thai, 27% Black (African/other), 25% White, 6% mixed B/W, 6% other

		QD	BID
No. of patients		N=86	N=87
CD4% median [range]		32 [17, 50]	34 [14, 53]
CD4 <30%		34 (40%)	28 (33%)
CD4 ≥30% to <40%		42 (49%)	37 (43%)
CD4 ≥40%		9 (11%)	21 (24%)
Viral load (HIV-1 RNA)			
≥50 c/mL at randomisation		12 (14%)	4 (5%)
≥50 c/ml confirmed at 4 weeks		5	0
VL : median [range]		*120 [51, 91201]*	*134.5 [57, 270]*
Baseline ART, 1st regime		18 (21%)	17 (20%)
Exposed to 3 classes of ART		41 (48%)	46 (53%)
NRTI backbone	**AZT + 3TC/FTC**	34 (40%)	43 (49%)
	ABC + 3TC/FTC	19 (22%)	15 (17%)
	Any NRTI + TDF	15 (17%)	14 (16%)
	other combos	18 (21%)	15 (17%)

WITHIN PATIENT LOPINAVIR PK RESULTS

	BID (baseline) geometric mean (95% CI) N=26	QD (4 weeks) geometric mean (95% CI) N=26	QD / BID geom. mean ratio (90% CI) N=26	Adult data (SPC) mean (SD) N=24	KONCERT mean (SD) N=26
AUC_{0-24} (h*mg/L)	223.9 (194.8, 257.4)	160.9 (138.4, 187.0)	**0.72 (0.61, 0.85)**	154.1 (61.4)	171.5 (60.2)
C_{max} (mg/L)	12.5 (11.1, 14.0)	14.0 (12.7, 15.6)	**1.13 (0.99, 1.28)**	11.8 (3.7)	14.5 (1.9)
C_{last} (mg/L)	5.69 (4.58, 7.07)	1.03 (0.61, 1.75)	**0.18 (0.11, 0.29)**	3.2 (2.1)	1.94 (1.89)
Clearance/ F (L/(h*kg))	0.084 (0.074, 0.096)	0.115 (0.099, 0.134)	**1.37 (1.16, 1.61)**		

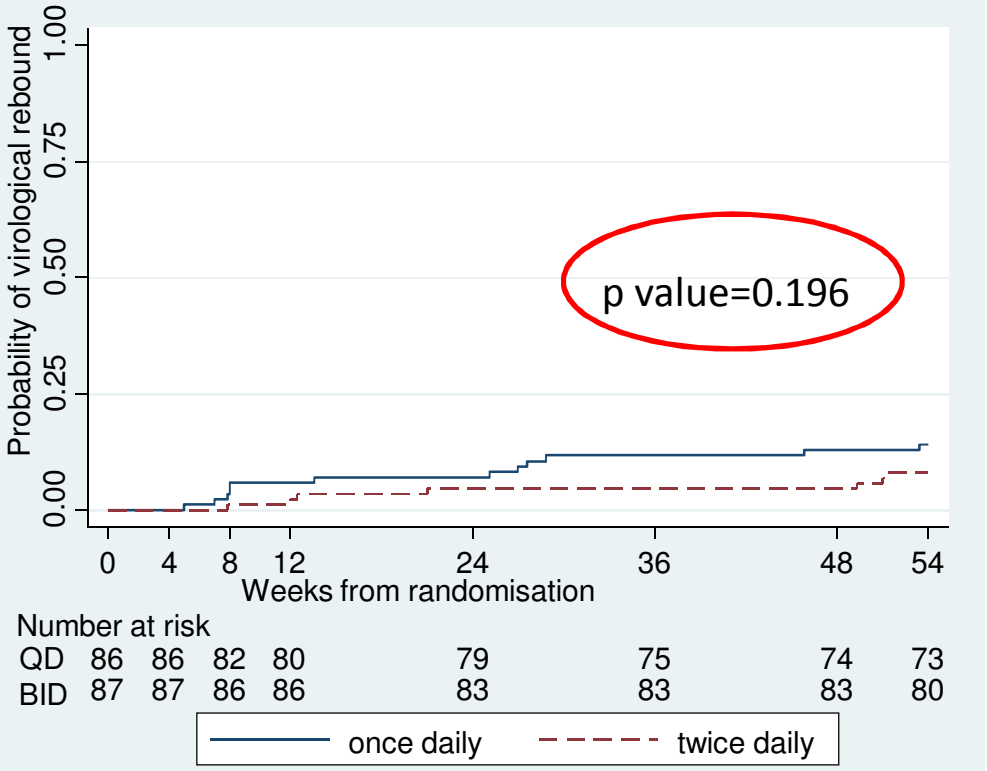
PK sub-study and subsequent viral rebound:

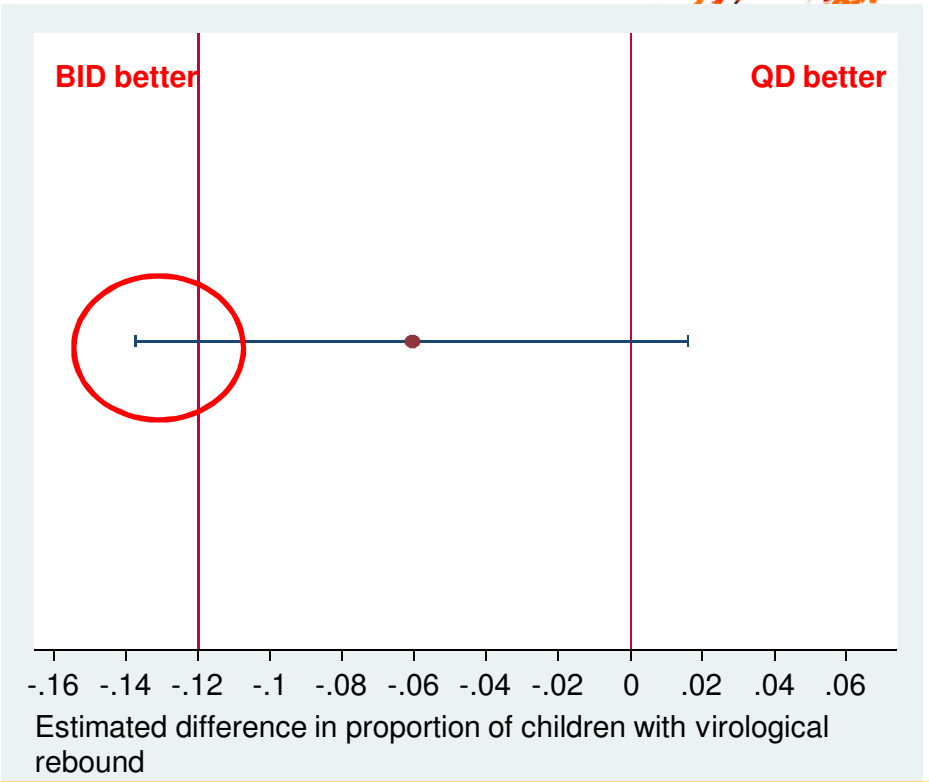
One child on BID → trough Lopinavir level – 6.4 mg/L

One child on QD → trough Lopinavir level – 2.1 mg/L

PRIMARY ENDPOINT: HIV ≥50 at 48 weeks

Difference in time to rebound (BID – QD) – 6%, 90% CI (-14% to 2%)

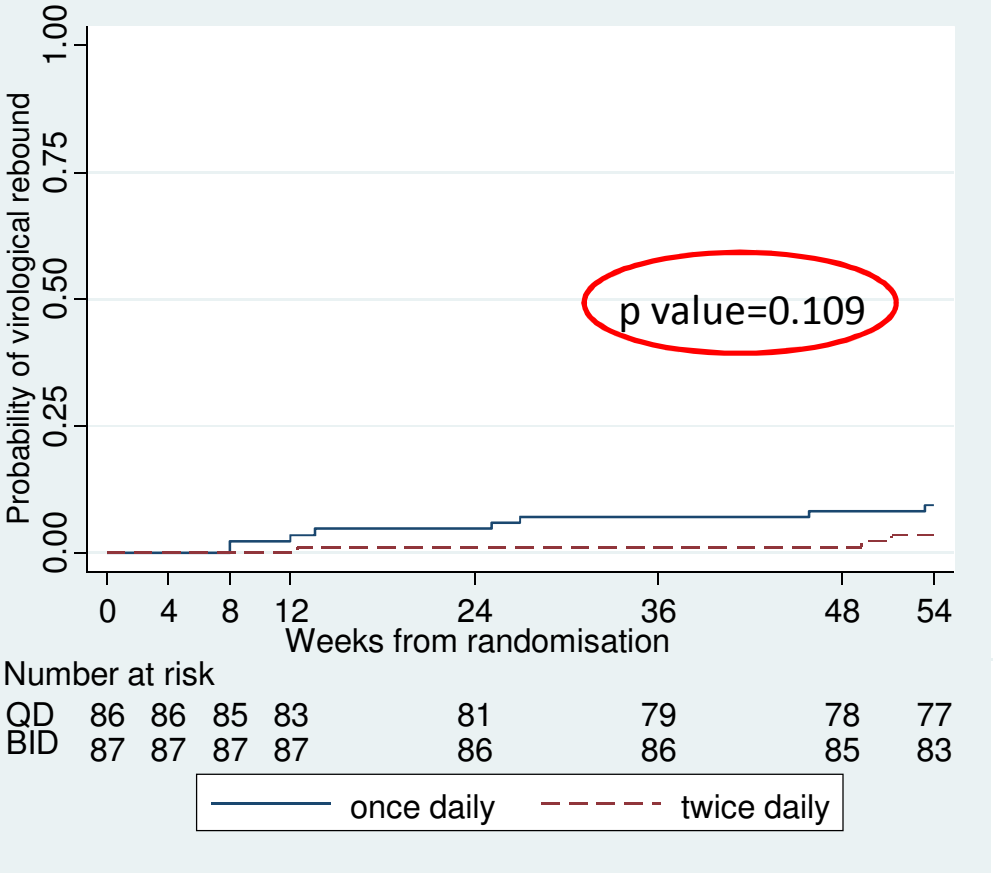


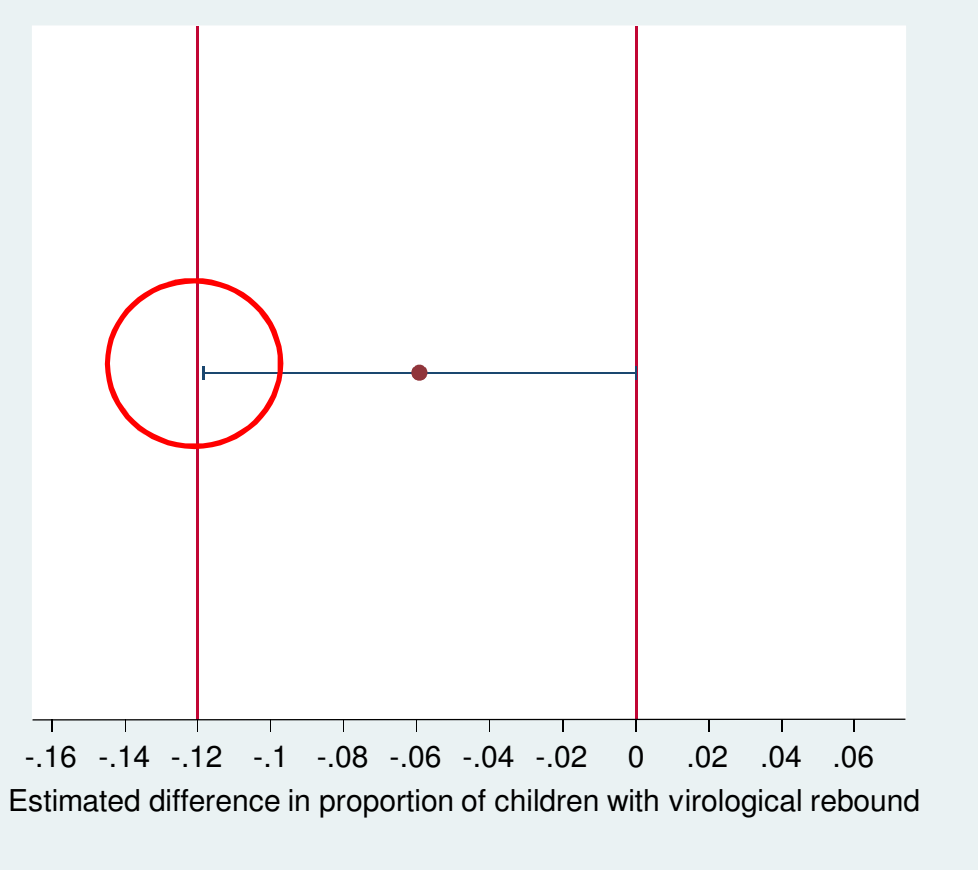


Week 48 assessment				
		Number of events	Estimated probability of VL rebound	(90% CI)
BID	7	87.02	0.080	(0.044, 0.145)
QD	12	80.84	0.141	(0.090, 0.217)
		Difference (BID - QD)	-0.061	(-0.136, 0.015)

SECONDARY ENDPOINT: HIV ≥400 at 48 weeks

Difference in time to rebound (BID – QD) – 6%, 90% CI (-12% to 0%)





Week 48 assessment				
	Number of events	Person years at risk	Estimated probability of VL rebound	(90% CI)
BID	3	89.06	0.035	(0.014, 0.087)
QD	8	83.75	0.094	(0.054, 0.162)
	Difference (BID - QD)		-0.059	(-0.119, -0.000)

SECONDARY ENDPOINT: VIRAL REBOUND & RESISTANCE

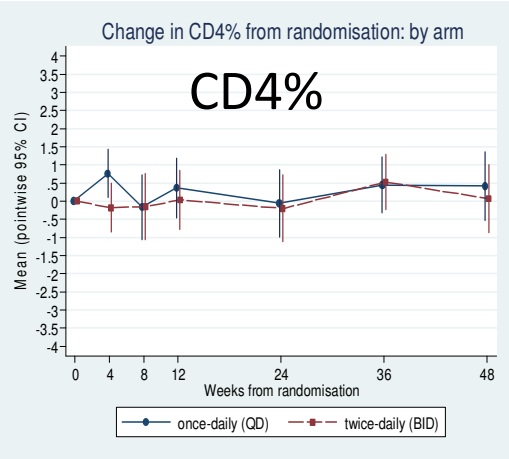
Patients with viral rebound (overall 11%)	QD	BID
VL ≥50 copies/ml at any point up to 48 week	12	7
Remained on same dosing regime	9	6
Re-suppressed	7	4
Switched back to BID	1	-
Break in treatment	1	0
Changed to another regimen	1	1

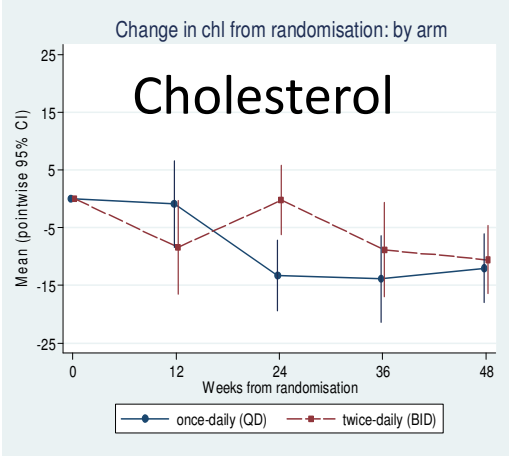
5 patients (3QD , 2 BID) with “new” in- trial major mutations

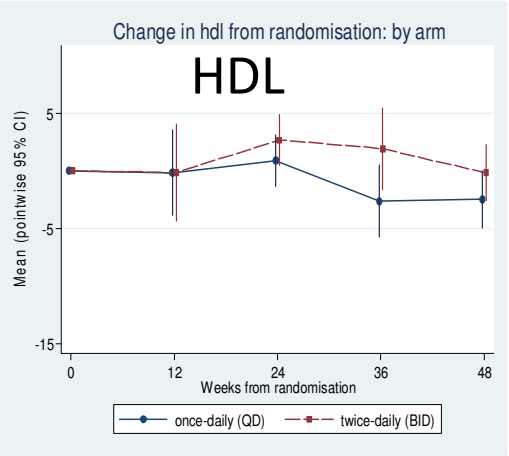
Arm	New mutations in-trial	Mutations pre-trial	ART Exposure: Baseline (pre trial)
QD	L101I	V75A, Y181I, M184V	**ZDV + ddI + LPV/r** (3TC, d4T, NVP)
QD	L74V	No previous test	**DDI + TDF + LPV/r** (ZDV, 3TC, D4T, ABC)
QD	**M184V**	No previous test	**ZDV + 3TC + LPV/r**
BID	D67N, K70R, **M46I, V82A**	M184V, V106M	**ZDV + TDF + LPV/r** (3TC, ABC, EFV)
BID	**M184V**, **L90M**	No previous test	**ZDV + 3TC + LPV/r** (DDI, D4T, NFV)

Further SECONDARY ENDPOINTS TO 48 WEEKS

No significant difference in change in **CD4** or **metabolic parameters**







Acceptability questionnaires → strong preference for QD dosing (baseline & end study)

- 84% of children/carers said they preferred QD to BID

Adherence questionnaires → no significant difference between arms

- 9% (QD) and 7% (BID) children/carers reported missing a dose within **3** days of a clinic visit (p=0.206)

CLINICAL EVENTS & SAFETY TO 48 WEEKS

No deaths or new CDC stage C events

3 new stage B events (all QD - pneumonia, herpes zoster, sepsis & cholecystitis)

	QD		BID		p value
	episodes	(children)	episodes	(children)	
Total AEs	273	(73)	232	(76)	0.91*
Grade 1 and 2 AEs	255	(71)	221	(76)	0.82*
Grade 3 and 4 AEs	18	(10)	11	(7)	0.61*
AEs leading to treatment modification	4	(2)	1	(1)	1*
SAEs	9	(8)	6	(6)	0.78*
SAE rate per hundred person years (95% CI)	0.10	(0.05, 0.19)	0.07	(0.03, 0.15)	0.57**

*Fisher's exact test

**p value from Poisson regression model

All SAEs were hospitalisations - one with diarrhoea, ***POSSIBLY*** related to lopinavir/r

2 QD changed back to BID because of AEs, at weeks 1 & 8 (GI related)

KONCERT SUMMARY & CONCLUSIONS

Non-inferiority was not demonstrated for maintaining VL <50c/ml on QD v BID

→ **KONCERT results do not support routine use of QD lopinavir/r for simplification**

- However , there were chance baseline imbalances in viral rebound & CD4%
- Adjusted analysis – difference in time to rebound (BID – QD) – 4%, 90% CI (-11% to 4%)

But - this is a "forgiving" boosted PI regimen →

- 86% on QD & 92% on BID remained virologically suppressed
- 7 of 9 with viral rebound on QD re-suppressed
- No child on QD developed new major PI mutations (one new M184V)

Within-Patient PK → QD resulted in lower daily lopinavir/r exposure, & trough levels

- What is the role of dosing versus adherence in viral rebound?
- Further "sparse" PK studies from full cohort underway

Thank-you very much for listening, any questions?