

KONCERT (PENTA 18) Trial

A Kaletra ONCE daily Randomised Trial of the pharmacokinetics, safety and efficacy of twice-daily versus once-daily lopinavir/ritonavir tablets dosed by weight as part of combination antiretroviral therapy in HIV-1 infected children (PENTA 18).

1.1 Aims and Objectives

The trial will evaluate the pharmacokinetics, safety, efficacy and acceptability of twice- and once-daily dosing of lopinavir/ritonavir tablets (Kaletra) dosed by weight in HIV-1 infected children who are currently taking lopinavir/ritonavir as part of their combination antiretroviral therapy and who are currently achieving virological suppression (<50 copies/ml). Specifically:

- To confirm weight-based dosing recommendations by evaluating the pharmacokinetics of twice-daily lopinavir/ritonavir half strength formulation tablets dosed on body weight and comparing to historical adult and paediatric data of pharmacokinetics of lopinavir/ritonavir soft gel capsules and oral solution respectively.
- To compare the pharmacokinetics of twice-daily lopinavir/ritonavir tablets with once-daily dosing in the same children.
- To evaluate whether once-daily dosing of lopinavir/ritonavir is comparable to twice-daily dosing in terms of virological suppression at 48 weeks. Adherence and acceptability will also be compared.

1.2 Design

KONCERT is a prospective, open label, multicentre, randomised (1:1) phase II/III trial. Children will be randomised (1:1) either to continue the same HAART regimen with lopinavir/ritonavir tablets taken twice-daily or to continue the current HAART regimen but switch to lopinavir/ritonavir tablets dosed once-daily. Randomisation will be stratified by body weight band (≥ 15 to ≤ 25 kg, > 25 to ≤ 35 kg, > 35 kg). Children will be followed for a minimum 48 weeks.

Once-daily dosing of lopinavir/ritonavir will be the same total daily dose as twice-daily dosing but lopinavir/ritonavir will only have to be taken at one time during the day.

A pharmacokinetic (PK) study will be performed on a minimum of the first 16 children enrolled in each of the three body weight bands; a minimum total of 48 children. Children enrolled in the PK study will have lopinavir and ritonavir pharmacokinetics determined on twice-daily dosing before randomisation. Only if randomised to once-daily dosing, children will have a second pharmacokinetic assessment of lopinavir and ritonavir at 4 weeks. If a child in the PK study does not have full evaluable PK data, further children will be recruited to the PK part of the

trial from the relevant body weight band as replacements. Children with non-evaluative PK data will still continue to be followed in their randomised arm.

The non-inferiority design of the randomised part of the trial requires 160 children to be enrolled (80 in each arm) in order to exclude differences of 12% in the percentage of children maintaining HIV-1 RNA <50 copies/ml to 48 weeks between once-daily and twice-daily dosing, with 80% power and 5% significance level (one-sided).

1.3 Population

160 HIV-1 infected children aged <18 years, ≥ 15 kg in weight and able to swallow tablets, with viral suppression (HIV-1 RNA <50 copies/ml) for at least the prior 24 weeks. Participants must have been on an antiretroviral regimen that includes lopinavir/ritonavir for at least 24 weeks.

At the screening visit lopinavir/ritonavir should be changed to tablet formulation if the child is not already taking tablets and the current dose of lopinavir/ritonavir (twice-daily) should be adjusted to follow the recommended FDA dosing plan based on body weight bands as necessary. The first 48 children enrolled in the PK study should change to 100/25mg strength lopinavir/ritonavir tablets only.

Children will be recruited from clinical centres in countries participating in the PENTA, HIV NAT (Thailand) and PHPT (Thailand) networks.

1.4 Outcome measures

Primary Outcomes:

- HIV-1 RNA ≥ 50 copies/ml (confirmed) at any of week 4, 8, 12, 24, 36 or 48
- AUC, C_{\min} and C_{\max} values of lopinavir after twice-daily dosing compared to historical adult and paediatric data
- AUC, C_{\min} and C_{\max} values of lopinavir after once-daily and twice-daily dosing (in the same children)

Secondary Outcomes:

- HIV-1 RNA <400/<50 copies/ml at 24 and 48 weeks
- HIV-1 RNA ≥ 400 copies/ml at any of week 4, 8, 12, 24, 36 or 48
- number of HIV-1 mutations present at week 4, 8, 12, 24, 36 or 48 conferring resistance to drugs taken at randomisation or during the trial
- change in CD4 (absolute and percentage) from baseline to 24 and 48 weeks
- change in ART (defined as any change from the ART regimen at randomisation)
- ART-related grade 3 or 4 clinical and laboratory adverse events
- new CDC stage C diagnosis or death
- child and family acceptability of and adherence to twice-daily lopinavir/ritonavir 100/25mg tablets dosed on body weight, over 48 weeks as assessed by patient/carer completed questionnaires
- child and family acceptability of and adherence to once-daily compared to twice-daily dosing of lopinavir/ritonavir tablets, over 48 weeks as assessed by patient/carer completed questionnaires

1.5 Follow-up

All children will be seen for clinic visits at weeks -4 to -2 (screening), 0, 4, 8, 12, 24, 36 and 48. Where required, PK assessments will be carried out at weeks 0 and 4.

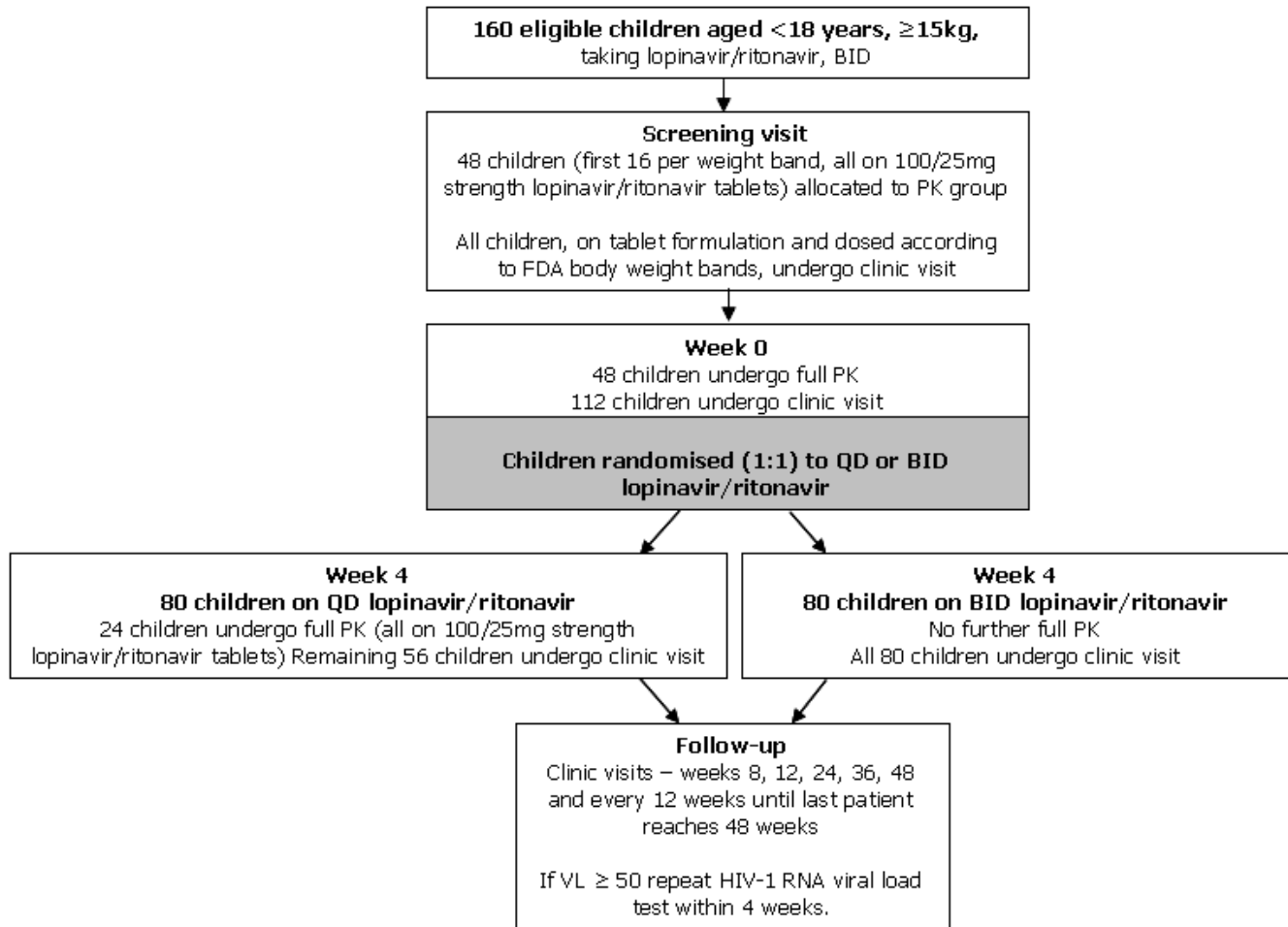
The paediatrician may request more frequent visits for children if required. The flowsheet indicates the minimum for protocol completion and data recording. However, it is the investigator's responsibility to see participants as frequently as necessary, particularly for the monitoring of adverse events.

All children with a viral load ≥ 50 copies/ml will be asked to come back as soon as possible and within 4 weeks for a confirmatory re-test.

1.6 Duration

Children will be recruited over 18 months and followed until the last child to be randomised has completed 48 weeks of follow-up. Participants being followed after week 48 should be seen every 12 weeks, until the last child has completed follow-up. Participants randomised to the once-daily dosing arm should continue to take once-daily lopinavir/ritonavir unless the clinician or the family have concerns which they should discuss with the relevant Trials Unit.

1.7 Schematic diagram



NB: 48 children is the minimum number of children who will be recruited to the PK study. If a child in the PK study does not complete one or both PK assessments (if randomised to switch to lopinavir/ritonavir tablets dosed once-daily) or has no evaluable PK data, further children will be recruited to the PK part of the trial from the relevant body weight band as replacements. Children with non-evaluable PK data will still continue to be followed in their randomised arm.

1.8 Assessment flowsheet

WEEKS	SCREENING -4 TO -2	0 (FASTING)	4	8	12	24 (FASTING)	36	48 (FASTING)	Further follow-up	END OF TRIAL VISIT
Signed informed consent	X	(CONFIRM)								
Clinical assessment ^a	X	X	X	X	X	X	X	X	Every 12 weeks	X
Local HIV-1 RNA viral load	X	X	X	X	X	X	X	X	Every 12 weeks	X
T cell lymphocyte subsets inc.	X	X	X	X	X	X	X	X	Every 12 weeks	X
Biochemistry ^b	X	X			X	X	X	X	Every 12 weeks	X
Haematology ^c	X	X			X	X	X	X	Every 12 weeks	X
Lipids and glucose (fasting) ^d		X				X		X	Every 48 weeks	
Pregnancy Test ^e	X					X		X	Every 24 weeks	X
Tanner scales ^f		X				X		X	Every 24 weeks	X
EDTA sample ^g	X	X	X	X	X	X	X	X	Every 12 weeks	X
Adherence questionnaire	X	X	X		X	X		X	Every 24 weeks	X
Acceptability Questionnaire		X						X ^h	Every 48 weeks	X
Full PK assessment		X ⁱ	X ^j							

Note: If insufficient blood is drawn, priorities are: T cell subsets, local HIV-1 RNA, plasma store, lipids/glucose, biochemistry, haematology

(a) Clinical assessment: Height & weight (adjust doses); Presence of adverse events and change in HIV disease stage (including clinical lipodystrophy) not measured at screening visit.

(b) Biochemistry: Creatinine, Bilirubin, ALT, AST, Alkaline Phosphatase, Albumin

(c) Haematology: Hb, MCV, WBC, Lymphocytes, Neutrophils, Platelets

(d) Lipids/Glucose: Triglycerides, Cholesterol (Total, HDL, LDL, VLDL), Glucose.

(e) Pregnancy Test: This pregnancy test could be either a urine sample or blood sample test. This test will be performed for all females of childbearing potential at different time-points during the trial or if requested. The initial pregnancy test must be done within 72 hours of enrolment and its results must be received before randomisation.

(f) Tanner scales: Only in children >30kg or 9 years old

- (g) 8ml in EDTA for separation and storage of plasma at -80°C (see Manual of Operations for instructions for plasma handling and storage). Only 6ml if child having a full PK assessment on that visit.
- (h) Acceptability questionnaire: only children on QD arm (if BID dosing is resumed earlier, complete acceptability questionnaire at this time)
- (i) All children enrolled in PK study – assessment on BID lopinavir/ritonavir
- (j) Children in PK study randomised to QD dosing of lopinavir/ritonavir