KONCERT

(PENTA 18) Trial Summary

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 Inclusion criteria

- aged <18 years (up to 18th birthday) with confirmed HIV-1 infection
- weight ≥15 kg
- able to swallow tablets
- stable (i.e. CD4 not declining) on a combination antiretroviral regimen that has included lopinavir/ritonavir for at least 24 weeks
- taking lopinavir/ritonavir dosed twice-daily and be willing at the screening visit to change to tablet formulation (if not currently taking tablets) and to change the lopinavir/ritonavir dose to follow the recommended FDA dosing plan based on body weight bands as necessary (see 7.2.2); if participating in the PK study*, be willing at the screening visit to change to lopinavir/ritonavir half strength formulation tablets (100/25mg) only, dosed twice-daily and change the lopinavir/ritonavir dose to follow the recommended FDA dosing plan based on body weight bands as necessary (see 7.2.1)
- most recent HIV-1 RNA viral load <50 copies/ml, and viral suppression for the previous 24 weeks. Where viral suppression is defined as HIV-1 RNA <50 copies/ml, with the exception of a single measurement ≥50 but <400 copies/ml
- children and caregivers willing to participate in the PK study if they are among a minimum of 16 children enrolled in each body weight band in the trial, including a second PK assessment if randomised to switch to once-daily lopinavir/ritonavir.
- parents/carers and children, where applicable, give informed written consent

*.a minimum of 16 children per weight band will be entered into the PK study and must be willing to change to taking **half-strength formulation lopinavir/ritonavir tablets (100/25mg) only**, dosed according to the FDA recommended dosing plan based on their body weight, at the screening visit. Once it has been confirmed that evaluable PK data have been obtained for each weight band on twice- and once-daily dosing, it will no longer be necessary for children entering the trial to take half strength formulation lopinavir/ritonavir tablets only.

1.3 Exclusion criteria

- children on an antiretroviral regimen that includes a NNRTI or any PI other than lopinavir/ritonavir
- children who have previously failed virologically on a PI containing regimen (where virological failure is defined as two successive HIV-1 RNA results>1000 copies/ml (confirmed) more than 24 weeks after starting HAART, i.e. changes for toxicity are not counted as failure)
- acute illness
- abnormal renal or liver function (grade 3 or above)
- receiving concomitant therapy except for prophylaxis; Some treatments may be allowed, but must first be discussed with a trial medical expert
- pregnancy or risk of pregnancy in females of child bearing potential

1.4 Population

160 HIV-1 infected children aged <18 years, ≥15kg 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.

1.5 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

Tertiary Outcomes:

- Tanner Scale at 24 and 48 weeks

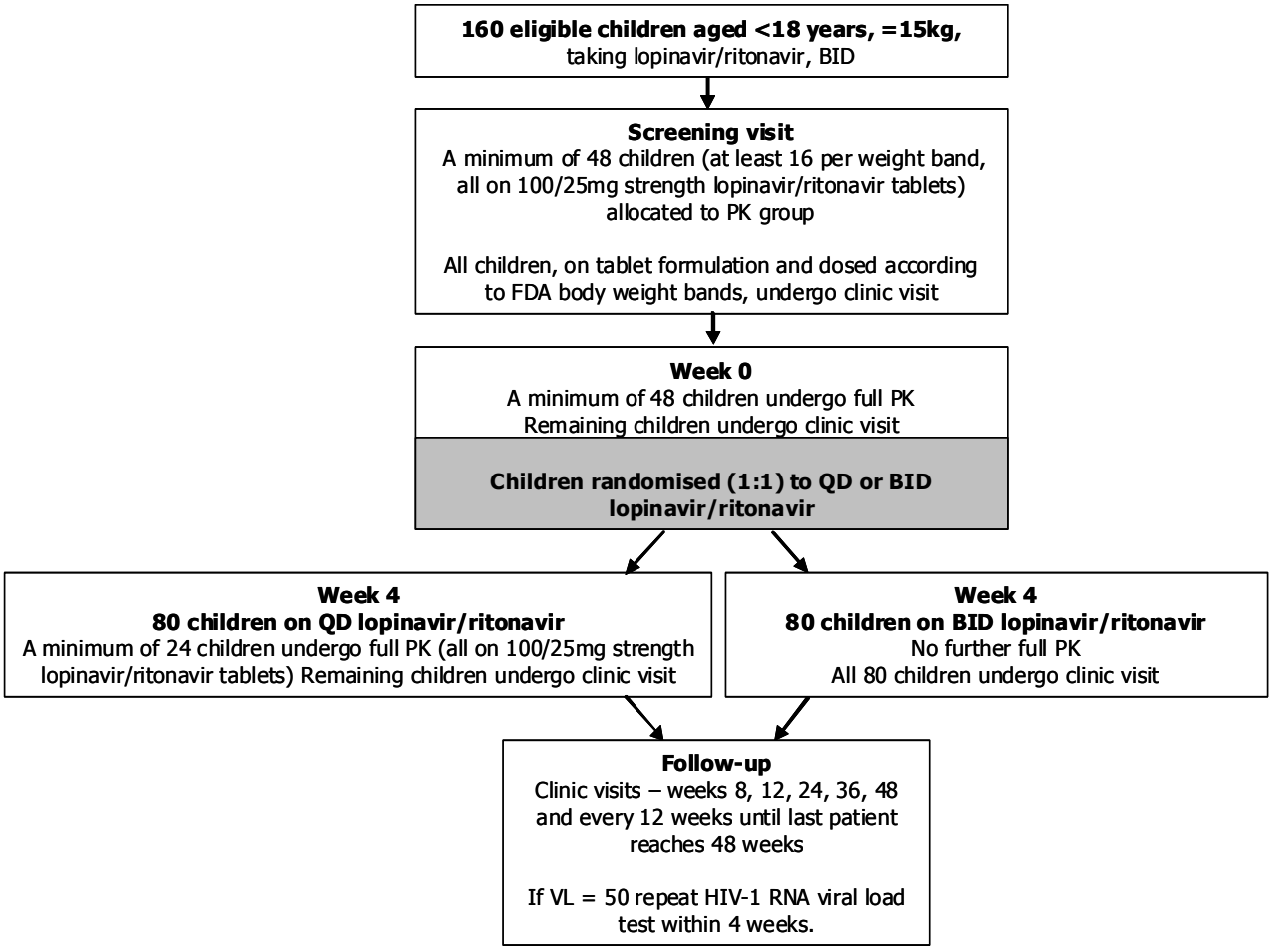
1.6 Follow-up

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.

1.7 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.

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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