

The Interim Analysis of a Phase IV Randomised, Open-Label, Multicentre Trial to Evaluate Safety and Efficacy of Indinavir/Ritonavir (800/100 mg bid) vs. Saquinavir/Ritonavir (1000/100 mg bid) in Adult HIV-1 Infection: The MaxCmin1 Trial

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ABSTRACT

Background: The MaxCmin1 trial is the first head-to-head comparison of ritonavir-boosted PI treatments. MaxCmin1 primarily compares the virological failure rate at 48 weeks for the indinavir (INDV) arm relative to the saquinavir (SAQV) arm. **Methods:** Open-label, randomised (1:1), multi-centre, phase IV trial evaluating the safety and efficacy of INDV (800/100 mg bid) versus SAQV (1000/100 mg bid) in adult HIV-1 infected patients with clinical indication for a ritonavir-boosted PI regimen. Use of NRTI/NNRTI was decided prior to randomisation by the treating physician. One scheduled intention-to-treat (ITT) interim analysis was done on all Week 24 data from subjects exposed to the study drugs. The ITT analysis was done using the Peto method of repeated significance with a significance level of 0.001. **Results:** Beginning September 2000, 317 patients were randomised of whom 306 initiated treatment. Patients are primarily Caucasian (93% men (78% infected through sex with other men (49%)). At 24 weeks, 13% (INDV) vs. 16% (SAQV) experienced virological failure. No difference was seen in viral suppression through 24 weeks (table). At weeks 4, 12 and 24, the CD4 T cell count increase from baseline was 30, 43 and 40 (INDV) and 33, 42 and 58 cells/mm³ (SAQV). Time to increase of > 100 CD4 T cells/mm³ was 13 (12) weeks mean (median, n=8) for INDV and 12 (5) weeks mean (median, n=42) for SAQV. No statistically significant difference was seen between the study arms in number (%) of grade 3/4 adverse events (AEs). **Conclusion:** In the interim analysis at 24 weeks of this randomised trial no differences were observed in virological or immunological response to the two ritonavir-boosted study PIs nor in the proportion of patients with grade 3/4 AEs. No changes are warranted in the conduct of the trial following the Data & Safety Monitoring Board's evaluation of the week 24 data. Final results available in third quarter 2002.

	Percentage with HIV-1 RNA < 100 c/ml	
	SAQV (N = 148)	INDV (N = 158)
Baseline	36	35
Week 4	48	47
Week 12	66	61
Week 24	71	68

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PRIMARY OBJECTIVE

To address whether there is a difference in the incidence of virological failure for the indinavir/ritonavir (INDV/r) arm relative to the saquinavir/ritonavir (SAQV/r) arm

RESULTS

From September 2000 to March 2001 317 patients were enrolled, of whom 306 initiated the randomised treatment. At Baseline no differences between the study arms were observed in demographic, clinical and laboratory variables (see Baseline table). No differences between the study arms were observed in use of any antiretroviral drug prior to inclusion and at Baseline (see ART table). Patients are primarily Caucasian (93% men (78% infected through sex with other men (49%)). Twenty-two % of patients are women.

At 24 weeks, 13% (INDV) vs. 16% (SAQV) experienced virological failure (see figure). Only 4 (<1%) patients discontinued the randomised treatment due to virological failure. No difference was seen in viral suppression through 24 weeks (see bar table). At weeks 4, 12 and 24, the CD4 T cell count increase from Baseline was 30, 43 and 40 (INDV) and 33, 42 and 58 cells/mm³ (SAQV). Time to increase of > 100 CD4 T cells/mm³ was 13 (12) weeks mean (median, n = 8) for INDV and 12 (5) weeks mean (median, n = 52) for SAQV. No statistically significant difference was seen between the study arms in number (%) of grade 3/4 adverse events (AEs) (see AE table).

METHODS

A phase IV, randomised, open-label, parallel group, and multi-centre trial. All patients are seen for follow-up at Baseline, Weeks 4, 12, 24, 36, and 48. Concomitant use of ≥ 2 NRTI(s) / NNRTI(s) were decided prior to the randomisation by the treating physician. The randomisation was centralised at CHIP.

Power calculation and statistics

The primary populations for analysis was the intention-to-treat (ITT/e) including all randomised patients that had taken at least one dose of the assigned treatment. Analysis where discontinuation of the randomised treatment = HIV-1 RNA ≥ 400 (100) copies/ml. were also performed.

The Peto method of repeated significance testing with a significance level of 0.001 was used for the interim analysis presented to the DSMB.

Equivalence trial with 80% chance that the 95% CI for the difference in failure rates will exclude a difference greater than 15% in either direction if

- Sample size of 150 per group
- Underlying failure rates are 20% in both groups at Week 48

Definition of virological failure

- Viral load at Baseline < 200 copies/ml: HIV-RNA ≥ 200 copies/ml
- Viral load at Baseline ≥ 200 copies/ml: Any rise in HIV-RNA ≥ 0.5 log₁₀ *and / or
- ≥ 50,000 at Week 4 and / or
- ≥ 5,000 at Week 12 and / or
- ≥ 200 at Week 24

All cases of suspected virological failure was confirmed by a second VL determination.

- Death, withdrawn consent and loss to follow-up

Baseline characteristics

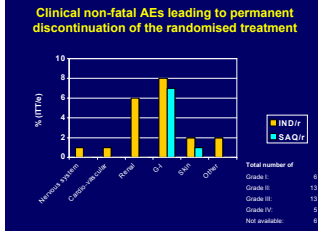
BASILINE PARAMETER	INDV n = 158	SAQV/ n = 148	Total N = 306
Antiretroviral naive / PI-naive (%)	22 / 37	28 / 41	25 / 39
PI-experienced viral load > 400 c/ml (%)	25	22	23
PI-experienced viral load < 400 c/ml (%)	38	37	38
CD4 (cell/cmm)	263	33	311
HIV-1 RNA (c/ml) (geom. median)	4.0	4.0	4.0
HIV-1 RNA < 400 c/ml (%)	42	37	40
CD4+ (10 ⁶ /l, median)	280	275	277
Nadir CD4+ (10 ⁶ /l, median)	88	58	81

ART use by study arm (No.)

	Prior to randomisation	At Baseline	SAQV
ABACAVIR	14	10	11
AZIDUThIMIDINE	1	1	1
ABEFORVIR	6	8	8
DDI	41	44	28
ZTC	112	94	125
DIT	13	45	47
ZDC	11	45	1
AZT	105	27	81
DELAVIRINE	1	2	0
EFAVIRAZ	13	6	4
LOVIRAZ	1	2	0
NEVIRAZ	20	17	2
RETRAVIR	48	45	103
NEVIRAZ	21	1	1
RTDMSAZ	20	22	103
RTDMSAZ	2	17	0
SAQINAVIR	20	16	0

Patients disposition at Week 24

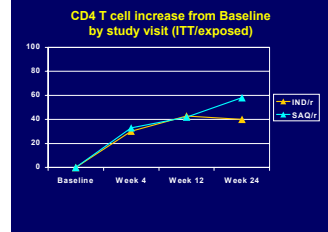
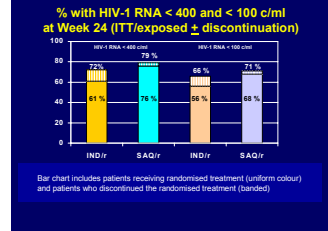
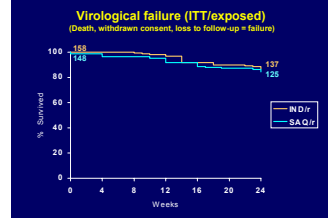
STATUS	INDV No. (%)	SAQV/ No. (%)	Total No. (%)
Initiated n=317	158 (99)	148 (94)	306 (97)
Never initiated n=16	1 (<1)	15 (7)	11 (3)
Initiated but permanently discontinued n=74	42 (27)	25 (17)	67 (22)
Reason for discontinuation			
Virological failure	2 (1)	2 (1)	4 (1)
Death	1 (<1)	1 (<1)	2 (<1)
Clinical non-fatal AE	21 (20)	12 (8)	43 (14)
Laboratory AE	1 (<1)	0 (0)	1 (<1)
Withdrawal consent	1 (<1)	1 (<1)	2 (<1)
Lost to follow-up	3 (2)	5 (3)	8 (3)
Other	3 (2)	4 (3)	7 (2)
Still on randomised treatment	116 (73)	123 (83)	239 (78)



Total number of grade 3/4 adverse events (AEs)

Organ system	INDV	SAQV
Nervous system	6	3
Pulmonary	4	1
Cardio-vascular	2	0
Renal	10	0
G-I	18	14
Skin & hair	10	6
Fatigue and/or fever	3	3
Laboratory	15	16
Other	7	2
Total	75*	45*

* Some subjects experienced > one grade 3/4 AE



CONCLUSION

This interim analysis performed on Week 24 data from all randomised patients showed

- Low virological failure rates in a heterogeneous population without difference between the treatment arms
- No differences in HIV-1 RNA and CD4 T cell responses between treatment arms
- Difference in AE type between the treatment arms but no significant difference (at the 0.001 level) in number of grade 3/4 AEs
- No changes warranted following DSMB evaluation
- Final results available by 3rd quarter 2002