

GSK "Backup" Integrase Inhibitor Looks Strong in People With HIV: 10-day monotherapy study

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A once-daily integrase inhibitor from Shinogi and GlaxoSmithKline, S/GSK1349572 (572), impressed attendees at IAS 2009 in Cape Town and at this meeting with its potency in a 10-day monotherapy trial [1] and its apparently higher barrier to resistance than raltegravir [2]. At ICAAC's only data-driven HIV slide session, S/GSK unveiled early findings on a so-called backup integrase inhibitor, S/GSK1265744 (744), that would presumably be developed if 572 stumbles [3]. In the first study of 744 in HIV-infected people, this alternative agent also displayed robust activity during and after 10 days of monotherapy.

This phase 1-2a trial had three parts. In parts A and B 48 healthy volunteers took doses of 744 suspension ranging from 5 to 50 mg. After safety and pharmacokinetic reviews following parts A and B, investigators gave 30 mg of 744 (six 5-mg tablets) to people with HIV. Part A was a single-dose escalation study in which an alternating panel of two cohorts took placebo or different doses of 744. Part B was a repeat-dose escalation study involving sequential groups taking 744 or placebo.

In part C 11 antiretroviral-naïve or currently untreated antiretroviral-experienced people took 744 alone for 10 days. Everyone had a viral load at or above 5000 and a CD4 count at or above 200 at screening. Eight people took 30 mg of 744 once daily and 3 took placebo for 10 days, followed by a 3-antiretroviral regimen for 2 weeks starting on day 14. The purpose of the triple-drug regimen was to prevent emergence of 744-resistant virus as drug levels faded. This integrase inhibitor has a half-life of about 30 hours. Results were revealed to patients and physicians on day 11.

All 11 people with HIV were white men with a median age of 42. (Women were not enrolled because safety during pregnancy had not been established.) Median pretreatment viral loads were 4.1 log in the 744 group and 4.8 log in the placebo group (about 12,000 and 65,000 copies). Median CD4 counts were 395 with 744 and 380 with placebo.

Parts A and B showed that 744 is dose-proportional (meaning more drug yields proportionately higher concentrations) in people without HIV. Drug level variation from person to person was low.

At the lowest dose of 5 mg, area under the curve (AUC) averaged 32.5 micrograms/h/mL and maximum concentration 2.1 micrograms/mL. At 25 mg AUC averaged 160 micrograms/h/mL and maximum concentration 9.5 micrograms/mL. Trough concentration at 25 mg averaged 5.4 micrograms/mL, more than 30 times

above the protein binding-adjusted 90% inhibitory concentration.

In part C, the study involving people with HIV, 10 days of 744 at 30 mg daily lowered viral loads by a median 2.6 log (range 3.0 to 1.0 log) on day 11. Loads continued to fall after 744 stopped, so that after 14 days (when triple therapy could start) 7 of 8 people (88%) had fewer than 50 copies. CD4 counts climbed by a median of 15 cells through 11 days.

In the 10-day monotherapy trial of S/GSK's first integrase inhibitor, 572, viral load dropped by 2.46 log with the highest dose (50 mg), and 7 of 10 people taking that dose had a load under 50 copies 1 day after dosing stopped [1]. Nine of 10 had a load under 400 copies on day 11.

No signature mutations conferring resistance to raltegravir or elvitegravir emerged during the study of 744. Phenotypic testing showed no decrease in viral susceptibility to the backup integrase inhibitor.

Fatigue, headache, dizziness, and indigestion affected 1 person each during 744 dosing in the study of people with HIV. There were no serious or severe adverse events. No lab or ECG abnormalities turned up.

References

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