GSK364735 is a Potent Inhibitor of HIV Integrase and Viral Replication

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Figure 1(a-c). GSK364735 Inhibits Integration of Viral DNA with a Concentrated Increase in 2-LTR Circles, with No Effect on Viral DNA Production

Methods
- A novel recombinant HIV integrase activity was measured in a strand transfer assay using a recombinant integrase with a target sequence 2-LTR circles.
- GSK364735 inhibited recombinant HIV integrase activity with nanomolar potency and displaced a radiolabelled INI with potency consistent with competitive binding at the 2-metal binding inhibitor site.

Background
- After many years of pharmaceutical research, HIV integrase has evolved into a highly desirable target for drug development.

Results and Discussion
- Table 1. Inhibition of Recombinant HIV Integrase and HIV Replication by GSK364735 and Clinically Relevant INIs

Table 2. Inhibition of Different HIV Clades and Clinical Isolates by GSK364735

Table 3. Integrate Mutations Generated by Passage of Virus in GSK364735-Containing Medium

Figure 2. Examples of Combination Studies Using GSK364735 with Marked HIV Antiretroviral Drugs

Results
- GSK364735 was tested against a panel of clinical HIV-1 subtype isolates and HIV-2 isolates in PBMCs. Twenty-five virus isolates were evaluated, which included three individual isolates from each of the HIV-1 group M subtypes A, B, C, D, E, F and G, as well as the tank-adapted group M subtype B virus, and three HIV-1 group O isolates. GSK364735 was equi-potent against all isolates containing the integrase coding region from clade B clinical isolates and two control strains (HIV-1 Ba-L and HIV-1M) on an equivalent basis. GSK364735 retained full potency against HIV strains resistant to marketed INIs.

Conclusions
- GSK364735 is a potent non-nucleoside inhibitor of HIV replication in cellular assays through the mechanism of inhibiting HIV integrase.

References

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No antagonism was observed in any study. In seven of the 17 
combination studies. The structure of GSK364735 is shown below. It belongs to the two-metal binding scaffold naphthyridinone, or NTD. The NTD scaffold will be thoroughly described in future publications.

Likewise, its antiviral potency in three different cellular assays was low nanomolar and very similar to potencies of the three INIs that have shown clinical efficacy (L-870,810, MK-0518 and GS-9137). In addition, four HIV-1 isolates (three of which were also evaluated in 
early non-nucleoside drugs. In vitro recombinant HIV integrase activity was measured in a strand transfer assay using a recombinant integrase with a target sequence 2-LTR circles. GSK364735 was studied in combination with 17 marketed drugs used to treat HIV infection primarily to confirm that there was no antagonistic 
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