Once-daily dolutegravir versus raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study

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Summary

Background: Dolutegravir (S/GSK1349572) is a once-daily HIV integrase inhibitor with potent antiviral activity and a favourable safety profi le. We compared dolutegravir with HIV integrase inhibitor raltegravir, as initial treatment for adults with HIV-1.

Methods: SPRING-2 is a 96 week, phase 3, randomised, double-blind, active-controlled, non-inferiority study that began on Oct 19, 2010, at 100 sites in Canada, USA, Australia, and Europe. Treatment-naive adults (aged ≥18 years) with HIV-1 infection and HIV-1 RNA concentrations of 1000 copies per mL or greater were randomly assigned (1:1) via a computer-generated randomisation sequence to receive either dolutegravir (50 mg once daily) or raltegravir (400 mg twice daily). Study drugs were given with coformulated tenofovir/emtricitabine or abacavir/lamivudine. Randomisation was stratifi ed by screening HIV-1 RNA (≤100 000 copies per mL or >100 000 copies per mL) and nucleoside reverse transcriptase inhibitor backbone. Investigators were not masked to HIV-1 RNA results before randomisation. The primary endpoint was the proportion of participants with HIV-1 RNA less than 50 copies per mL at 48 weeks, with a 10% non-inferiority margin. Main secondary endpoints were changes from baseline in CD4 cell counts, incidence and severity of adverse events, changes in laboratory parameters, and genotypic or phenotypic evidence of resistance. Our primary analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01227824.

Findings: 411 patients were randomly allocated to receive dolutegravir and 411 to receive raltegravir and received at least one dose of study drug. At 48 weeks, 361 (88%) patients in the dolutegravir group achieved an HIV-1 RNA value of less than 50 copies per mL compared with 351 (85%) in the raltegravir group (adjusted diff erence 2.5%; 95% CI −2.2 to 7.1). Adverse events were similar between treatment groups. The most common events were nausea (59 [14%] patients in the dolutegravir group vs 53 [13%] in the raltegravir group), headache (51 [12%] vs 48 [12%]), nasopharyngitis (46 [11%] vs 48 [12%]), and diarrhoea (47 [11%] in each group). Few patients had drugrelated serious adverse events (three [<1%] vs fi ve [1%]), and few had adverse events leading to discontinuation (ten [2%] vs seven [2%] in each group). CD4 cell counts increased from baseline to week 48 in both treatment groups by a median of 230 cells per μL. Rates of graded laboratory toxic eff ects were similar. We noted no evidence of treatment-emergent resistance in patients with virological failure on dolutegravir, whereas of the patients with virologic failure who received raltegravir, one (6%) had integrase treatment-emergent resistance and four (21%) had nucleoside reverse transcriptase inhibitors treatment-emergent resistance. Interpretation The non-inferior effi cacy and similar safety profi le of dolutegravir compared with raltegravir means that if approved, combination treatment with once-daily dolutegravir and fi xed-dose nucleoside reverse transcriptase inhibitors would be an eff ective new option for treatment of HIV-1 in treatment-naive patients.

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