UKE Paper of the Month November 2011

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Once daily dolutegravir (S/GSK1349572) in combination therapy in antiretroviral-naive adults with HIV: planned interim 48 week results from SPRING-1, a dose-ranging, randomised, phase 2b trial.

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Abstract: **Background**: Dolutegravir (S/GSK1349572) is a new HIV-1 integrase inhibitor that has antiviral activity with once daily, unboosted dosing. SPRING-1 is an ongoing study designed to select a dose for phase 3 assessment. We present data from preplanned primary and interim analyses. **Methods**: In a phase 2b, multicentre, dose-ranging study, treatment-naive adults were randomly assigned (1:1:1:1) to receive 10 mg, 25 mg, or 50 mg dolutegravir or 600 mg efavirenz. Dose but not drug allocation was masked. Randomisation was by a central integrated voice-response system according to a computer-generated code. Study drugs were given with either tenofovir plus emtricitabine or abacavir plus lamivudine. Our study was done at 34 sites in France, Germany, Italy, Russia, Spain, and the USA beginning on July 9, 2009. Eligible participants were seropositive for HIV-1, aged 18 years or older, and had plasma HIV RNA viral loads of at least 1000 copies per mL and CD4 counts of at least 200 cells per µL. Our primary endpoint was the proportion of participants with viral load of less than 50 copies per mL at week 16 and we present data to week 48. Analyses were done on the basis of allocation group and included all participants who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT00951015. **Findings**: 205 patients were randomly allocated and received at least one dose of study drug: 53, 51, and 51 to receive 10 mg, 25 mg, and 50 mg dolutegravir, respectively, and 50 to receive efavirenz. Week 16 response rates to viral loads of at most 50 copies per mL were 93% (144 of 155 participants) for all doses of dolutegravir (with little difference between dose groups) and 60% (30 of 50) for efavirenz; week 48 response rates were 87% (139 of 155) for all doses of dolutegravir and 82% (41 of 50) for efavirenz. Response rates between nucleoside reverse transcriptase inhibitor subgroups were similar. We identified three virological failures in the dolutegravir groups and one in the efavirenz group—we did not identify any integrase inhibitor mutations. We did not identify any dose-related clinical or laboratory toxic effects, with more drug-related adverse events of moderate-or-higher intensity in the efavirenz group (20%) than the dolutegravir group (8%). We did not judge that any serious adverse events were related to dolutegravir. **Interpretation**: Dolutegravir was effective when given once daily without a pharmacokinetic booster and was well tolerated at all assessed doses. Our findings support the assessment of once daily 50 mg dolutegravir in phase 3 trials.

Statement: Antiretroviral combination therapy against HIV has been extended by a new drug class that inhibits the integration of proviral DNA into the host genome. Our study is the first phase 2b trial to report on antiretroviral combination therapy with dolutegravir in populations of patients with HIV who have not been previously treated. So far, raltegravir is the only licensed inhibitor of HIV integrase that is approved for use in populations of patients that are both previously untreated and treated. Two other integrase inhibitors are in later stages of clinical development at present: elvitegravir and dolutegravir. All integrase inhibitors have a unique antiviral profile with a very rapid decay of viral load in previously untreated patients when combined with other antiretroviral drugs. Potential advantages of dolutegravir include once daily application as a single tablet, no need for pharmacological boosting, established dose–response characteristics, higher genetic barrier to resistance, and good tolerability. On the basis of our findings, this new compound is being carried forward into larger phase 3 studies both in previously untreated and treated patients. If the favourable findings of our study are confirmed by ongoing phase 3 trials, dolutegravir has the potential to be used as a first-line option and a salvage therapy in a majority of individuals with HIV infection.

This work was performed at the Infectious Diseases Clinical Trial Unit of the of the Department of Medicine in the group of Jan van Lunzen who holds a professorship at UKE since 2011. It is the result of a collaboration of a multinational, multicentre clinical trial team which was headed by JvL. The work represents an example of growing expertise in performing groundbreaking clinical studies according to GCP guidelines at the UKE. The infrastructure for conducting these clinical studies has been continuously improved over the past years at the UKE including the foundation of the Clinical Trial Center North as well as optimization of study administration, study nurse education and on site technical equipment. JvL has a strong research interest in the development of new antiretroviral treatment strategies with a special focus on immune based therapy including therapeutic vaccination and gene therapy in HIV.