Preliminary safety and efficacy data of brecanavir, a novel HIV-1 protease inhibitor: 24 week data from study HPR10006

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Background: Breccanavir, a novel protease inhibitor (PI), has sub-nM in vitro antiviral activity against multi-PI-resistant HIV-1 and in vitro is >100-fold more potent than previously marketed PIs and approx. 10-fold more potent than the recently marketed PI, darunavir.

Methods: HPR10006 is an open label, single-arm, descriptive 48 week study, with 8 and 24 week interim analyses. Thirty-one HIV-1-infected patients were enrolled and received breccanavir/ritonavir 300 mg/100 mg twice daily, with two nucleoside reverse transcriptase inhibitors, based on history and genotype.

Results: At baseline, 25/31 had PI-sensitive virus and 6/31 had PI-resistant virus (median of two primary PI and five secondary PI mutations). Median baseline HIV-1 RNA was 5.0 and 4.2 log10 copies/mL, respectively. Four patients discontinued prior to Week 24. At Week 24, 77% (24/31) had HIV-1 RNA <50 copies/mL regardless of screening genotype, including 5/6 patients with PI-resistant virus (6/6 had HIV-1 RNA <400 copies/mL). Breccanavir/ritonavir was well tolerated with no serious adverse events or clinically concerning changes in laboratory parameters. Of 31 patients, 10 (32%) experienced drug-related Grade 2–4 adverse events [most frequent events were fatigue (13%), dyspepsia (10%) and nausea (10%)]. Baseline isolate breccanavir IC50 values for all patients ranged from 0.1 to 0.2 nM. Median plasma trough concentration at Week 4 was 150 ng/mL. Correcting the IC50 (0.2 nM) value for protein binding (6-fold increase in vitro with 50% human serum) gives a corrected inhibitory quotient of 180.

Conclusions: Breccanavir/ritonavir was well tolerated and showed potent antiviral activity in HIV-1-infected patients harbouring both PI-sensitive and PI-resistant virus, following 24 weeks of dosing.

Keywords: antiretroviral therapy, acquired immune deficiency syndrome, AIDS, HIV-1 infection

Introduction

Triple combination highly active antiretroviral therapy (HAART) containing a protease inhibitor (PI) with two nucleoside reverse transcriptase inhibitors (NRTIs) has resulted in dramatic decreases in HIV-1-related morbidity and mortality and is currently considered a standard of care for the initial treatment of HIV-infected patients.1–4 Although HIV PIs have dramatically improved the treatment for HIV patients since their introduction in 1996, resistance to these drugs can develop and render them a suboptimal or even ineffective treatment option in many cases. Therefore, there is a need for new molecules that inhibit all HIV-1 virus strains, including those resistant to currently marketed PIs.

HIV is now generally approached as a long-term chronic illness. As such, new drugs to treat the disease must be potent against both wild-type and resistant virus, and must be well tolerated with minimal long-term toxicity. One of many possible approaches to improve clinical outcome is the development of ultra-potent and selective versions of current therapeutics, such as the new HIV-1 PI breccanavir.

Breccanavir is a novel PI that has sub-nM in vitro antiviral activity against multi-PI-resistant HIV-1 and in vitro is >100-fold more potent than previously marketed PIs and approx. 10-fold more potent than the recently marketed PI, darunavir.5 Breccanavir has a mean IC50 in PBMCs of 0.03 nM and a binding affinity for the HIV protease of 15 fM (10- to 100-fold higher affinity than any other PI). Although breccanavir is a

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substrate for cytochrome p450 3A4, it is neither a significant inducer nor inhibitor of this enzyme. Its bioavailability is significantly increased with moderate fat meals and ritonavir,\(^7\) and ritonavir boosting would be required in clinical practice. HPR10006 is the first study of the safety and efficacy of brecanavir in HIV-infected patients.

**Methods**

**Participants**

Patients were recruited from centres in the USA, and were eligible for enrolment if they were HIV-infected, \(\geq 18\) years of age, either antiretroviral therapy (ART)-naive or -experienced, had a plasma HIV-1 RNA \(\geq 1000\) copies/mL, and CD4\(^+\) cell count \(>200\) cells/\(\text{mm}^3\). Patients were excluded if they had medical conditions that could compromise their safety or interfere with drug absorption, if they required use of prohibited medications, or if they had protocol-specified abnormal laboratory values.

The study was approved by the ethics review boards at each participating centre and all patients provided written informed consent. This study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki (October 1996).

**Design and interventions**

This was an open label, single-arm, descriptive 48 week proof of concept study with 8 and 24 week planned interim analyses. Based primarily on feasibility considerations, the sample size was 30 HIV-infected patients. All enrolled patients received brecanavir/ritonavir 300 mg/100 mg twice daily with optimized background NRTIs of the investigators choice, based on history and genotype. The NRTIs that were allowed at the time of enrolment included zidovudine, lamivudine, didanosine, stavudine and emtricitabine. Following preliminary safety results and data from drug–drug interaction studies, background NRTIs could be changed to include abacavir and tenofovir, at the investigator’s discretion.

**Procedures and assessments**

Patients were evaluated at screening, Day 1 (baseline) and Day 7, and at Weeks 2, 4, 8, 12, 16, 20, 24, 32, 40 and 48 and every 8 weeks thereafter through withdrawal and follow-up. At each visit, samples for plasma HIV-1 RNA, CD4\(^+\)/CD8\(^+\) lymphocyte subsets, clinical chemistries and haematology were collected and analysed. Additional screening assessments included hepatitis B and C serology, Centers for Disease Control (CDC) Classification and \(\beta\)-human chorionic gonadotropin (\(\beta\)-HCG) where appropriate. Full pharmacokinetic profiles were taken on Day 1 and at Weeks 2 and 4. Plasma HIV-1 RNA was measured by the Roche Cobas Amplicor HIV-1 Monitor\(^{TM}\) Test (version 1.5) at screening and baseline and by the Roche Cobas Amplicor HIV-1 Ultrastensitive Monitor\(^{TM}\) Test (version 1.5) post-baseline. Samples exceeding the upper limit of the ultrasensitive assay were retested using the Roche Cobas Amplicor HIV-1 Monitor\(^{TM}\) Test.

Adverse events (AEs) were assessed at each visit and graded using the 1992 Division of AIDS toxicity grading scale.\(^6\) Viral genotypes and phenotypes were determined by Monogram Biosciences Inc. (CA, USA) at baseline and at time of virological failure. Genotypic mutations were defined according to the IAS-USA Resistance Table\(^9\) on samples from patients meeting protocol-defined virological failure criteria. All laboratory tests, excluding those for viral genotype and phenotype, were performed centrally by Quest Diagnostics (CA, USA).

**Outcome measures**

The primary endpoints were the proportions of patients with plasma HIV-1 RNA levels <400 copies/mL at Weeks 2, 12, 16, 24 and 48, the plasma concentrations of brecanavir at Weeks 2 and 4, as well as specific safety and tolerability parameters (Grade 2 or higher thyroid function abnormalities, rash and serious AEs). Secondary endpoints included the proportion of patients with HIV-1 RNA plasma levels <400 and <50 copies/mL over time, absolute values and changes from baseline in plasma HIV-1 RNA and CD4\(^+\) cell counts over time, plasma brecanavir and ritonavir PK following single dose administration and steady-state plasma brecanavir trough concentrations (detailed PK data not presented).

**Virology analysis**

Samples for viral genotyping and phenotyping were drawn and stored for possible future analyses at Day 1 (baseline), at Weeks 2, 8, 12, 16, 24, 32, 40 and 48 and every 8 weeks thereafter through withdrawal and follow-up. Virological failure was defined as either a reduction of plasma HIV-1 RNA to <400 copies/mL with a subsequent increase to \(\geq 400\) copies/mL on two consecutive occasions, or a failure to achieve a plasma HIV-1 RNA <400 copies/mL by Week 16. Subjects experiencing virological failure had plasma samples drawn at the time of confirmation of suspected virological failure to better define the evolution of drug-associated resistance selection.

**Statistical analysis**

This was a descriptive study; therefore no formal hypothesis testing was done. Efficacy analysis was presented for each time point using both an observed analysis and a missing/discontinuation = failure (MD = F) analysis, where missing data or data collected after discontinuation of study medication were considered failures. The intent-to-treat exposed (ITT-E) and safety populations included all patients exposed to at least one dose of study medication.

**Results**

**Patient disposition and baseline characteristics**

During the recruitment period (October 2004 through February 2005), 31 patients from 8 centres were enrolled. Twenty-seven (87\%) of the 31 patients in the ITT-E population completed Week 24. Baseline characteristics are shown in Table 1. At baseline, 25/31 had PI-sensitive virus and 6/31 had PI-resistant virus (median of two primary PI mutations, five secondary PI mutations and five NRTI mutations, as shown in Table 2). Of the 31 patients, only 12 reported a history of prior ART, and 4/12 (33\%) had primary PI mutations while 8/12 (66\%) did not. Interestingly, two subjects with primary PI mutations at baseline did not report prior ART.

The patients with PI-sensitive virus had higher median baseline plasma HIV-1 RNA values (5.0 log\(_{10}\) copies/mL) than the patients with PI-resistant virus (4.2 log\(_{10}\) copies/mL). Zidovudine/lamivudine as a fixed-dose combination tablet (Combivir) was the background NRTI therapy for 27/31 (87\%) patients. Four
patients discontinued prior to Week 24, two due to AEs (one drug-related nausea and vomiting, and one non-drug-related Grade 3 increased liver enzymes) and two withdrew consent for reasons unrelated to study medication.

**Antiviral activity**

At Week 24, in an MD = F analysis, 81% (25/31) of patients had HIV-1 RNA <400 copies/mL and 77% (24/31) of patients had HIV-1 RNA <50 copies/mL regardless of screening genotype, including 5/6 patients with PI-resistant virus (6/6 had HIV-1 RNA <400 copies/mL). In an observed analysis, 93% (25/27) of patients had HIV-1 RNA <400 copies/mL and 89% (24/27) of patients had HIV-1 RNA <50 copies/mL, regardless of screening genotype. Virological response based on the MD = F algorithm (HIV-1 RNA <400 copies/mL) is shown in Figure 1.

Immunological recovery was observed with a median CD4+ cell count increase of 84 cells/mm³ [interquartile range (IQR): 22, 169]. No patients experienced disease progression to CDC Class C or death.

Six subjects entered the study with PI-resistant HIV-1 (defined as the presence of one or more PI resistance-associated mutations). These subjects had similar virological responses to those subjects with PI-sensitive HIV-1. On-therapy genotypes have been obtained for three subjects who were classified as virological failures. Two of the three subjects had no genotypic and phenotypic changes at the point of virological failure. The third subject accumulated multiple NRTI, non-NRTI and PI resistance-associated amino acid substitutions, probably associated with previous drug history.

**Table 2. NRTI backbone and resistance-associated amino acid substitutions (RAS) present in the six subjects with PI resistance**

<table>
<thead>
<tr>
<th>Subject</th>
<th>Backbone therapy</th>
<th>NRTI RAS&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Non-NRTI RAS&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PI RAS&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>A&lt;sup&gt;b&lt;/sup&gt;</td>
<td>COM</td>
<td>T215D&lt;sup&gt;c&lt;/sup&gt;</td>
<td>L100I, K103N</td>
<td>L10I, I54V, I62V, L63P, A71V, V82A, L90M</td>
</tr>
</tbody>
</table>

COM, Combivir; ddI, didanosine; 3TC, lamivudine; d4T, stavudine.
<sup>a</sup>Resistance-associated amino acid substitutions (RAS) used were those presented in the IAS USA Resistance Table, Fall 2005.<sup>9</sup>
<sup>b</sup>Subject was reportedly ART-naive.
<sup>c</sup>Exception to <sup>a</sup>, this substitution is considered a revertant of T215Y/F and potentially indicates the presence of archived virus with T215Y/F.
Baseline isolate brecanavir IC$_{50}$ values for all patients ranged from 0.1 to 0.2 nM. Median plasma trough concentration at Week 4 was 150 ng/mL. Correcting the IC$_{50}$ (0.2 nM) value for protein binding (6-fold increase in vitro with 50% human serum) gives a corrected median inhibitory quotient of 180.

Safety results

The safety population consisted of 31 patients. Median exposure to all study medications was 196 days (range: 7–236 days). Brecanavir/ritonavir was well tolerated with no serious AEs or clinically concerning changes in laboratory parameters. Of 31 patients, 10 (32%) experienced drug-related Grade 2–4 AEs. The most frequent were fatigue (4/31, 13%), dyspepsia (3/31, 10%) and nausea (3/31, 10%), and all were Grade 2 in intensity. Additional Grade 2–4 drug-related AEs experienced by a single patient each included: abnormal dreams, anxiety, increased bilirubin, depression, epigastric discomfort, increased hepatic enzyme, upper abdominal pain and vomiting. Specifically, there were no cases of Grade 2–4 drug-related diarrhoea through 24 Weeks, and only one case of non-treatment limiting rash, which was Grade 1 in severity.

Grade 3–4 laboratory abnormalities were also rare and included: elevated creatine phosphokinase (CPK) (3/31, 10%), hypertriglyceridaemia (2/31, 6%), increased aspartate transaminase (AST) (1/31, 3%), increased gamma-glutamyl transpeptidase (GGT) (1/31, 3%), hypoglycaemia (1/31, 3%), increased bilirubin (1/31, 3%) and neutropenia (1/31, 3%). Lipid increases were moderate, with median increases from baseline of total cholesterol: 30.9 mg/dL, high density lipoprotein (HDL): 3.9 mg/dL, low density lipoprotein (LDL): 0.0 mg/dL and triglycerides: 62.3 mg/dL. Even with these increases, the median value for total cholesterol at 24 Weeks was 198 mg/dL and the median value for triglycerides was 199 mg/dL.

The only case of Grade 3 treatment-emergent elevations in liver enzymes and bilirubin occurred in a patient who was co-infected with hepatitis C. This 53-year-old female developed increased AST and bilirubin at Week 20, which was attributed to hepatitis C virus and concurrent alcohol use. She was withdrawn from the study, and her liver enzymes and bilirubin returned to baseline values within 4 weeks of study withdrawal.

Discussion

This study is the first trial of ritonavir-boosted brecanavir in HIV-1-infected patients. This regimen was well tolerated and showed potent antiviral activity in PI-sensitive and PI-resistant HIV-1-infected patients over a 24 week period. Individuals who had confirmed virological failure were uncommon. The majority of treatment failures in this analysis were due to treatment discontinuation ($n = 4$), rather than virological failure (≥400 copies/mL, $n = 2$). In fact, in the observed analysis, 93% of patients on brecanavir/ritonavir had HIV-1 RNA <400 copies/mL and 89% had HIV-1 RNA <50 copies/mL. CD4+ cell responses were robust and increased throughout the 24 week treatment period. The intrinsic potency of brecanavir led to IC$_{50}$ values that were nearly identical for PI-sensitive and PI-resistant viruses. Median trough plasma levels exceeded corrected IC$_{50}$ values by ~180-fold.

Tolerability and AE profiles appear very promising. Brecanavir/ritonavir was well tolerated with few Grade 2–4 drug-related AEs, and no serious AEs or deaths. Specifically, there were no cases of Grade 2–4 drug-related diarrhoea or rash. While increases in total cholesterol and triglycerides are clearly a consequence of most ritonavir-enhanced PI therapies, the increases seen in this study were modest, and the median absolute values for both cholesterol and triglycerides remained below the treatment threshold.$^{10}$

Factors that influence the choice of ART are complex. These 24 week data indicate that brecanavir shows promise to be a potent and well-tolerated PI. Dose ranging studies of brecanavir/ritonavir in a large population of very heavily treatment-experienced subjects were initiated. However, due to insurmountable difficulties in producing a formulation of brecanavir that achieved target exposures in the primary patient population of heavily treatment-experienced patients, the brecanavir development programme has been terminated.

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Transparency declarations

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References


