New Antiretrovirals in Development: The View in 2002

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I. New Nucleoside/Nucleotide Analogues

Emtricitabine (Coviracil)

Emtricitabine (Coviracil), formerly known as FTC, is a thiacytidine nucleoside analogue being developed by Triangle Pharmaceuticals. The drug has in vitro anti-hIV activity comparable to its sister compound lamivudine (Epivir) in human cell lines (Hazen, 2001). Unfortunately, the M184V mutation associated with lamivudine resistance also confers decreased sensitivity to emtricitabine.

Results from an open-label dose-ranging trial were published last year (Rousseau, 2001). Lamivudine- and abacavir-naïve patients received 25 mg bid, 100 mg qd, 100 mg bid, 200 mg qd, or 200 mg bid of emtricitabine as a single agent for 14 days. A dose-response relationship for the antiviral activity of emtricitabine was established, with total daily doses of 200 mg or more producing the greatest median viral load suppression: 1.72–1.92 log. Based on these data, a once-daily dose of 200 mg was selected for further long-term clinical study. “This is what we’re looking forward to with emtricitabine,” commented Dr. Gulick. “We’ll soon be in a position to offer patients once-daily regimens.”

Preliminary results from two randomized studies—FTC-302 and FTC-303—were reported by Dr. Charles van der Horst and his colleagues at the 8th croi, held in February 2001 in Chicago (van der Horst, 2001). FTC-302 was a blinded comparison of emtricitabine and lamivudine, both in combination with stavudine (Zerit) and either efavirenz (Sustiva) or nevirapine (Viramune). Four hundred sixty-eight an-

Table 1. Investigational Drugs 2002: Existing and New Classes (Partial List)

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<thead>
<tr>
<th>HIV Reverse Transcriptase Inhibitors</th>
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<tr>
<td>Nucleoside Analogues</td>
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<tr>
<td>emtricitabine (FTC)*</td>
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<td>amdoxovir (DAPD)*</td>
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<td>BCH-10618</td>
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<td>DPC 817</td>
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<td>Non-Nucleoside Reverse Transcriptase Inhibitors</td>
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<td>capravirine (Ag1549)</td>
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<td>DPC 083*</td>
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<td>DPC 961</td>
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| Protease Inhibitors                  |
| atazanavir (BMS 232,632)*            |
| tipranavir*                          |
| mozenavir (DMP-450)                  |
| TMC 114*                             |
| TMC 126                              |
| TMC 15                               |

| HIV Entry Inhibitors**               |
| Attachment Inhibitors                |
| PRO 542                              |

| Co-Receptor Inhibitors               |
| CXCR4 inhibitors                     |
| CCR5 inhibitors                      |
| SC-351125 (SCH-C)                    |
| PRO 140                              |
| SCH-D                                |
| UK-427,857                           |

| Fusion Inhibitors                    |
| T-20 (enfuvirtide)                   |
| T-1249                                |
| d-peptides                           |
| 5-helix                              |

| HIV Integrase Inhibitors             |
| compound C (diketo acid)*            |
| s-1360*                              |

* Reviewed in this article.
** Reviewed in the March 2002 issue of The PRN Notebook.
tiretoviral-naive South Africans were enrolled in this study. After 24 weeks of treatment, approximately 61% to 65% of the study volunteers had hiv-rna levels below 50 copies/mL, irrespective of which regimen they received. However, viral rebound after initial suppression below 400 copies occurred in 12% of the emtricitabine recipients compared to 6% of lamivudine recipients (p<0.05). The cause of this disparity may have been the result of less than optimal adherence to the experimental regimen, since 60% of those who experienced viral load rebound receiving emtricitabine had wild-type virus, compared to 23% of those in the lamivudine group, and only 15% had the 184V mutation in the emtricitabine group compared to 54% of the 3TC group (p=0.03).

FTC-303 was an open-label switch study that enrolled 440 HIV-positive individuals who had HIV-RNA levels below 400 copies/mL for at least 12 weeks while receiving a lamivudine-containing regimen. Patients were randomized in a 2:1 fashion to switch to emtricitabine or remain on lamivudine. After 48 weeks of follow-up, viral load rebound rates were similar in both groups (8%). Both emtricitabine and lamivudine were generally well tolerated by the majority of patients in both FTC-302 and FTC-303. Adverse reactions were predominantly mild to moderate in both groups with the exception of some episodes of grade 3/4 hepatotoxicity in study FTC-302. In this study, severe liver toxicity was seen in 17% of the patients receiving nevirapine (14% in the emtricitabine arm and 19% in the lamivudine arm), whereas none of the patients receiving efavirenz concomitantly with 3TC or FTC developed such hepatotoxicity. The overall rate of liver toxicity observed in study FTC-302 is consistent with that observed in other published studies with nevirapine, including those where neither emtricitabine nor lamivudine was part of the regimen.

Also discussed by Dr. Gulick were data from ANRS 091, an open-label study evaluating a once-daily regimen consisting of emtricitabine, didanosine (Videx), efavirenz (Sustiva), and didanosine (Videx) in 40 antiretroviral-naive HIV-positive patients. Median viral load at baseline was 4,774 copies/mL and the median CD4 cell count was 272 cells/mm³. After 96 weeks of treatment, 34/40 (85%) patients maintained viral suppression below 400 copies/mL; 80% had a viral load less than 50 copies/mL (see Figure 1). Additionally, 8/9 (89%) patients with baseline viral loads greater than 100,000 copies/mL had HIV-RNA below 400 copies/mL for the same time period. The median increase in CD4 cell count observed at week 96 was 272 cells/mm³.³

In addition to these studies, Triangle is currently conducting FTC-301, a phase III, 48-week, double-blind, placebo-controlled trial planned for 100 clinical sites in the United States, Europe and Latin America. Patients will receive didanosine and efavirenz in combination with either emtricitabine or stavudine. The ANRS is completing enrollment in its ALIZE study, an open-label study in France. In this study, patients with HIV-RNA levels below the level of detectability while receiving a lamivudine-containing HAART regimen will be randomized to continue the regimen or switch to a once-a-day regimen of emtricitabine, extended-release didanosine and efavirenz.

### Amdoxovir

DAPD, which now carries the generic name amdoxovir, is a second NRTI being developed by Triangle Pharmaceuticals. It is a novel dioxolane purine analogue that is rapidly converted intracellularly by adenosine deaminase into D-dioxolane guanine (dxg), a metabolite that has potent activity against HIV and hiv.

According to in vitro data published earlier this year in the Journal of Acquired Immune Deficiency Syndromes, amdoxovir demonstrated anti-HIV activity comparable to that of lamivudine and abacavir (Zagen) (Mewshaw, 2002). The drug had less activity than didovudine and emtricitabine against wild-type laboratory strains, but had greater activity than stavudine, didanosine, and efavirenz. The activity of amdoxovir against zidovudine-, lamivudine-, and NNRTI-resistant viruses was also confirmed by phenotypic analysis of recombinant viruses that had a combination of zidovudine and lamivudine resistance mutations and NNRTI resistance mutations. All the viruses were susceptible to inhibition by amdoxovir. As for reverse transcriptase mutations that typically confer multi-NNRTI resistance, clinical isolates containing only K65R were said to be moderately resistant to amdoxovir (5.6-fold increase in IC₅₀). The presence of the Q151M mutation, alone, also produced virus that was moderately resistant to amdoxovir (9.6-fold increase in IC₅₀), whereas virus containing the combination of K65R and Q151M was highly resistant to amdoxovir (>20-fold increase in IC₅₀). In contrast to findings from earlier reports, viruses containing the L74V mutation alone remained susceptible to amdoxovir.

As for phase I clinical trial results, Dr. Joseph Eron and his colleagues treated six patients who had failed prior regimens containing either zidovudine/lamivudine or stavudine/lamivudine with amdoxovir monotherapy (Eron, 2000). The patients underwent a seven-day washout prior to receiving their first dose of amdoxovir (ei-
Preliminary results from two clinical trials—one involving antiretroviral-naive patients and another involving antiretroviral-experienced volunteers—were presented at the 9th croi in Seattle. In the first study, patients received zidovudine and lamivudine and one of three DPC 083 doses (50 mg, 100 mg, or 200 mg qd) or efavirenz (Ruiz, 2002). Each of the four groups had between 29 and 38 patients. Approximately 60% to 70% of patients in each group had hiv-rra levels below 50 copies/mL after 16 weeks of treatment.

In the second study enrolling patients who had experienced virologic failure while on a previous nRTI-based regimen, once-daily doses of 100 mg and 200 mg DPC 083 were used, in combination with two nRTIs (Ruiz, 2002a). At baseline, mutations consistent with nRTI resistance were present in 94% of the study population. Approximately 70% of patients had hiv containing either the K103N or Y181C mutations. Of the 10 patients who did not switch nRTIs at baseline, four (40%) had hiv-rra <50 copies/mL after eight weeks of treatment. Better yet were the results in patients who switched at least one nRTT upon entering the study: 13/18 (72%) who switched one of their nRTIs had hiv-rra levels below 50 copies/mL and 10/15 (67%) who switched both of their nRTIs at entry had hiv-rra levels below 50 copies/mL at week 8.

Rash was the most common side effect in these two trials. In the antiretroviral-naive study, grade 3 rash—which required discontinuation of study drug—occurred in 14% of patients in the 200 mg DPC 083 group, 8% in the 100 mg group, 4% in the 50 mg group, and 9% in the efavirenz group. In the study involving antiretroviral-experienced patients, rash occurred more frequently in the 100 mg DPC 083 group than in the 200 mg group. The other side effect described most commonly was central nervous system effects (e.g., somnolence, headache).

**II. New Non-Nucleoside Reverse Transcriptase Inhibitors**

**DPC 083**

DPC 083 is the lead candidate of four quinazolinone nRTIs being developed by Bristol-Myers Squibb (DPC 082, DPC 961, and DPC 963 are the other three). In vitro, DPC 083 demonstrates activity against wild-type hiv equivalent to efavirenz. The drug is also active against hiv strains containing single reverse transcriptase mutations that typically confer high-level resistance to current nRTIs, such as L100I and K103N, and against some double-substitution variants including K103N/V181C, K103N/V108I, and K103N/P225H. It is still not known how active the drug is against hiv variants containing multiple nRTI-related mutations in reverse transcriptase.

DPC 083 is less highly bound to plasma proteins than efavirenz, which results in higher levels of free drug at equivalent total plasma concentrations and a significant (10- to 20-fold) improvement in antiviral activity relative to efavirenz. To examine the pharmacokinetics of DPC 083, researchers conducted a study in which five groups of hiv-negative male volunteers were given varying doses of DPC 083, ranging from 50 mg to 400 mg per day (Fiske, 2000). One group of female volunteers received 100 mg per day. Two doses were administered on the first day, followed by single daily doses for the following eight days, for a total of ten doses. According to preliminary data presented at the 7th croi, held in San Francisco in 2000, DPC 083 had a very long terminal half-life, ranging from 143 to 175 hours. Interestingly, the half-life was longer, on average, in women than in men. After 10 doses of >100 mg DPC 083, the average trough concentration exceeded the calculated protein-binding-adjusted concentration needed for 90% inhibition of wild-type viruses by >172-fold, of K103N virus by >11-fold, of K103N + P225H by >1.9-fold, or K103N + V108I by >2.9-fold, and of K103N + Y181C by >1.6-fold.

“Essentially, we’re looking at a half-life of more than 90 hours with DPC 083,” Dr. Gulick pointed out. “This definitely supports once-daily dosing. Less frequent dosing might also be possible, perhaps twice or three times a week.”
days of TMC125 monotherapy resulted in a 1.99 log reduction in HIV-RNA (Gruzdev, 2001). In fact, data presented at the 9th Conference on Retroviruses and Opportunistic Infections (cROI) suggest that the drug—as monotherapy—results in a similar initial rate of decline of HIV-RNA during the first week of treatment as a five-drug, PI- and NNRTI-containing regimen (Sankasing, 2002).

Also presented in Seattle were the short-term effects of TMC125 in NNRTI-experienced patients with high levels of drug resistance to currently available NNRTIs (Gazzard, 2002). Sixteen patients, most of whom had greater than 100-fold resistance to either efavirenz (Sustiva) or nevirapine (Viramune), received TMC125 900 mg bid for seven days. The median decrease in HIV-RNA—again, as monotherapy—was 0.9 log. Twelve patients had a decrease in viral load of at least 0.5 log; in seven patients a decrease in excess of 1 log was observed. For side effects, diarrhea occurred in approximately 30% of patients; headaches occurred in 25%, and abdominal pain, flatulence, insomnia, and musculoskeletal pain occurred in 6% of patients.

### III. Protease Inhibitors

**Atazanavir**

BRISTOL-MYERS SQUIBB’S ATAZANAVIR (BMS-232,632) is a semi-symmetrical azapeptide agent with an IC\(_50\) of 2.6 to 5.3 nM, thus more potent in *vitro* than the currently approved protease inhibitors. In dose-ranging studies involving HIV-negative volunteers, single doses of 100 mg up to 1,200 mg appeared to be well tolerated (O’Mara, 1999). The drug was well absorbed and had a half-life ranging between 2.9 and 6.5 hours. Atazanavir doses of 400 mg or higher resulted in plasma concentrations above the necessary IC\(_{50}\) for more than 24 hours. Based on these results, a dose of 400 mg—two 200 mg tablets—once a day with food has been selected for continued development.

*In vitro* passage of HIV in the presence of inhibitors showed that atazanavir selected for resistant variants more slowly than nel-finanvir (Viracept) or ritonavir (Norvir) (Gong, 2000). Genotypic and phenotypic analysis of three different HIV strains resistant to atazanavir indicated that an n88 substitu-

tion in the protease gene appeared first during the selection process in two of the three strains. An n84 change appeared to be an important substitution in the third strain used. Mutations were also observed at the protease cleavage sites following drug selection. Of note, the evolution to resistance seemed distinct for each of the three strains used, suggesting multiple pathways to resistance and the importance of the viral genetic background.

A cross-resistance study involving five other protease inhibitors indicated that atazanavir-resistant virus remained sensitive to saquinavir (Fortovase), while it showed various levels—0.1 to 71-fold decrease in susceptibility—of cross-resistance to nelfinavir, indinavir, ritonavir, and amprenavir. In reciprocal experiments, the atazanavir susceptibility of HIV variants selected in the presence of each of the currently approved protease inhibitors showed that the nelfinavir-, saquinavir-, and amprenavir-resistant strains of HIV remained sensitive to atazanavir, while indinavir- and ritonavir-resistant viruses displayed six- to ninefold changes in atazanavir sensitivity.

One clinical trial discussed by Dr. Gulick was BMS-A1424-009, which compared two doses of atazanavir (400 mg or 600 mg) to nelfinavir; both in combination with stavudine (Zerit) and lamivudine (Sanne, 2001). At baseline, the 467 antiretroviral-naive patients had viral loads of approximately 4.77 log. Using an intent-to-treat analysis, 64% in the 400 mg atazanavir group, 67% in the 600 mg atazanavir group, and 53% in the nelfinavir group had HIV-RNA levels below 400 copies/mL at 48 weeks. Approximately 35% in all three groups had HIV-RNA levels below 50 copies/mL. Comparable increases in CD4+ counts—between 210 and 240 cells above baseline—were seen in three groups. These data, along with the preliminary results of a similar study in antiretroviral-naive patients (BMS-A1424-007), indicate that atazanavir is at least comparable to nelfinavir in efficacy when used as part of a combination regimen.

Another important study is BMS-A1424-009, a 48-week safety and efficacy study comparing dual-protease inhibitor combina-

### Beyond atazanavir’s potential efficacy for antiretroviral-experienced patients, there has been a great deal of interest in the drug’s minimal impact on lipid levels in clinical trials conducted thus far. In study 009, mean baseline fasting triglycerides levels were between 177 mg/dL and 223 mg/dL, and cholesterol levels were between 181 mg/dL and 202 mg/dL (Piliero, 2002). After 48 weeks of treatment, total cholesterol increased 11% in the ritonavir/saquinavir group (fasting LDL decreased by 23%), compared to a 5% decrease in the 600 mg atazanavir group (fasting LDL decreased by 7%). In the 400 mg atazanavir group, total cholesterol and LDL cholesterol remained roughly the same throughout the 48 weeks of study. Fasting triglycerides increased 94% in the ritonavir/saquinavir group and decreased approximately 5% in the 400 mg atazanavir group and 27% in the 600 mg atazanavir groups. Similar results were reported in 48-week analyses of studies 007 and 008.

Jaundice—due to increased indirect bilirubin, similar to that seen with indinavir treatment—was reported in study 009 and has been seen in other clinical trials of atazanavir. Approximately 13% and 19% of patients in the 400 mg and 600 mg atazanavir groups, respectively, experienced symptomatic hyperbilirubinemia in this study. However, Dr. Gulick pointed out that other liver enzymes were not elevated in these patients and that jaundice resolved in all cases upon discontinuation of atazanavir.

An expanded access program for atazanavir was recently opened by Bristol-Myers Squibb (see sidebar on page 21).
Tipranavir

**TIPRANAVIR IS A NONPEPTIDIC DIPHROPYRONE**, a new class of protease inhibitors believed to have greater flexibility in conforming to enzyme variants resistant to current protease inhibitors. The compound was originally developed by Pharmacia & Upjohn and has since been sold to Boehringer Ingelheim.

As with its unique mechanism of action, tipranavir also differs from other currently available protease inhibitors in its metabolism. The drug induces the cytochrome P450 pathway, whereas current protease inhibitors either inhibit or both inhibit and induce this enzyme system. In early phase II studies, a whopping 1500 mg of tipranavir, taken three times daily, was required to achieve the necessary trough concentration. To circumvent this hurdle, the manufacturer has developing a self-emulsifying drug delivery system (seDDS) for the compound. Tipranavir will likely need to be combined with low doses of ritonavir (100 mg) to reverse the rapid metabolism of the drug by cytochrome P450 and to allow for twice-daily dosing with food (McCallister, 2002).

An initial glimpse into the *in vitro* activity of tipranavir against multiple-protease inhibitor-resistant HIV strains was published by Dr. Brendan Larder and his colleagues two years ago in * AIDS* (Larder, 2000). Studied by Dr. Larder’s team were 134 clinical viral isolates documented to be highly cross-resistant to currently available protease inhibitors. Of 105 isolates with more than tenfold resistance to three or four protease inhibitors—with an average of 6.1 key protease inhibitors mutations per sample—95 (90%) were susceptible to tipranavir; eight (8%) had four- to tenfold resistance to tipranavir; and only two (2%) had more than tenfold resistance.

At the 41st International Conference on Antimicrobial Agents and Chemotherapy (ICPAC), held late last year in Chicago, data from study BI 1182.4 were reported, a clinical trial comparing tipranavir (500 mg or 1250 mg bid) and saquinavir, both in combination with ritonavir and to allow for twice-daily dosing.

The drug induces the cytochrome P450 pathway, whereas current protease inhibitors—aside from ritonavir—and the NNRTI have not been elucidated.

**Table 2. Investigational Drugs 2002: Future Classes**

- Budding inhibitors: interferon
- DC-SIGN inhibitors
- Regulatory protein (e.g., NEF, VIF, TAT) inhibitors
- Uncoating inhibitors
- RNAase H inhibitors
- Zinc finger (DNA complex) inhibitors
- Capsid protein polymerization inhibitors
- Assembly inhibitors
- Adjunctive therapy:
  - Hydroxyurea (ribonucleotide reductase inhibitor)
  - Mycophenolic acid (IMP dehydrogenase inhibitor)
- Immunomodulators

At baseline, 40/41 (97%) clinical isolates were considered to be susceptible to tipranavir—defined as a less than tenfold reduction in IC50—despite decreases in susceptibility to a mean average of 2.9 currently available protease inhibitors. There was no association between the number of protease mutations at baseline and the magnitude of viral load reduction. For example, in the 500 mg tipranavir group, individuals with < 5 baseline protease mutations experienced reductions in viral load of -2.39 log at week 48, compared to a reduction of -2.24 in patients with >5 protease mutations at baseline. Decreased tipranavir susceptibility was associated with a mean of 16 mutations including two or three mutations at positions 82, 84, and 90. Five of the six HIV isolates with decreased tipranavir susceptibility had protease mutations at position V82T, and 4/6 had either L33I, V, or F.

The optimal dose of tipranavir has not yet been defined, and its pharmacokinetic interactions with other protease inhibitors—aside from ritonavir—and the NNRTI have not been elucidated.

**TMC114**

**MUCH LIKE ITS NNRTI CONTENDER TMC 125 (DISCUSSED ABOVE), Tibotec-Virco dubbed TMC114—its lead protease inhibitor candidate—a “resistant-repellent” compound. More specifically, TMC114 has been designed not only to bind to typical active sites of the protease enzyme with high affinity, but also to remain flexible in the event of mutations that arise during therapy with other protease inhibitors.**

**In vitro**, the drug is active against wild-type and protease inhibitor-resistant HIV (De Bethune, 2001). Of 261 randomly selected recent recombinant clinical isolates, 32% showed a greater than tenfold increase in the EC50 for at least one protease inhibitor. What’s more, there was no greater than a fivefold increase in EC50 when tested against a panel of 20 HIV variants resistant to current protease inhibitors.

A dose-escalating study of TMC114 has been conducted (Van der Geest, 2001). Two groups of nine HIV-negative volunteers (six active, three placebo) received alternating doses of 100 mg, 200 mg, 400 mg, 800 mg, 1200 mg, or 1600 mg. Because the maximum tolerated dose was not reached, an additional panel was...
added to receive 2400, 3200 and 4000 mg. Initially, plasma concentrations increased more than proportionally with the dose. No further increases were observed between 2400 mg and 3200 mg. The mean $C_{max}$ was 14.4 – 15.3 mg/ml at these dose levels. The elimination half-life was approximately ten hours, irrespective of dose. For 800 mg doses and higher, plasma levels at eight to 12 hours post-dose exceeded protein-adjusted $C_{50}$'s for isolates resistant to currently approved protease inhibitors. All doses were considered safe. Diarrhea—because of polyethylene glycol (PEG) in the formulation—occurred at high dose levels and limited further escalation. Short-term localized oral and peripheral paresthesias were observed in 3/6 (50%) volunteers receiving the 3200 mg tmc114 dose.

Tibotec-Virco’s next step will be to conduct proof-of-concept studies using a non-PEG formulation of tmc114 to examine its safety and efficacy in hiv-positive patients. “This drug, much like tipranavir, will likely be studied in combination with ritonavir to boost its pharmacokinetics,” Dr. Gulick added. “Ritonavir has a profound effect on tmc114 concentrations, which should make for easier dosing and greater potency.”

**IV. Integrase Inhibitors**

**THE HIV INTEGRASE GENE IS ESSENTIAL FOR hiv replication and facilitates the integration of proviral hiv-**

DNA forms inactive and unstable circular structures, and the virus is unable to replicate. Two earlier enzymatic functions of the integrase gene—assembly of pre-integration complexes and 3’ processing of the viral DNA ends—are not inhibited by diketo acids. They specifically inhibit the third step—strand transfer of viral DNA to cellular DNA.

Using a specific assay for the inhibition of integrase, researchers at Merck have discovered a series of diketo acids that have activity in vitro and in vivo (1.708,906 and L-731,988) (Hazuda, 2000). Interestingly, when viruses were repeatedly passaged in the presence of these compounds and mutations conferring resistance emerged, the replicative capacity of HIV became significantly impaired.

Neither of these compounds will be studied further by Merck, given unfavorable pharmacokinetic profiles, but it’s likely that derivatives of these compounds could serve as precursors to potent integrase inhibitors for future development.

**S-1360 (GW810781)**

Currently in phase I clinical trials is S-1360, an integrase inhibitor being developed by Shinogi & Company, Ltd., in collaboration with GlaxoSmithKline Pharmaceuticals. In vitro studies have demonstrated that S-1360 has potent integrase inhibition with an $IC_{50}$ of 20 nM (Yoshinaga, 2002). The drug had potent antiviral activity against a variety of clinical isolates. The mean $EC_{50}$ and $EC_{90}$ values were 140 nM and 990 nM, respectively. S-1360 was active against both X4 tropic and R5 tropic strains, and against known NRTI, NNRTI, and PI drug-resistant variants. S-1360 was also synergistic.

**Atazanavir (BMS-232632) Expanded Access Program Now Open**

Bristol-Myers Squibb has started enrolling patients in an early access program (EAP) to provide their protease inhibitor atazanavir to eligible patients who are in need of an investigational antiretroviral agent.

The initial phase of this program, which began May 15, provides atazanavir to patients worldwide who need atazanavir and meet specified entry criteria. As Bristol-Myers Squibb compiles safety data from its ongoing phase III clinical trials, the EAP and data on interactions between atazanavir and other drugs, the company expects to modify some of the protocol restrictions which currently apply. This could allow a greater number of patients to access atazanavir.

The initial stage of the EAP will provide atazanavir to patients who are failing their current antiretroviral therapy (defined as an HIV-RNA level >5000 copies/mL and a CD4+ count of < 300 cells/mm$^3$) and who are in need of atazanavir in order to construct a viable alternative treatment regimen. This stage of the program will also provide atazanavir to patients who have severe HAART-associated hyperlipidemia despite lipid-lowering therapy, defined as a triglyceride level >750 mg/dL or a cholesterol level meeting NCEP guidelines for use of a lipid-lowering agent. The aforementioned viral load and CD4+ cell count restrictions do not apply to this latter group of patients.

Some restrictions will apply during the initial phase of the EAP, regarding combined use of atazanavir with some of the other medications available for the treatment of HIV, until more is known about drug interactions between these agents and atazanavir.

To find out more about the atazanavir EAP, clinicians can call 1-877-78MSEAP (1-877-726-7327).
tic in combination with various NRTIs, NNRTIs and PIs. S-1360 resistant mutants were isolated, also in vitro, and the amino acid substitutions responsible for drug resistance were in close proximity to the integrase active site. The role of the mutation at position 66 and others conferring s-1360 resistance was confirmed by site-directed mutagenesis.

“S-1360 is not metabolized by CYP3A4, which is good news in terms of drug-drug interactions,” Dr. Gulick added. “We’re now looking at this drug in treatment-experienced HIV-positive patients.”

**Conclusion**

**IN SUMMATION, DR. GULICK STRESSED THAT there is an urgent need to continue developing compounds that are unique, particularly with respect to their resistance profiles, and that a number of promising candidates are in development in both existing classes and new classes. Clinical development of any new drug is a challenge, but a continued sense of cautious optimism that the therapeutic options will meaningfully expand is warranted.**

**References**


