Promising HIV Treatments in Late-Stage Clinical Development

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Human immunodeficiency virus (HIV) infection involves one of two similar retroviruses (HIV-1 and HIV-2) that destroy CD4-positive lymphocytes and impair cell-mediated immunity, thereby increasing the risk of certain opportunistic infections and cancers.1

Treatments for HIV infection are generally aimed at inhibiting HIV enzymes, which in turn suppresses viral replication.1 More than 25 HIV medications have been approved by the Food and Drug Administration (FDA).2 Usually, a patient’s first HIV regimen includes two nucleotide reverse transcriptase inhibitors (NRTIs) plus an integrase strand transfer inhibitor (INSTI), a non-nucleotide reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) boosted with cobicistat (Tybost, Gilead Sciences) or ritonavir (Norvir, Abbott Laboratories). Cobicistat or ritonavir increases (boosts) the effectiveness of the PI.3

Despite the abundance of HIV medications, analysts have identified several unmet needs in the marketplace, including:3

- Long-acting regimens that require less frequent administration to improve patient adherence
- Safe and effective treatments for patients with drug-resistant HIV strains
- Therapies with improved safety and tolerability profiles
- Progress toward a functional cure

With these needs in mind, pharmaceutical companies are working to develop novel treatments for patients with HIV infection (Table 1). The following monotherapies and combination regimens are in late-stage clinical development or FDA review.

The fixed-dose regimen of bictegravir 50 mg, a novel investigational INSTI, and emtricitabine/tenofovir alafenamide 200 mg/25 mg (Descovy, Gilead Sciences), a dual-NRTI backbone, is an unboosted anti-HIV regimen that combines these drugs into a single, once-daily tablet.4,5 In July 2017, Gilead announced detailed 48-week results from two phase 3 studies evaluating the efficacy and safety of this three-drug combination for the treatment of HIV-1 infection in treatment-naïve adults. Bictegravir/emtricitabine/tenofovir alafenamide was found to be statistically noninferior to regimens containing dolutegravir 50 mg (Tivicay, Viiv Healthcare) in combination with a dual-NRTI backbone. The most commonly reported adverse events in the trials were nausea, diarrhea, and headache.

The results, along with data from two ongoing phase 3 studies in treatment-experienced patients, formed the basis of Gilead’s regulatory applications in the United States and the European Union.6 If approved, bictegravir/emtricitabine/tenofovir alafenamide is likely to be positioned for treatment-naïve adults (18 years of age and older) with HIV-1 infection.3

Janssen is developing a four-drug combination consisting of darunavir (Prezista, Janssen), cobicistat, and emtricitabine/tenofovir alafenamide as a single once-daily tablet for use in both treatment-naïve and treatment-experienced adults with HIV infection. Darunavir is a PI; emtricitabine and tenofovir alafenamide are NRTIs; and cobicistat is a pharmacokinetic booster with no effect on HIV.3 The efficacy of this PI-based combination is being evaluated in two phase 3 studies—one in treatment-naïve adults and the other in treatment-experienced adults.7,8 The first study is scheduled to be completed in March 2018,7 and the second in November 2020.8

Viiv Healthcare is developing a once-daily, fixed-dose combination tablet consisting of dolutegravir and lamivudine (Epivir) for adults with HIV-1 infection. Dolutegravir is an INI, and lamivudine is an NRTI for which the FDA requires a boxed warning.3 The treatment is being compared with dolutegravir plus tenofovir disoproxil fumarate/emtricitabine (Truvada, Gilead) in two identical phase 3, randomized, double-blind trials (Gemini 1 and Gemini 2). Approximately 700 HIV-infected patients will be evaluated at week 48 and week 148 in each study. The scheduled completion date for both trials is in 2024.9,10

Janssen and Viiv Healthcare are collaborating on the single-tablet, two-drug regimen of dolutegravir plus rilpivirine (Edurant, Janssen). Janssen announced in June that regulatory submissions to both the FDA and the European Medicines Agency have been completed. The submissions were based on phase 3 studies that included more than 1,000 patients who previously achieved viral suppression on a three- or four-drug antiretroviral regimen. The most commonly reported adverse events in the trials were nasopharyngitis, headache, diarrhea, and upper respiratory tract infection. If approved, this will be the first two-drug regimen for the maintenance treatment of HIV-1 infection.11,12

Doravirine (MK-1439) is an experimental NRTI under development by Merck.3 It has been combined with lamivudine and tenofovir disoproxil fumarate in a once-daily, fixed-dose single tablet. The new regimen was compared with a fixed-dose combination of efavirenz, emtricitabine, and tenofovir disoproxil fumarate and met efficacy and safety endpoints in a phase 3 trial in treatment-naïve adults infected with HIV-1. The most commonly reported adverse events in the trial were headache, diarrhea, nasopharyngitis, dizziness, nausea, abnormal dreams, and rash. Merck plans to submit new drug applications to the FDA by the end of 2017.13

A long-acting injectable formulation of the dolutegravir analogue cabotegravir, an investigational INSTI developed by Viiv Healthcare, plus Janssen Science’s rilpivirine, an NNRTI, is being codeveloped by the two companies as an HIV-1 treatment.14 If approved, the combination has the potential to replace NRTI-
based therapies. In July, ViiV Healthcare announced positive results from a phase 2b, open-label study that evaluated injectable cabotegravir and rilpivirine dosed once every four or eight weeks compared with daily oral dosing with cabotegravir plus two NRTIs. The most commonly reported adverse events not related to injection-site reactions for the injectable treatment groups were nasopharyngitis, headache, and diarrhea.

ViiV Healthcare and Janssen Sciences are conducting a phase 3 study of this injection. Experts expect the combination treatment to be launched in the U.S. in 2020 as the first integrase inhibitor (INI)-based, NRTI-free, long-acting injectable formulation to reach the market.

Fostemsavir, a prodrug of temsavir, was developed by Bristol-Myers Squibb and acquired by ViiV Healthcare in February 2016. The drug, which received a breakthrough therapy designation from the FDA, is being evaluated in heavily treatment-experienced adults with multidrug-resistant (MDR) HIV-1 in a phase 3 clinical trial. Phase 2a and 2b studies showed a positive safety profile for fostemsavir, but no severe adverse events or deaths occurred.

Ibalizumab, an investigational human monoclonal antibody (mAb), is being developed by TaiMed Biologics and Theratechnologies. It is the first humanized mAb for the treatment of HIV-1 to reach phase 3 development. The ongoing trial is being conducted in patients with

### Table 1 Therapies in Late-Stage Development for Human Immunodeficiency Virus Infection

<table>
<thead>
<tr>
<th>Drug(s)</th>
<th>Therapeutic Class</th>
<th>Mode of Administration</th>
<th>Anticipated U.S. Pricing Strategy</th>
<th>Estimated U.S. Cost Per Year</th>
<th>Anticipated U.S. Launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bictegravir + emtricitabine/TAF</td>
<td>STR (INSTI + NNRTIs)</td>
<td>Single tablet, once daily</td>
<td>5% premium over Triumeq (abacavir/dolutegravir/lamivudine, ViiV Healthcare) because of its novel chemical entity (bictegravir); its reduced toxicity profile (including risk of hypersensitivity); and its once-daily regimen</td>
<td>$30,759</td>
<td>2018</td>
</tr>
<tr>
<td>Cabotegravir + rilpivirine</td>
<td>LAI (INSTI + NNRTI)</td>
<td>Long-acting injection</td>
<td>10% premium over Triumeq because of novelty of compound and formulation</td>
<td>$32,224</td>
<td>2020</td>
</tr>
<tr>
<td>Darunavir/cobicistat/ emtricitabine/TAF</td>
<td>STR (boosted PI + NRTIs)</td>
<td>Single tablet, once daily</td>
<td>10% discount from Descovy (emtricitabine/TAF, Gilead) and Prezobix (darunavir/cobicistat, Janssen) because of competition from INI-based STRs and because of patent expiro of Descovy and Prezista (darunavir, Janssen) before 2025</td>
<td>$33,047</td>
<td>Undetermined</td>
</tr>
<tr>
<td>Dolutegravir/lamivudine</td>
<td>STR (INI + NRTI)</td>
<td>Single tablet, once daily</td>
<td>5% premium over Tivicay (dolutegravir, ViiV Healthcare) and Epivir (lamivudine, ViiV Healthcare) because of improved convenience</td>
<td>$23,404</td>
<td>2019</td>
</tr>
<tr>
<td>Dolutegravir/rilpivirine</td>
<td>STR (INI + NNRTI)</td>
<td>Single tablet, once daily</td>
<td>5% premium over Triumeq because product does not contain an NRTI; therefore, fewer adverse effects may be expected</td>
<td>$30,759</td>
<td>2018</td>
</tr>
<tr>
<td>Doravirine/lamivudine/TDF</td>
<td>FDC (NRTI + NNRTIs)</td>
<td>Single tablet, once daily</td>
<td>15% discount from Atripla (efavirenz/emtricitabine/TAF, Bristol-Myers Squibb/Gilead) because of competition</td>
<td>$24,732</td>
<td>2019</td>
</tr>
<tr>
<td>Fostemsavir</td>
<td>EFI</td>
<td>Single tablet, twice daily</td>
<td>10% premium over Fuzeon (enfuvirtide, Genentech) because of novelty and high unmet medical need</td>
<td>$17,352</td>
<td>2018</td>
</tr>
<tr>
<td>Ibalizumab</td>
<td>EFI (mAb)</td>
<td>IV injection, twice monthly</td>
<td>110% premium over Selzentry (maraviroc, ViiV Healthcare) because of novelty and high unmet medical need</td>
<td>$33,128</td>
<td>2018</td>
</tr>
<tr>
<td>PRO-140</td>
<td>EFI (mAb)</td>
<td>SC injection, once weekly</td>
<td>100% premium over Selzentry because of novelty and high unmet medical need</td>
<td>$31,550</td>
<td>2018</td>
</tr>
</tbody>
</table>

EFI = entry/fusion inhibitor; FDC = fixed-dose combination; INI = integrase inhibitor; INSTI = integrase strand transfer inhibitor; IV = intravenous; LAI = long-acting injection; mAb = monoclonal antibody; NNRTI = non-nucleotide reverse transcriptase inhibitor; NRTI = nucleotide reverse transcriptase inhibitor; PI = protease inhibitor; SC = subcutaneous; STR = single-tablet regimen; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate.
MDR HIV-1. The treatment received breakthrough therapy and orphan drug designations from the FDA and is under priority review with the agency. The drug is being administered as a twice-monthly intravenous injection in trials, but it is also being evaluated as a monthly or twice-monthly intramuscular injection.

In phase 2 studies, the most commonly reported adverse events, most of which were considered mild to moderate, were rash, diarrhea, headache, lymphadenopathy, and hypertension.

PRO-140 (CytoDyn, Inc.), another investigational fully humanized mAb in development, is being studied in treatment-experienced adults with HIV-1 in a phase 2b/3 trial. This mAb has received fast-track and breakthrough therapy status from the FDA. Patients enrolled in the phase 2a trial most commonly experienced diarrhea, headache, rash, diarrhea, headache, and nausea.

REFERENCES


5. Descovy (emtricitabine and tenofovir alafenamide tablets) prescribing information. Foster City, California: Gilead Sciences; April 2017.


