NIHR | Innovation Observatory

Newcastle University

Health Technology Briefing
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Lenacapavir with optimised background regimen for treating multidrug resistant human immunodeficiency virus (HIV)-1 infection in people aged 12 years and older

Company/Developer	Gilead Sciences

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28648	NICE ID: 11775	UKPS ID: N/A

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Lenacapavir is in clinical development for the treatment of multidrug resistant (MDR) human immunodeficiency virus (HIV)-1 infection in people who are heavily treatment-experienced. HIV is caused by a virus that attacks the body's immune system so that it is unable to sufficiently respond to infections and illnesses. Without treatment, HIV can lead to the development of acquired immune deficiency syndrome (AIDS), which is life-threatening. People with HIV show flu-like symptoms two to six weeks after infection, after which they may be asymptomatic for many years until HIV has significantly damaged the immune system, and the body struggles to fight other illnesses and infections. Drug resistant HIV may be developed, as the virus mutates slightly every replication, which can result in current treatments becoming ineffective.

Lenacapavir acts by interfering with the HIV's shell that protects its genetic material and enzymes needed for replicating, thereby preventing the virus from multiplying and reducing the amount of HIV in the body. If licensed, lenacapavir would be the first multi-acting inhibitor of HIV where administration is twice a year by subcutaneous (under the skin) injection, and it would offer an additional treatment option to heavily treatment-experienced people living with HIV, with MDR.

Proposed Indication

Heavily treatment-experienced adults and adolescents aged 12 years and older weighing ≥35kg, living with HIV-1 infection with multidrug resistance (MDR) and on a failing antiretroviral (ARV) regimen.[1]

Technology

Description

Lenacapavir (Sunlenca, GS-6207) is a long-acting HIV-1 capsid inhibitor, with a multi-stage mechanism of action.[1-3] Capsid inhibitors interfere with HIV capsid, a protein shell that protects HIV's genetic material and enzymes needed for replication. Capsid inhibitors can disrupt HIV capsid during multiple stages of the viral life cycle. This prevents HIV from multiplying and can reduce the amount of HIV in the body.[4,5]

Lenacapavir is in clinical development in combination with an optimised background regimen (OBR), for heavily treatment-experienced adults and adolescents aged 12 years and older weighing ≥35kg, living with HIV-1 infection with MDR on a failing ARV regimen. In the phase II/III clinical trial (CAPELLA, NCT04150068), participants receive oral lenacapavir 600mg tablet on Days 1 and 2, and 300 mg tablet on Day 8, followed by a subcutaneous (SC) lenacapavir 927mg injection and will initiate an OBR at Day 1 SC visit (14 days after the first dose of oral lenacapavir). Participants will receive their subsequent SC lenacapavir injection at Week 26 Visit (relative to Day 1 SC). At Week 52 (relative to Day 1 SC), participants will be given an option to receive SC lenacapavir injections every 6 months (26 weeks).[1]

Key Innovation

Whilst most antivirals act on just one stage of viral replication, lenacapavir is designed to inhibit HIV-1 at multiple stages of its lifecycle and has no known cross resistance to other existing drug classes. If approved, lenacapavir would be the only HIV-1 treatment option administered twice yearly.[2]

In the ongoing phase II/III clinical trial (CAPELLA, NCT04150068), lenacapavir has demonstrated high rates of virologic suppression and clinically meaningful increases in CD4 counts in people living with HIV whose virus was no longer effectively responding to their current therapy.[2]

Regulatory & Development Status

Lenacapavir does not currently have Marketing Authorisation in the EU/UK for any indication.

In the EU, lenacapavir is undergoing Marketing Authorisation Application (MAA) for the treatment of HIV-1 infection.[6]

As of May 2019, lenacapavir has US FDA Breakthrough Therapy Designation for the treatment of HIV infection in heavily treatment-experienced patients with MDR in combination with other antiretroviral drugs.[7]

Lenacapavir is in phase II and III clinical trials for treatment of HIV-1 infection and as a pre-exposure prophylaxis (PrEP) of HIV-1 infection.[8]

Patient Group

Disease Area and Clinical Need

HIV damages cells in the immune system and weakens the body's ability to fight infections and disease. When the immune system is severely damaged by HIV this can lead to AIDS, which describes several potentially life-threatening infections and illnesses. There is no cure for HIV, however with early diagnosis and treatment people with HIV will not develop AIDS-related illnesses and live a near-normal lifespan.[9] HIV is transmitted by blood and body fluids through the lining of the anus, vagina, genitals, mouth and eyes, cuts and sores in the skin, and injecting into the bloodstream with shared injection equipment (e.g. needles).[10] Most people have a flu-like illness two to six weeks after initial HIV infection, after which symptoms may not appear for many years afterwards as the HIV damages the immune system.[9] In the UK, the most common cause of HIV is having unprotected sex with a person with HIV, particularly vaginal or anal sex.[10]

HIV can become drug resistant, as every time the virus replicates it creates a slightly different copy of itself (mutates), sometimes resulting a resistance to treatment drugs. This can be a pre-existing resistance prior to first-line treatment, or one that develops due to non-adherence (not taking the prescribed treatment as advised e.g., the correct time, every day). Drug resistant HIV could lead to a current treatment not working, and potentially other drugs within the same class, which is called cross-resistance. The next combination of drugs given as an alternative treatment may be more complicated or cause more side effects.[11]

In the UK, in 2019, there were a total of 98,552 people including 285 children aged under 15, that received HIV care.[12] In England (2020) there were an estimated 97,740 people living with HIV. The number of all new HIV diagnoses decreased by 33% between 2019 and 2020, from 3,950 to 2,630, respectively. In 2020 there were 614 deaths among people with HIV.[13] In the UK, in 2016, 9.6% people who tested positive for HIV had a detectable drug resistance mutation. This included increases in resistance to nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) (3.4% to 4.2%) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) (3.3% to 4.1%), compared to the previous year.[14] Based on the estimated people living with HIV (England, 2020) and the percentage of people with a detectable drug resistance mutation (UK, 2016), there may be approximately 9,383 people, in England, living with HIV that have a strain of drug resistant HIV.[13,14]

Recommended Treatment Options

Resistance tests are recommended when a person is diagnosed with HIV, about to start treatment for the first time or about to change treatment. This is to identify if the strain of HIV is resistant to any anti-HIV drugs.[11,14]

People whose HIV are resistant to the three main classes of drugs; NRTIs, NNRTIs, and protease inhibitors, are recommended by Terrence Higgins Trust:[11]

- Protease inhibitors (darunavir and tipranavir)
- Etravirine
- Integrase inhibitors (raltegravir, elvitegravir and dolutegravir)
- Maraviroc
- Enfuvirtide

Clinical Trial Information

Trial	**CAPELLA; NCT04150068; EudraCT 2019-003814-16;** A Phase 2/3 Study to Evaluate the Safety and Efficacy of Long Acting Capsid Inhibitor GS-6207 in

	Combination With an Optimized Background Regimen in Heavily Treatment Experienced People Living With HIV-1 Infection With Multidrug Resistance **Phase II/III** – Active, not recruiting **Location(s):** 4 EU countries, United States, Canada and other countries **Study completion date:** October 2023
Trial Design	Randomised, quadruple masked (participant, care provider, investigator, outcomes assessor), sequential assignment.
Population	N=72 (actual), aged 12 years and older and weighing ≥35kg, currently receiving a stable failing ARV regimen for >8 weeks, have MDR.
Intervention(s)	Experimental cohort 1: Oral lencapavir 600mg and 300mg + SC lencapavir 927mg + Failing ARV Regimen+OBR. Experimental cohort 2: Oral lencapavir 600mg and 300mg + SC lencapavir 927mg + OBR.
Comparator(s)	Oral lenacapavir placebo + oral lencapavir 600mg and 300mg +SC lencapavir 927mg + Failing ARV Regimen + OBR
Outcome(s)	**Primary outcome measure:** Percentage of Participants in Cohort 1 (intervention group) Achieving a Reduction of ≥ 0.5 $\log_{10}$ Copies/mL in Human Immunodeficiency Virus-1 Ribonucleic Acid (HIV-1 RNA) From Baseline to the End of Functional Monotherapy Period [Time Frame: Baseline up to Day 1 SC Visit (14 days after the first dose of oral lencapavir) or Day 15] See trial record for full list of other outcomes.
Results (efficacy)	In cohort 1 (intervention group), a decrease of at least 0.5 $\log_{10}$ copies per milliliter in the viral load by day 15 was observed in 21 of 24 patients (88%) in the lenacapavir group and in 2 of 12 patients (17%) in the placebo group (absolute difference, 71 percentage points; 95% confidence interval, 35 to 90). At week 26, a viral load of less than 50 copies per milliliter was reported in 81% of the patients in cohort 1 and in 83% in cohort 2 (intervention group), with a least-squares mean increase in the CD4+ count of 75 and 104 cells per cubic millimeter, respectively.[15]
Results (safety)	No serious adverse events related to lenacapavir were identified. In both cohorts, lenacapavir-related capsid substitutions that were associated with decreased susceptibility developed in 8 patients during the maintenance period (6 with M66I substitutions).[15]

Trial	**CALIBRATE; NCT04143594;** A Phase 2 Randomized, Open Label, Active Controlled Study Evaluating the Safety and Efficacy of Long-acting Capsid Inhibitor GS-6207 in Combination With Other Antiretroviral Agents in People Living With HIV

	Phase II – Active, not recruiting **Location(s):** United States, Dominican Republic and Puerto Rico **Study completion date:** May 2023
Trial Design	Randomised, open label parallel assignment.
Population	N=183 (actual); age 18 years and older; living with HIV.
Intervention(s)	Experimental arm 1: Oral lenacapavir + oral emtricitabine/tenofovir alafenamide (F/TAF) + SC lenacapavir+ oral tenofovir alafenamide (TAF) Experimental arm 2: Oral lenacapavir + oral F/TAF + SC lenacapavir + oral bictegravir (BIC) Experimental arm 3: Oral lenacapavir + oral F/TAF
Comparator(s)	Oral bictegravir/emtricitabine/tenofovir alafenamide (BIC/F/TAF)
Outcome(s)	**Primary outcome measure:** Proportion of Participants with HIV-1 RNA < 50 Copies/mL at Week 54 as Determined by the US FDA-defined Snapshot Algorithm [Time Frame: Week 54] See trial record for full list of other outcomes.
Results (efficacy)	High rates of viral suppression were seen in all arms; however, there was one case of drug resistance in one of the subcutaneous lenacapavir arms.[16]
Results (safety)	Lenacapavir regimens led to no study drug-related serious adverse events and only mild or moderate injection site reactions.[16]

Estimated Cost

The cost of lenacapavir is not yet known.

Relevant Guidance

NICE Guidance

No relevant guidance found.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract For Specialised Human Immunodeficiency Virus Services (Adults). B06/S/a.

Other Guidance

- British HIV Association (BHIVA). BHIVA guidelines on antiretroviral treatment for adults living with HIV-1 2022 – consultation version. 2022.[17]

- BHIVA. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update). August 2016.[18]

Additional Information

Gilead Sciences Ltd have not engaged with NIHR Innovation Observatory correspondence regarding pipeline queries since 2020 and contacted NICE directly to provide Marketing Authorisation Application timelines.

Gilead Sciences Ltd did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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