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HEALTH TECHNOLOGY BRIEFING
JULY 2021

Leronlimab in addition to antiretroviral therapy for treatment experienced adult HIV-1 patients

NIHRIO ID	17194	**NICE ID**	10625
Developer/Company	CytoDyn Inc	**UKPS ID**	Not Available

Licensing and market availability plans	Currently in phase III/II clinical trials.

SUMMARY

Leronablim is in clinical development to treat experienced adult HIV-1 patients infected with C-C chemokine receptor type 5 (CCR5)-tropic virus. Antiretroviral medicines are used to treat HIV. However, poor adherence and the subsequent development of drug resistance is one reason why HIV treatment can fail and therefore requires more treatment options.

Leronlimab is an antibody that targets a protein displayed on the surface of HIV (human immunodeficiency virus) treatment. Leronlimab has a unique mechanism of action by binding to the CCR5 protein with high affinity, and ultimately inhibiting HIV entry into CD4 cells. It is administered via subcutaneous (SC) injection. Leronalimab has been shown to be effective safe and effective compared to the standard of care. If licensed, leronlimab will offer an additional treatment option for treatment-experienced adult HIV-1 patients infected with CCR5-tropic virus, who currently have no well-tolerated therapies available.

PROPOSED INDICATION

Treatment-experienced adult HIV-1 patients infected with C-C chemokine receptor type 5 (CCR5) tropic virus.[1,2]

TECHNOLOGY

DESCRIPTION

Leronlimab (Vyrologix, PRO-140) is a humanized IgG4, kappa monoclonal antibody directed towards CCR5 that has re-emerged as a potential novel agent for HIV treatment. Leronlimab has a unique mechanism of action by binding to CCR5 with high affinity, and ultimately inhibiting HIV entry into CD4 cells. Leronlimab binds specifically to the N-terminus and extracellular loop 2 domain of CCR5 to interfere with the final phase of viral binding to the CD4 cell.[3]

In the phase IIb/III trial (NCT02483078), patients in the experimental arm received 350mg weekly subcutaneous (SC) injection, and existing antiretroviral therapy (ART). After one week, all subjects entered the 24 week single-arm open label treatment period. During this period, all subjects received leronlimab SC injection and optimized background therapy chosen on the basis of a subject's resistance test results and treatment history.[1]

INNOVATION AND/OR ADVANTAGES

Leronlimab is the world's first self-injectable, SC injection for HIV. Advantages over the current standard of care, highly active antiretroviral therapy (HAART), include no serious side effects and no serious adverse events related to leronlimab with exposure to over 800 patients, enhanced compliance, and longer half-life. 76% of patients have resistance to at least one drug with HAART. There has been no drug resistance identified in patients taking leronlimab in monotherapy for over 4 years.[4]

In pre-clinical studies, leronlimab has demonstrated the ability to mimic CCR5 deficiency by binding to CCR5 receptors, thereby preventing HIV from interacting with its primary co-receptor.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Leronlimab as monotherapy or in addition to ART does not currently have Marketing Authorisation in the EU/UK for any indication.

Leronlimab is in phase III/II clinical development for the following indications:[5]

- Locally advanced or metastatic solid tumours
- COVID-19
- Nonalcoholic steatohepatitis
- Triple negative breast neoplasms

Leronlimab in addition to ART has received Fast Track designation by the U.S. Food and Drug Administration.[4]

PATIENT GROUP

DISEASE BACKGROUND

HIV is a virus that attacks the body's immune system.[6] It damages the cells in the immune system and weakens the ability to fight everyday infections and disease. If HIV is not treated, it can lead to AIDS (acquired immunodeficiency syndrome).[7]

There are two main types of HIV; HIV-1 (the most common) and HIV-2 (relatively uncommon and less infectious). The strains of HIV-1 can be classified into four groups. Of these, M is the 'major' group and is responsible for the majority of the global HIV epidemic.[8]

The most common way of acquiring HIV in the UK is through having unprotected anal or vaginal sex. Other ways of getting HIV include: sharing needles, syringes or other injecting equipment; transmission from mother to baby during pregnancy, birth or breastfeeding; and through contaminated blood transfusions.[9,10]

Most people infected with HIV experience a short, flu-like illness that occurs 2-6 weeks after infection. After this, HIV may not cause any symptoms for several years. It is estimated up to 80% of people who are infected with HIV experience this flu-like illness. The most common symptoms are: fever, sore throat, body rash. Other symptoms can include: tiredness, joint pain, muscle pain and swollen glands. The symptoms usually last 1-2 weeks, but can be longer. They are a sign that the immune system is putting up a fight against the virus. Once the immune system becomes severely damaged, symptoms can include: weight loss, chronic diarrhoea, night sweats, skin problems, recurrent infections and serious life-threatening illnesses.[11]

People who have experienced HIV treatment, are at greater risk than the general population of non-infectious comorbidities such as cardiovascular and metabolic complications, liver disease, including chronic hepatitis C, and non-AIDS malignancies.[12]

Increased use of HIV medicines has been accompanied by the emergence of HIV drug resistance, the levels of which have steadily increased in recent years. HIV drug resistance is caused by changes in the genetic structure of HIV that affect the ability of drugs to block the replication of the virus. All current antiretroviral drugs, including newer classes, are at risk of becoming partly or fully inactive because of the emergence of drug-resistant virus strains. If not prevented, HIV drug resistance can jeopardize the efficacy of antiretroviral drugs, resulting in increased numbers of HIV infections and HIV-associated morbidity and mortality.[13]

CLINICAL NEED AND BURDEN OF DISEASE

The total number of people newly diagnosed with HIV continued to decrease in the UK in 2019 to 4,139 (1,139 females and 3,000 males); a 10% fall from 4,580 in 2018 and a fall of 34% from a peak of 6,312 new diagnoses reported in 2014. In 2019, a total of 98,552 people (30,388 females and 68,088 males) were seen for HIV care in the UK.[14]

In 2019, it was estimated that there are 105,200 people living with HIV in the UK. 94% of these people are diagnosed, and therefore know that they have HIV. This means that around 1 in 16 people living with HIV in the UK do not know that they have the virus. 98% of people diagnosed with HIV in the UK are on treatment, and 97% of those on treatment are virally suppressed which means they cannot spread the virus. Of all the people living with HIV in the UK, 89% are virally suppressed.[15]

The number of deaths among people with HIV has remained stable with 622 deaths (498 males and 124 females) in 2019. This represents a crude mortality rate of 631 per 100,000 population living with diagnosed HIV infection.[14]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

While there is no cure for HIV, there are very effective treatments that enable most people with the virus to live a long and healthy life. HIV is treated with antiretroviral medicines, which work by stopping the virus replicating in the body. This allows the immune system to repair itself and prevent further damage. A combination of HIV drugs is used because HIV can quickly adapt and become resistant.[16]

ART is usually a combination of three or more medications from several different drug classes. This approach has the best chance of lowering the amount of HIV in the blood. There are many ART options that combine three HIV medications into one pill, taken once daily. Each class of drugs blocks the virus in different ways. Treatment involves combinations of drugs from different classes to: account for individual drug resistance (viral genotype), avoid creating new drug-resistant strains of HIV, and maximize suppression of virus in the blood. Two drugs from one class, plus a third drug from a second class, are typically used.[17]

CURRENT TREATMENT OPTIONS

British HIV Association (BHIVA) recommend patients with extensive drug resistance are switched to a new ART regimen containing at least two preferably three fully active agents with at least one active ritonavir-boosted protease inhibitor (PI/r) such as twice-daily darunavir/r or darunavir/cobicistat and one agent with a novel mechanism (an integrase inhibitor (INI), maraviroc or enfuvirtide) with etravirine an option based on viral susceptibility. Individuals with extensive drug resistance including reduced darunavir susceptibility may receive dolutegravir as the INI.[18]

PLACE OF TECHNOLOGY

If licensed, leronlimab will offer an additional treatment option for treatment-experienced adult HIV-1 patients infected with CCR5-tropic virus, who currently have no well-tolerated therapies available.

CLINICAL TRIAL INFORMATION

Trial	**NCT02483078; A Multi-center, Randomized, Double-blind, Placebo-controlled Trial, Followed by Single-arm Treatment of PRO 140 in Combination With Optimized Background Therapy in Treatment-Experienced HIV-1 Subjects** **Phase II/III** - completed **Location(s):** USA and Puerto Rico **Actual study completion date:** July 2018
Trial design	Randomised, parallel assignment, quadruple-blinded
Population	N=52 (actual); treatment-experienced HIV-1 adults
Intervention(s)	- Leronlimab 350mg weekly SC Inj. + existing ART for one week. After one week, all subjects will enter the 24-week single-arm, open-label treatment period. During this period, all subjects will receive leronlimab SC injection and Optimized Background Therapy
Comparator(s)	- Placebo weekly SC Inj. + existing ART for one week. After one week, all subjects will enter the 24-week single-arm, open-label treatment period. During this period, all subjects will receive leronlimab SC injection and Optimized Background Therapy
Outcome(s)	Proportion of participants with ≥ 0.5 log10 reduction in HIV-1 RNA viral load from baseline at the end of the 1-week double-blind treatment period [Time Frame: 1 week] See trial record for full list of other outcomes
Results (efficacy)	81% of patients completing trial achieved HIV viral load suppression of < 50 cp/mL.[4]
Results (safety)	-

Trial	**NCT03902522; A Multi-center, Two-Part, Single-Arm, Open Label, 25-Week Trial With PRO 140 in Treatment-Experienced HIV-1 Subjects** **Phase II/III** - completed **Location(s):** USA **Primary study completion date:** December 2019
Trial design	Single group assignment, open label
Population	N=25 (estimated); treatment-experienced HIV-1 adults
Intervention(s)	- ART for one week followed by leronlimab 700mg weekly SC Inj. + existing ART for the next week. Subsequently, all subjects will enter the 24-week single-arm, open-label treatment period. During this period, all subjects will receive leronlimab SC injection and Optimized Background Therapy

Comparator(s)	No comparator
Outcome(s)	Proportion of participants with ⩾ 0.5 log10 reduction in HIV-1 RNA viral load from baseline at the end of the initial 1-week treatment period [Time Frame: 1-week]
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of leronlimab is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Cabotegravir with rilpivirine for the oral treatment of HIV-1 [GID-TA10604]. Expected date of issue to be confirmed
- NICE technology appraisal in development. Fostemsavir for treating adults with multidrug resistant HIV-1 for whom it is not possible to construct a suppressive anti-viral regimen [GID-TA10605]. Expected date of issue to be confirmed
- NICE technology appraisal in development. Ibalizumab for treating adults infected with multidrug resistant HIV-1 for whom it is not possible to construct a suppressive anti-viral regimen [GID-TA10657]. Expected date of issue to be confirmed
- NICE guideline. HIV testing: increasing uptake among people who may have undiagnosed HIV [NG60]. December 2016

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for specialised human immunodeficiency virus services (Adult): B06/S/a.
- NHS England. Clinical Commissioning Policy Statement: Dolutegravir/lamivudine for the treatment of Human Immunodeficiency Virus (HIV-1) infected adults and adolescents over 12 years of age (1920). 200301P. March 2020.
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- NHS England. Clinical Commissioning Policy: Elvitegravir/ cobicistat/ emtricitabine/ tenofovir for treatment of HIV in adults. F03/P/a. July 2015.

- NHS England. Clinical Commissioning Policy: Treatment as Prevention (TasP) in HIV infected adults. F03/P/c. July 2015.

OTHER GUIDANCE

- NICE Clinical Knowledge Summary. HIV infection and AIDS. 2020.[19]
- Ryom L, Cotter A, de Miguel R, Beguelin C, Podlekareva D, Arribas JR et al. 2019 update of the European Aids Clinical Society guidelines for treatment of people living with HIV version 10.0. 2019.[20]
- British HIV Association. BHIVA guidelines for the routine investigation and monitoring of adult HIV-1-positive individuals (2019 interim update). 2019.[21]
- British HIV Association. BHIVA guidelines for the treatment of HIV-1-positive adults with antiretroviral therapy 2015 (2016 interim update). 2016.[18]

ADDITIONAL INFORMATION

CytoDyn Inc 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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