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HEALTH TECHNOLOGY BRIEFING
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Ibalizumab in combination with other antiretroviral(s) for multidrug-resistant HIV-1 infection

NIHRIO ID	17193	**NICE ID**	10230
Developer/Company	Theratechnologies Inc	**UKPS ID**	654337

Licensing and market availability plans	Marketing authorisation approval in EU was granted in September 2019.[1,2]

SUMMARY

Ibalizumab in combination with other antiretroviral(s) has been developed for the treatment of adults infected with multidrug-resistant HIV-1 (MDR HIV-1). HIV is a virus that damages the cells in the immune system and weakens the ability to fight everyday infections and diseases. HIV-1 is the most common type of HIV infection, which is incurable but there are effective treatments that enable most infected people to live a healthy life. Antiretroviral medicines are used to treat HIV. There are however limited effective treatments for some treatment-experienced patients with extensive MDR HIV-1.

Ibalizumab is given by intravenous infusion. It is an antiretroviral medicine that acts against HIV-1. It stops the virus entering the target cells by binding to a receptor called CD4 receptor and prevents the viral transmission that occurs via HIV to host cell fusion and infected host cell to uninfected host cell fusion. Ibalizumab in combination with other antiretroviral(s) will offer an additional treatment option for patients infected with MDR HIV-1 for whom it is otherwise not possible to construct a suppressive antiviral regimen. This patients group currently have limited effective therapies available.

PROPOSED INDICATION

Ibalizumab in combination with other antiretroviral(s), is indicated for the treatment of adults infected with multidrug-resistant HIV-1 (MDR HIV-1) for whom it is otherwise not possible to construct a suppressive antiviral regimen.[3]

TECHNOLOGY

DESCRIPTION

Ibalizumab (Trogarzo)[4-8] is a recombinant humanised monoclonal antibody that blocks HIV-1 from infecting CD4+ T-cells by binding to domain 2 of CD4 and interfering with post-attachment steps required for the entry of HIV-1 virus particles into host cells and preventing the viral transmission that occurs via HIV to host cell fusion and infected host cell to uninfected host cell fusion .[8]

Ibalizumab in combination with other antiretroviral(s) has been developed for the treatment of patients infected with MDR HIV-1 for whom it is otherwise not possible to construct a suppressive antiviral regimen.[3] In the phase III clinical trial (NCT02475629), participants received 2000 mg IV ibalizumab (loading dose) on day 7 followed in 14 days (on day 21) by 800 mg IV ibalizumab administered once every two weeks, plus an Optimised Background Regimen (OBR) beginning on day 14 followed up to week 25.[4,9] In the phase III clinical trial (NCT02707861), eligible patients enrolled in the previous study continued to receive IV infusions of ibalizumab at the dosage 800 mg once every two weeks for up to 96 weeks. A limited number of long-term patients received 2000 mg once every four weeks as a continuation of an earlier phase IIb study.[5]

INNOVATION AND/OR ADVANTAGES

The binding specificity of ibalizumab to domain 2 of CD4 allows ibalizumab to block viral entry into host cells without causing immunosuppression. Epitope mapping studies indicate that ibalizumab binds to a conformational epitope located primarily in domain 2 of the extracellular portion of the CD4 receptor. This epitope is positioned on the surface of CD4 opposite to the site in domain 1 that is required for CD4 binding of the MHC class II molecules and therefore does not interfere with CD4-mediated immune functions. Additionally, ibalizumab does not interfere with gp120 attachment to CD4.[8] As a result, this new mechanism of action is a new class to which multi-drug resistant HIV has not previously been exposed provides new ability to control the patient's progression toward AIDS and death. Unlike new drugs in existing antiretroviral classes, Ibalizumab does not have cross-resistance with other antiretrovirals which is essential in patients with limited options.[8,10,a]

In the event of resistance-related treatment failure, HIV treatment guidelines recommend the initiation of new regimens with at least two, preferably three, fully active agents. The availability of a CD4-directed post-attachment HIV-1 inhibitor with non-overlapping resistance provides an opportunity to construct a regimen to suppress the viral load and maintain immune status in patients that currently do not have one.[9,11] Further, a heavily mutated and drug-resistant virus can be transmitted to other people leading to advanced virus in newly diagnosed persons. This increases the burden of HIV disease and NHS costs in caring for this complex patient type.

[a] Information provided by Theratechnologies Inc

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

In July 2019, the Committee for Medicinal Products for Human use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product ibalizumab, intended for the treatment of HIV infection.[3] Ibalizumab was approved on 26th September 2019 by the European Commission. The company indicated that they will initiate their launch plan to introduce ibalizumab sequentially on a country-by-country basis as they obtain public reimbursement.[1]

Ibalizumab is being studied in a phase III trial to administer as an undiluted "IV push" over a reduced interval in clinically stable HIV-1 infected ibalizumab experienced patients.[12]

PATIENT GROUP

DISEASE BACKGROUND

Human immunodeficiency virus (HIV) is a virus that damages the cells in the immune system and weakens the ability to fight everyday infections and disease.[13] The acquired immune deficiency syndrome (AIDS) is a diagnosis given to all patients when their CD4 cell count goes below 200 cells/mL. These patients are immunocompromised leading to a number of potentially life-threatening infections and illnesses that happen when the immune system has been severely damaged by HIV.[14]

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.[15]

The ability of HIV to mutate and reproduce itself in the presence of antiretroviral drugs is called HIV drug resistance. The consequences of HIV drug resistance include treatment failure and further spread of drug resistant HIV. This can compromise the effectiveness of the limited therapeutic options to reach the last 90 target (90% of all people accessing ART will have viral load suppression) which would further reduce HIV incidence, mortality and morbidity.[16,17]

Most people diagnosed with HIV in the UK acquire the virus through unprotected vaginal or anal sex. Also HIV infection can be transmitted through unprotected oral sex and sharing sex toys with someone infected with HIV.[18] Other risk factors for getting HIV include sharing needles, syringes and other injecting equipment; transmission of the virus from mother to baby before or during birth or by breastfeeding; receiving unsafe injections, blood transfusions (now very rare in the UK); experiencing accidental needle stick injuries, including among health workers.[18,19] Those health workers or others exposed to multi-drug resistant HIV via these methods contract an already advanced strain from diagnosis that is more difficult to prevent with Post-Exposure Prophylaxis.[20]

The symptoms of HIV vary depending on the stage of infection. Though people living with HIV tend to be most infectious in the first few months, many are unaware of their status until later stages.[19] Most people experience a short flu-like illness two to six weeks after HIV infection, which lasts for a week or two. After these symptoms disappear, HIV may not cause any symptoms for many years, although the virus continues to damage the immune system.[13] Consequently an individual can develop other signs and symptoms, such as swollen lymph nodes, weight loss, fever, diarrhoea and cough. Without treatment, they could also develop severe illnesses such as tuberculosis, cryptococcal meningitis, severe bacterial infections and cancers such as lymphomas and Kaposi's sarcoma, among others.[19]

CLINICAL NEED AND BURDEN OF DISEASE

In 2017, 4,363 people were newly diagnosed with HIV and it was estimated that there were 101,600 people living with HIV in the UK.[21] In 2017, 92% (Credible interval (CrI) 88 to 94%) of the estimated 101,600 (CrI 99,300 to 106,400) people living with HIV infection in the UK were diagnosed, 98% of people diagnosed were receiving treatment and 97% of people receiving treatment were virally suppressed. Overall, 87% of people living with HIV in the UK were estimated to have an undetectable viral load and therefore unable to pass on the infection.[22] The remaining 13% of the predicted population would be at risk of transmission.[23]

Of the 87,057 people attending for care in 2015, 97% were retained in care 2 years later in 2017.[22] In the UK, the population of people living with diagnosed HIV infection (93,385) is growing older and diversifying.[22] In the UK, among drug-experienced patients, the prevalence of HIV resistance to any drug class fell markedly from 72.4% in 2002 to 30% in 2014.[24]

In 2017, 428 people with HIV infection died from any cause and over half of deaths (62%) were among people aged 50 years and over. In 2017, the crude overall mortality rate among those aged 15 to 59 years who had their HIV infection diagnosed promptly (CD4 cell count ≥350 cells/mm^3) was 1.22 per 1,000 compared to 1.66 per 1,000 in the general population of the same age group.[22] Patients with resistance to the three major classes of ARTs had a greater chance of dying when controlling for CD4 cell count, plasma HIV RNA level, clinical stage, gender, age, and drug exposure.[25,26] The same study conducted Kaplan-Meier analyses for death, AIDS-related death, and new AIDS death for patients with no resistance mutations compared to those patients with resistance to as many as three major drug classes (MDR HIV-1). At 48 months, mortality for patients with HIV-1 was 8.9% vs. 27.1% for those patients with MDR HIV-1, chance of AIDS-related death was 6.1% for HIV-1 vs. 21.5% for MDR HIV-1, and chance of a new AIDS event/death was 16.0% in HIV-1 vs. 35.9% in MDR HIV-1 Since the time of this study, a new class of ART, i.e. INSTIs, have come onto the market. However, patients have also developed resistance to the drugs in the INSTI class and most recently including resistance to dolutegravir.[27,28]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

While there is currently 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 medications, 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.[29] Such combinations should have synergistic or additive activity while ensuring that their toxicity is not additive. It is recommended that viral sensitivity to antiretroviral drugs is established before starting treatment or before switching drugs if the infection is not responding.[30]

Recommendations for treatment of individuals diagnosed with HIV-1 in the UK issued by the British HIV Association (BHIVA) show that overall, therapy selection in patients with MDR HIV-1 is complex and individualised, and must consider, among others, contraindications and drug-drug interactions (ARV and concomitant medication), tolerability, cross-resistance within ARV classes; viability of CCR5-antagonists in only a proportion of patients, viral load and

CD4+ cell count, treatment history, drug resistance profile, adherence, as well as future salvage regimens.[31]

CURRENT TREATMENT OPTIONS

Etravirine has been licensed in the UK since 2008 for adults with HIV infection resistant to other non-nucleoside reverse transcriptase inhibitor and protease inhibitors in combination with other antiretroviral drugs (including a boosted protease inhibitor).[32]

PLACE OF TECHNOLOGY

Ibalizumab in combination with other antiretroviral(s) will offer an additional treatment option for patients infected with MDR HIV-1 for whom it is otherwise not possible to construct a suppressive antiviral regimen.

CLINICAL TRIAL INFORMATION

Trial	NCT02475629, **TMB-301; ibalizumab in combination with OBR; phase III**	NCT02707861, **TMB-311; ibalizumab in combination with OBR; phase III extension**
Sponsor	TaiMed Biologics Inc.	TaiMed Biologics Inc.
Status	Published	Complete but unpublished
Source of Information	Trial registry;[4] publication,[9] abstract[33,34]	Trial registry;[5] publication[9]
Location	USA, Puerto Rico, and Taiwan.	USA and Puerto Rico
Design	Single group assignment, open label.	Non-Randomized, open label, parallel assignment
Participants	n=40; aged 18 years and older; HIV-1 infection; no acquired AIDS-defining events in the 3 months before screening, other than cutaneous Kaposi's sarcoma or wasting syndrome due to HIV; life expectancy that is >6 months; viral load >1,000 copies/mL and documented resistance to at least one antiretroviral medication from each of three classes of antiretroviral medications as measured by resistance testing (resistance to antiretroviral was assessed based on patient's treatment history and genotypic and phenotypic assessments); a history of at least 6 months on antiretroviral treatment; receiving a stable highly active antiretroviral regimen for at least 8 weeks before Screening and are willing to continue that regimen until day 14,	n= 79; aged 18 years and older; Cohort 1: receiving ibalizumab via other TaiMed-sponsored or investigator-sponsored protocol; Cohort 2: HIV-1 infection; a viral load >1,000 copies/mL and documented resistance to at least one antiretroviral medication from each of three classes of antiretroviral medications as measured by previous viral resistance testing (resistance testing is not provided by the study for qualification purposes); a history of at least 6 months on antiretroviral treatment; receiving a failing antiretroviral regimen or have failed and are off therapy; viral sensitivity/susceptibility to at least one antiretroviral agent, other than ibalizumab, as determined by previous resistance test performed within 6 months of screening and

	or (in the past 8 weeks) have failed and are off therapy and are willing to stay off therapy until day 14 (for the 7-day control and 7-day functional monotherapy periods); [b] full viral sensitivity/ susceptibility to at least one antiretroviral agent, other than ibalizumab, as determined by the screening resistance tests and be willing and able to be treated with at least one agent to which the patient's viral isolate is fully sensitive/susceptible according to the screening resistance tests completed at baseline.[b]	be willing and able to be treated with at least one agent to which the patient's viral isolate is fully sensitive/susceptible according to the resistance tests used for screening as a component of OBR.
Schedule	Participants received 2000 mg of ibalizumab intravenously (loading dose, day 7 of the study) followed by a maintenance dose of 800 mg of ibalizumab intravenously every two weeks, starting on day 21 of the study. The optimisation of the OBR occurred on day 14, 7 days after the loading dose of ibalizumab.	Cohort 1 received continued administration of IV ibalizumab (combined with OBR) for patients completing a prior ibalizumab clinical trial (TaiMed-sponsored or Investigator-Sponsored). Patients continued to receive IV infusions of ibalizumab at the dosage assigned in the previous study - either 800 mg once every two weeks, or 2000 mg once every four weeks (if a patient was in this dosing arm of the phase 2b study). Patients were followed up to 96 weeks or until ibalizumab becomes commercially available.[b] Cohort 2 received IV ibalizumab (combined with OBR) 800 mg once every two weeks for qualifying patients who have never received ibalizumab. Administered for 48 weeks, or until ibalizumab becomes commercially available.
Follow-up	Active treatment duration was 24 weeks with a 1 week initial control period for a study duration of 25 weeks. All patients that completed study 301 according to the protocol could continue ibalizumab treatment in the extension study (Study TMB-311).	Active treatment duration: for 48 weeks, or until ibalizumab becomes commercially available in the US, whichever occurs first. Follow-up duration: 96 weeks
Primary Outcomes	• The percentage of patients who had a decrease in viral load of at	• Safety and tolerability of ibalizumab + OBR assessed by

[b] Information added by Theratechnologies Inc

	least 0.5 log_{10} copies per millilitre from during the Ibalizumab functional monotherapy period from loading dose administration on day 7 to day 14.	the occurrence of adverse events and discontinuations [Time frame: through 48 weeks] • Effectiveness of ibalizumab + OBR by viral load log10 Change from baseline (Cohort 2 only) [Time frame: at 7 days]
Secondary Outcomes	• Undetectable viral load as a measure of efficacy [Time frame: at week 25/end of study] • Mean change in viral load as a measure of efficacy [Time frame: at day 14 and week 25/end of study] • End of study viral load reductions as a measure of efficacy [Time frame: at week 25/end of study] • Mean Change in CD4+ Cell count as a measure of efficacy and safety [Time frame: at week 25/end of study] • Viral sensitivity/susceptibility changes associated with virologic failure after administration of Ibalizumab as a measure of efficacy [Time frame: through week 25/end of study] • CD4 Receptor density as a measure of pharmacodynamics [Time frame: through week 25/end of study] • CD4 receptor occupancy as a measure of pharmacodynamics [Time frame: through week 25/end of study] • Number of participants with physical examination abnormalities as a measure of safety and tolerability [Time frame: through week 25/end of study] • Number of participants with vital sign measurement abnormalities as a measure of safety and tolerability [Time frame: through week 25/end of study] • Number of participants with 12-lead electrocardiogram	• HIV resistance [Time frame: through 48 weeks] • Effectiveness of ibalizumab + OBR by viral suppression to <50 copies (Cohort 2 only) [Time frame: through 48 weeks] • Effectiveness of ibalizumab + OBR by viral suppression to <400 copies (Cohort 2 only) [Time frame: through 48 weeks] • Effectiveness of ibalizumab + OBR by mean change in viral load from baseline (Cohort 2 only) [Time frame: through 48 weeks] • Effectiveness of ibalizumab + OBR by 0.5 Log10 decrease in viral load from baseline (Cohort 2 only) [Time frame: through 48 weeks] • Effectiveness of ibalizumab + OBR by 1.0 Log10 decrease in viral load from baseline (Cohort 2 only) [Time frame: through 48 weeks]

	abnormalities as a measure of safety and tolerability [Time frame: through week 25/end of study] • Number of participants with abnormal clinical laboratory parameters as a measure of safety and tolerability [Time frame: through week 25/end of study] • Number of participants with adverse events as a measure of safety and tolerability [Time frame: through week 25/end of study] • Number of participants with Class C AIDS-defining events as a measure of safety and tolerability [Time frame: through week 25/end of study] • Immunogenicity of Ibalizumab as a measure of safety and tolerability [Time frame: through week 25/end of study] Other outcome measures: • Patient-related assessment - quality of life as a measure of tolerability [Time frame: week 25/end of study] • Ibalizumab serum concentrations as a measure of pharmacokinetics [Time frame: through week 25/end of study]	
Key Results	In this study, the median duration of HIV infection of 23 years, median CD4 cell count of 73 cells/µl (range 0 - 676), and mean CD4 cell count was 150± 182 cells/µl[9] are the most advanced for any registrational trial in antiretrovirals. Further, 33% of patients had a baseline CD4 cell count of <10 cells indicating patients have life-threatening HIV disease in this group.[c] A total of 31 patients completed the study. The mean baseline viral load was 4.5 log_{10} copies per	Cohort 1 enrolled 27 eligible patients from TMB-301, median viral load (VL) reduction from Baseline (of TMB-301) was 2.5 log10 at Week 25 and 2.8 log10 at Week 96 in the Intent-to-Treat-Missing- Equals-Failure analysis. Of 16 patients with HIV RNA <50 copies/mL at Week 25, 14 maintained viral suppression through Week 96, with one additional patient achieving viral suppression by Week 96. Median CD4+ T cell increase was 42 cells/µl from Baseline to Week 25

[c] Information provided by Theratechnologies Inc

	millilitre, and the mean CD4 count was 150 per microliter. Of the 40 patients in the intention-to-treat population, 33 (83%) had a decrease in viral load of at least 0.5 log_{10} copies per millilitre from baseline (P<0.001 for the comparison with the control period). The mean viral-load decrease was 1.1 log_{10} copies per millilitre. During the control period, 1 patient, who received the optimized background regimen prematurely, had a decrease in viral load of 0.5 log_{10} copies per millilitre. At week 25, patients who had received ibalizumab plus an optimised background regimen had a mean decrease of 1.6 log_{10} copies per millilitre from baseline; 43% of the patients had a viral load of less than 50 copies per millilitre, and 50% had a viral load of less than 200 copies per millilitre. Among 10 patients who had virologic failure or rebound, in vitro testing identified 9 who had a lower degree of susceptibility to ibalizumab than at baseline. It was found that ibalizumab combined with an OBR had antiviral and immunologic activity. The trial findings also showed the feasibility and acceptability of biweekly (every two weeks) intravenous administration of an antiretroviral therapy.[d]	(n=27), and 45 cells/µl at Week 96 among those who remained on study (n=22). Cohort 2 enrolled 38 patients new to Ibalizumab with a median age of 53 years, mostly male (87%) and white (53%). At Baseline, median VL was 4.7 log10 copies/mL, CD4 cell count was 26 cells/mm3 and overall susceptibility score of 1. A ≥0.5 log10 decrease in VL from Baseline was achieved in 28 of 37 patients (76%) at Day 7. Of 24 patients who completed the Week 24 visit, 11 (46%) had HIV-1 RNA levels <50 copies/mL. Of 17 patients with a VL assessment at Week 48, 8 (47%) achieved <50 copies/mL. Seven patients did not have a Week 48 endpoint because they withdrew from the study to receive commercial IBA. At both time points, the median change in VL from Baseline was -2.6 log10 copies/mL.[d]
Adverse effects (AEs)	The most common adverse event was diarrhoea (in 20% of patients). Four patients died from causes related to underlying illnesses; one had a serious adverse event (the immune reconstitution inflammatory syndrome (IRIS)) that was deemed to be related to ibalizumab therapy.	Ibalizumab plus OBR continued to be well tolerated for those in Cohort 1 with no new safety concerns emerging between week 25 and 96. Twenty-two of 27 patients completed treatment up to 96 weeks. Reasons for discontinuation included 2 consent withdrawals, 1 physician decision, and 2 deaths deemed unrelated to Ibalizumab (advanced cardiovascular disease and progression of CMV disease).

[d] Information provided by Theratechnologies Inc

		Ibalizumab plus OBR was well tolerated in patients starting Ibalizumab in Cohort 2. The most frequently reported treatment-emergent adverse events (TEAEs) were diarrhea (24%), headache (21%), and nausea, cough, rash, and fatigue (16% each). No injection site reactions related to ibalizumab were reported. Most events were mild; 9 patients reported Grade ⩾ 3 TEAEs. Two events were fatal (sepsis and cardiac arrest); neither deemed related to ibalizumab. One event of immune reconstitution inflammatory syndrome was reported and considered possibly related to Ibalizumab.[e]
Expected reporting date	-	Previously reported as November 2018

ESTIMATED COST

The cost of ibalizumab is not known yet.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE quality standard. HIV testing: encouraging uptake (QS157). September 2017.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

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ADDITIONAL INFORMATION

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