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ViiV Healthcare presents phase III data comparing once-daily maraviroc in combination with darunavir/ritonavir with emtricitabine/tenofovir plus darunavir/ritonavir in treatment-naïve adults with HIV-1

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An investigational two drug-regimen of maraviroc dosed once daily, combined with darunavir/ritonavir (DRV/r) showed inferior efficacy compared to emtricitabine/tenofovir (FTC/TDF) with DRV/r

London, UK – 22 July 2014 - ViiV Healthcare today presented, at the 20th International AIDS Congress in Melbourne, Australia, the analysis of the 48-week results from the phase III MODERN study comparing maraviroc (MVC; marketed as Celsentri® /Selzentry®) dosed once daily with darunavir/ritonavir (DRV/r) to emtricitabine/tenofovir (FTC /TDF) with DRV/r in antiretroviral-naïve subjects. The study did not meet the -10% non-inferiority endpoint. The proportion of study participants who were virologically suppressed (HIV-1 RNA <50 copies/mL) at week 48 was 77.3% for MVC+DRV/r compared to 86.8% for FTC /TDF +DRV/r (95% confidence interval -15.0% to -4.4%).

MODERN was designed as a double-blind, double dummy non-inferiority 96-week study, intended to determine if an investigational two-drug regimen of once-daily MVC (a CCR5 receptor antagonist) and DRV/r (a boosted protease inhibitor) could provide comparable antiviral activity when compared to a three-drug regimen consisting of two once-daily nucleosides (FTC /TDF) and DRV/r in antiretroviral-naïve subjects. More MVC subjects discontinued due to lack of efficacy (8.3% for MVC+DRV/r vs 2.0% for FTC /TDF +DRV/r) and there were more protocol defined treatment failures in the maraviroc arm (10.1% for MVC and 3.2% for FTC /TDF). There were no reports of viral resistance in subjects who failed in either arm of the study.

The secondary endpoints included safety and tolerability of maraviroc as well as the utility of genotypic and phenotypic testing and tropism change. There were no new or unique safety findings, and discontinuations due to adverse events were 4.8% for MVC+DRV/r and 4.5% for FTC /TDF +DRV/r. Category C events, grade 3/4 adverse events and laboratory abnormalities were similar between the two treatment arms.

The study was also designed to compare the performance of a genotypic tropism test with the phenotypic tropism test Trofile® (ESTA, Monogram Biosciences) to determine whether patients had R5-tropic HIV-1 virus and were therefore eligible for maraviroc treatment. This was the first trial to compare the treatment outcomes of patients prospectively randomized to either a genotypic or phenotypic tropism test. The proportion of subjects meeting the primary endpoint were comparable between the two arms in predicting a clinical response (for the MVC arm, difference was 6.86% in favour of genotyping, 95% confidence interval -1.28% to 15.0%; for FTC /TDF, difference was 0.3%, 95% confidence interval -6.4% to 6.9%).

“Although this investigational two-drug regimen was inferior to the three-drug regimen in this study, maraviroc remains a valuable antiretroviral therapy when used in combination with other antiretrovirals and dosed twice daily in adults with confirmed CCR5-tropic HIV.” said Dr. John Pottage, Chief Scientific and Medical Officer, ViiV Healthcare.

ViiV Healthcare decided to terminate the MODERN study in October 2013 following a preliminary review of the 48-week primary clinical efficacy data by the study’s external Independent Data Monitoring Committee (IDMC). This decision was not based on any new or unique drug-related safety events. The results presented today are the first analysis of the 48-week primary endpoint of this study. Further analyses of the secondary objectives will be presented at future conferences.

“ViiV Healthcare is committed to supporting innovative clinical programmes to better understand our therapies and the potential they could offer to people living with HIV.” said Dr. Dominique Limet, Chief Executive Officer, ViiV Healthcare. “The treatment of HIV has come a long way, but it is essential that we continue to pursue effective novel treatment strategies that minimise toxicity while maximising tolerability and convenience to meet our objective of delivering advances in care and treatment for all people living with HIV.”

About the MODERN study
‘Maraviroc Once daily with Darunavir Enhanced by Ritonavir in a Novel regimen’ (MODERN) was a Phase III, 96-week, multi-centre, randomised, double-blind, comparative study. The study started in 2011 and was carried out in 797 HIV-1 infected antiretroviral-naïve adults with HIV-1 RNA >1000 copies/mL (cpm) and without reported viral resistance from over 120 sites in the E.U., U.S., Australia and Canada. At baseline, the median age of subjects was 37 for MVC+DRV/r vs. 35 for FTC /TDF +DRV/r (9.1% vs. 8.5% were female respectively, and 81.3% in both arms were ethnically white). Subjects with HIV-1 RNA >100 000cpm at baseline was 20.5% vs. 20.7% for MVC+DRV/r and FTC /TDF +DRV/r respectively.

As per the protocol, the primary endpoint for MODERN was the proportion of patients with HIV-1 RNA <50 copies/mL at week 48. Secondary objectives included the proportion of patients with HIV-1 RNA below the limits of assay detection at week 96; change in CD4+ cell counts through 48 and 96 weeks; assessment of the safety and tolerability of maraviroc including the effects on peripheral fat distribution and trunk to limb fat ratio; the effects on bone mineral density and tropism change and evolution of viral resistance.

MODERN was also the first large Phase III trial to prospectively compare the performance of a genotypic test with a phenotypic test to identify patients with CCR5 tropic virus to determine eligibility for maraviroc. Patients were randomised to undergo screening with either the genotypic or phenotypic test. Genotypic tropism testing in the MODERN study was provided by Siemens Healthcare Diagnostics and phenotypic testing (Trofile®) by Monogram Biosciences.

About maraviroc
Maraviroc is an oral CCR5 entry inhibitor. It is approved in the U.S, under the name Selzentry®, for both treatment-naïve and treatment-experienced adult patients with CCR5-tropic HIV-1 virus in combination with other anti-HIV medicines. Selzentry® is known as Celsentri® outside of the U.S. where it is indicated for appropriate treatment-experienced patients. Tropism testing with a highly sensitive tropism assay is required for the appropriate use of Selzentry®/Celsentri®.

Important Safety Information about maraviroc
(Note: this is taken from the US label and local variations apply. Please refer to applicable local labeling: http://www.medicines.org.uk/EMC/medicine/20386/SPC/Celsentri+150mg+filmcoated+tablets/; http://www.medicines.org.uk/emc/medicine/23164/SPC/Celsentri+300mg+filmcoated+tablets/)

INDICATION AND USAGE

SELZENTRY, in combination with other antiretroviral agents, is indicated for adult patients infected with only CCR5-tropic HIV-1.

This indication is based on analyses of plasma HIV-1 RNA levels in two controlled studies of SELZENTRY in treatment-experienced patients and one study in treatment-naive patients. Both studies in treatment-experienced patients were conducted in clinically advanced, 3-class antiretroviral-experienced (NRTI, NNRTI, PI, or enfuvirtide) adults with evidence of HIV-1 replication despite ongoing antiretroviral therapy.

The following points should be considered when initiating therapy with SELZENTRY:

- Adult patients infected with only CCR5-tropic HIV-1 should use SELZENTRY
- Tropism testing must be conducted with a highly sensitive tropism assay that has demonstrated the ability to identify patients appropriate for SELZENTRY use. Outgrowth of pre-existing low-level CXCR4- or dual/mixed-tropic HIV-1 not detected by tropism testing at screening has been associated with virologic failure on SELZENTRY
- Use of SELZENTRY is not recommended in patients with dual/mixed or CXCR4-tropic HIV-1 as efficacy was not demonstrated in a Phase 2 study of this patient group
- The safety and efficacy of SELZENTRY have not been established in pediatric patients
- In treatment-naive patients, more patients treated with SELZENTRY experienced virologic failure and developed lamivudine resistance compared with efavirenz

IMPORTANT SAFETY INFORMATION

WARNING: Hepatotoxicity: See full Prescribing Information for complete Boxed Warning.
Hepatotoxicity has been reported, which may be preceded by severe rash or other features of a systemic allergic reaction (eg, fever, eosinophilia or elevated IgE). Immediately evaluate patients with signs or symptoms of hepatitis or allergic reaction.

CONTRAINDICATION

SELZENTRY should not be used in patients with severe renal impairment or end-stage renal disease (ESRD) (CrCl <30 mL/min) who are taking potent CYP3A inhibitors or inducers.

ADDITIONAL WARNINGS AND PRECAUTIONS

Hepatotoxicity

Hepatotoxicity accompanied by severe rash or systemic allergic reaction including potentially lifethreatening events has been reported in clinical trials and postmarketing. These events occurred approximately one month after starting treatment. Among reported cases of hepatitis, some were observed in the absence of allergic features or with no pre-existing hepatic disease.

Hepatic laboratory parameters including ALT, AST, and bilirubin should be obtained prior to starting SELZENTRY and at other time points during treatment as clinically indicated. If rash or symptoms or signs of hepatitis or allergic reaction develop, hepatic laboratory parameters should be monitored and discontinuation of treatment should be considered.

The safety and efficacy of SELZENTRY have not been specifically studied in patients with significant underlying liver disorders such as patients co-infected with viral hepatitis B or C. Caution should be used when administering SELZENTRY to patients with pre-existing liver dysfunction or who are coinfected with viral hepatitis B or C.

Cardiovascular events

Use with caution in patients at increased risk of cardiovascular events because cardiovascular events, including

myocardial ischemia and/or infarction, were observed in treatment-experienced and treatment-naive patients who received SELZENTRY.

Caution should be used when administering SELZENTRY in patients with a history of postural hypotension or who receive concomitant medication known to lower blood pressure. Patients should be advised that if they experience dizziness while receiving SELZENTRY, they should avoid driving or operating machinery.

Postural hypotension in patients with renal impairment
SELZENTRY should not be used in patients with severe renal impairment or end-stage renal disease (ESRD) (CrCl < 30 mL/min) who are taking potent CYP3A inhibitors or inducers due to an increased risk of postural hypotension as a result of increased SELZENTRY exposure in some patients.

SELZENTRY should be used in patients with severe renal impairment or ESRD only if they are not receiving a concomitant potent CYP3A inhibitor or inducer and no alternative treatment options are available. If patients with severe renal impairment or end-stage renal disease (ESRD) not receiving a concomitant potent CYP3A inhibitor or inducer experience any symptoms of postural hypotension while taking SELZENTRY 300 mg twice daily, the dose should be reduced to 150 mg twice daily.

Immune reconstitution syndrome
Immune reconstitution syndrome has been reported in patients treated with combination antiretroviral therapy, including SELZENTRY.

Potential risk of infection
SELZENTRY antagonizes the CCR5 co-receptor located on some immune cells, and therefore could potentially increase the risk of developing infections. Patients should be monitored closely for evidence of infection while receiving SELZENTRY.

Potential risk of malignancy
While no increase in malignancy has been observed with SELZENTRY, due to this drug's mechanism of action, it could affect immune surveillance and lead to an increased risk of malignancy. Long-term follow-up is needed to more fully assess this risk.

ADVERSE EVENTS
In treatment-experienced patients, the most common adverse events reported with SELZENTRY twicedaily therapy with frequency rates higher than placebo, regardless of causality, were upper respiratory tract infections (23% vs 13%), cough (14% vs 5%), pyrexia (13% vs 9%), rash (11% vs 5%), and dizziness (9% vs 8%).

In treatment-naive patients, the most common adverse events reported with SELZENTRY twice-daily therapy with frequency rates higher than efavirenz, regardless of causality, were bronchitis (13% vs 9%), upper respiratory tract infection (32% vs 30%), flatulence, bloating, and distention (10% vs 7%), upper respiratory tract signs and symptoms (9% vs 5%), GI atonic and hypomotility disorders not elsewhere classified (NEC) (9% vs 5%), and anemias NEC (8% vs 5%).

USE IN SPECIFIC PATIENT POPULATIONS
Pediatric Patients: There are no data available in pediatric patients; therefore, SELZENTRY should not be used in patients <16 years of age.

Hepatic Impairment: SELZENTRY is principally metabolised by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because SELZENTRY concentrations may be increased.

CONCOMITANT USE
SELZENTRY is a substrate of CYP3A and Pgp. Coadministration with potent CYP3A inhibitors, including protease inhibitors (except tipranavir/ritonavir) or delavirdine, will increase the concentration of SELZENTRY. Coadministration with potent CYP3A inducers, including efavirenz, may decrease the concentration of SELZENTRY. Healthcare providers should ensure that an appropriate dose adjustment of SELZENTRY is made when SELZENTRY is coadministered with potent CYP3A inhibitors and/or potent CYP3A inducers since concentrations, therapeutic effects, and the safety of SELZENTRY may be affected.

Concomitant use of SELZENTRY and St. John's Wort (Hypericum perforatum) or products containing St. John's Wort is not recommended.

About Tropism Testing
HIV enters a CD4 cell by attaching to one of two types of chemokine co-receptors, CCR5 or CXCR4, and tropism is defined by which co-receptor is used. To determine whether patients may be suitable for Celsentri®/Selzentry® (maraviroc), they must undergo tropism testing to verify that they have only R5- tropic HIV-1 infection. Use of Celsentri®/Selzentry® (maraviroc) is not recommended in patients who have X4 or dual/mixed tropic HIV-1 because efficacy was not demonstrated in a phase II study of this patient group.

About ViiV Healthcare
ViiV Healthcare is a global specialist HIV company established in November 2009 by GlaxoSmithKline (LSE: GSK) and Pfizer (NYSE: PFE) dedicated to delivering advances in treatment and care for people living with HIV. Shionogi joined as a 10% shareholder in October 2012. The company's aim is to take a deeper and broader interest in HIV/AIDS than any company has done before and take a new approach to deliver effective and new HIV medicines, as well as support communities affected by HIV. For more information on the company, its management, portfolio, pipeline and commitment, please visit www.viivhealthcare.com.

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