



New PREZISTA® Phase III Study meets primary objective of non-inferiority and secondary objective of superiority in virologic response vs. KALETRA® in treatment-experienced HIV patients

PREZISTA/ritonavir data published in The Lancet

CORK, Ireland, 6th July 2007 - Results from a Phase 3 head-to-head study showed that a significantly greater percent (77 percent) of treatment-experienced HIV-1 infected adults* taking Prezista® (darunavir)/ritonavir, with an optimised background regimen (OBR) of antiretroviral agents, reached a viral load of less than 400 copies/mL at week 48, compared to 68 percent of patients taking the widely prescribed medication lopinavir/ritonavir, with OBR, in a per-protocol analysis (95 percent confidence interval 2-16). In addition, significantly more patients receiving darunavir/r in this study reached an undetectable viral load (<50 copies/mL) compared to patients taking lopinavir/r (71 percent vs. 60 percent).

The 48-week efficacy and safety results, published in the 7 July 2007 issue of The Lancet, will also be presented at the 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention (IAS 2007) in Sydney, Australia on 24 July 2007.

The study met both the primary and secondary objective of non-inferiority and superiority. The primary objective was to demonstrate non-inferiority in virologic response with darunavir/ritonavir versus lopinavir/ritonavir, both combined with an individualised OBR, at week 48. If non-inferiority was established, the secondary objective was to demonstrate superiority in virologic response with darunavir/ritonavir versus lopinavir/ritonavir at week 48. Virologic response was defined as a confirmed plasma viral load of <400 copies/mL

"The POWER studies have shown us that darunavir is an option for highly treatment experienced patients, and the results of TITAN demonstrate that darunavir is also a treatment option for patients with early virological failure, which is representative of patients commonly encountered in clinical practice," said José Valdez Madruga, M.D., Centro de Referencia e Treinamento DST/AIDS, Mariana-São Paulo, Brazil.

Prezista, co-administered with low dose ritonavir (r), is indicated in combination with other antiretroviral medicinal products for the treatment of human immunodeficiency virus (HIV-1) infection in highly pre-treated adult patients who failed more than one regimen containing a protease inhibitor (PI). Prezista is currently approved in several areas including the United States, Canada, and the European Union, among others, and applications for approval also have been submitted or are planned for submission in many other countries.

About the TITAN study

TITAN (TMC114/r In Treatment-experienced pAtients Naïve to lopinavir) is an ongoing, randomised, controlled, open-label Phase 3 trial in which 595 treatment-experienced patients were treated. Participants enrolled in the study were lopinavir/r-naïve, HIV-1 infected adults with a viral load of >1000 HIV-1 RNA copies/mL and had previously failed highly active antiretroviral therapy (HAART) after at least 12 weeks of treatment, or were currently on structured treatment interruption. Patients with previous or current use of lopinavir, darunavir, tipranavir, and/or enfuvirtide were excluded, as were those currently receiving treatment with investigational antiretroviral drugs. Of the 595 patients, 31 percent were protease inhibitor-naïve and the majority were susceptible to four or more protease inhibitors.

Patients were randomised to receive darunavir/r (600 mg/100 mg) twice daily or lopinavir/r (400 mg/100 mg) twice daily, plus OBR. Investigator-selected OBR for each participant was chosen based on resistance testing and prior treatment history and included a combination of nucleoside reverse transcriptase inhibitors with or without non-nucleoside reverse transcriptase inhibitors.

TITAN 48-week study results

Among patients randomised to the darunavir/r arm (total n=298) vs. the lopinavir/r arm (total n=297), the 48-week per-protocol analysis showed for the primary endpoint that 77 percent of patients in the darunavir/r arm vs. 68 percent of patients in the lopinavir/r arm reached a viral load of <400 copies/mL (95 percent CI 2-16).

Pre-planned secondary endpoint findings include:

- 71 percent of patients in the darunavir/r arm reached an undetectable viral load (<50 copies/mL) vs. 60 percent of patients in the lopinavir/r arm, a statistically significant difference (p=0.005)
- 77 percent of patients in the darunavir/r arm achieved at least a 1 log₁₀ reduction in HIV RNA vs. 69 percent in the lopinavir/r arm, a statistically significant difference (p=0.028)
- The median increase from baseline in CD4 cell count was similar between the darunavir/r and lopinavir/r arms (88 cells per cubic millimeter vs. 81 cells per cubic millimeter)

Development of resistance also was studied. Findings include:

- 10 percent of patients in the darunavir/r arm experienced virological failure vs. 22 percent of patients in the lopinavir/r arm
- Among patients experiencing virologic failure who had baseline and endpoint genotype data, 21 percent of patients in the darunavir/r arm developed primary PI resistance mutations vs. 36 percent of patients in the lopinavir/r arm, and 14 percent of patients in the darunavir/r arm developed primary NRTI resistance mutations vs. 27 percent of patients in the lopinavir/r arm

The majority of adverse events in both arms were mild to moderate in severity, with a low incidence of discontinuation. In the darunavir/r arm, the most frequently reported adverse events (greater or equal to 10 percent of subjects) regardless of severity were diarrhoea (32 percent), nausea (18 percent), nasopharyngitis (12 percent), headache (11 percent), and upper respiratory tract infection (10 percent). In the lopinavir/r arm, the most frequently reported adverse events were diarrhoea (42 percent), nausea (21 percent) and nasopharyngitis (11 percent). Grade 2-4 diarrhoea occurred in 8 percent of patients taking darunavir/r compared with 15 percent of patients taking lopinavir/r. Skin rash (all grades regardless of causality) occurred in 16 percent of patients receiving darunavir/r compared with 7 percent of patients receiving lopinavir/r. Most rashes were mild and did not lead to discontinuation. 0.7% of patients in the darunavir/r group discontinued due to rash, compared to none in the lopinavir/r group. Discontinuations due to adverse events were 7 percent in the darunavir/r arm vs. 7 percent in the lopinavir/r arm.

Important Safety Information

PREZISTA does not cure HIV infection or AIDS, and does not prevent passing HIV to others.

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In the registrational studies, darunavir was generally well tolerated versus the investigator selected PIs. The majority of the adverse reactions reported during treatment with darunavir co-administered with 100 mg ritonavir twice daily were mild to moderate in severity. The most frequently reported moderate to severe adverse reactions of at least grade 2 severity were diarrhoea (2.6%), vomiting (2.2%) and hypertriglyceridaemia (2.0%). The most commonly reported adverse reactions of any grade were nausea (7.2%), diarrhoea (6.6%) and headache (3.3%). Skin rash can also appear but this is usually mild to moderate. One percent of patients discontinued treatment due to adverse events.

People who are allergic to darunavir or any of its ingredients, or ritonavir should not take darunavir. Before taking darunavir, patients should tell their doctor if they have any medical conditions, including diabetes, liver problems, haemophilia, or allergy to sulfa medicines and should tell their doctor if they are pregnant or planning to become pregnant, or are breastfeeding. Darunavir should not be used in patients with severe liver problems.

There were some relevant drug-drug interactions with other medications commonly used in HIV patient populations, such as other antiretroviral medications and lipid lowering agents. Patients should talk to their healthcare provider about all the medicines they are taking or plan to take, including prescription and non-prescription medicines, vitamins, and herbal supplements.

Please see full Product Information for more details.

About Darunavir

Darunavir was developed by Tibotec Pharmaceuticals Ltd. and is marketed in the European Union and other countries by Tibotec, a division of Janssen-Cilag. In the U.S., darunavir is marketed by Tibotec Therapeutics, a division of Ortho Biotech Products, L.P. In Canada, darunavir is marketed by Tibotec, a division of Janssen-Ortho Inc.

About Tibotec Pharmaceuticals Ltd.

Tibotec Pharmaceuticals Ltd., based in Cork, Ireland, is a pharmaceutical research and development company. The Company's main research and development facilities are in Mechelen, Belgium with offices in Yardley, PA. Tibotec is dedicated to the discovery and development of innovative HIV/AIDS drugs and anti-infectives for diseases of high unmet medical need.

Tibotec Pharmaceuticals is developing a Global Access Program to facilitate access to its antiretrovirals for patients living with HIV/AIDS in developing countries. The Global Access Program for PREZISTA includes access pricing, registration, medical education for appropriate use and voluntary licensing.

About Tibotec

Tibotec, a division of Janssen-Cilag, will bring innovative products for HIV/AIDS to patients in Europe, the Middle East and Africa. This new division was created within the Janssen-Cilag companies in October 2005 to focus on patients' and health care providers' specific needs in this disease domain. The company will also commercialise medicine to combat other viral diseases in the future.

Janssen-Cilag

Janssen-Cilag is a leader in traditional and biological medicines for disorders such as in gastroenterology, women's health, mental health and neurology as well as for pain, oncology, haematology and nephrology.

CONTACT: Hans Vanavermaete, office: +32 (0) 15 461 017

Mobile: +32 478 447 278

Footnotes:

* The TITAN Study included mild, moderate and highly treatment-experienced patients, which is outside the current licensed indication for PREZISTA in highly treatment-experienced patients.

1 IAS 2006