Roche and Japan Tobacco are in a licensing agreement to develop and commercialize dalcetrapib, a cholesteryl ester transfer protein (CETP) inhibitor to slow or prevent atherosclerosis. This drug is currently in phase III development. This review discusses the development history and scientific profile of this new compound.

1. Introduction

Dalcetrapib, a thioester, is a cholesteryl ester transfer protein (CETP) inhibitor that is being developed by Roche and Japan Tobacco to slow or prevent atherosclerosis. CETP is a plasma glycoprotein that mediates the transfer of cholesteryl ester from high-density lipoprotein (HDL)-cholesterol to proatherogenic very low-density lipoprotein (VLDL)-cholesterol and low-density lipoprotein (LDL). Dalcetrapib is in phase III trials worldwide and in a phase II trial in Japan for the treatment of hyperlipidemia (dyslipidemia).

1.1 Company Agreements

In October 2004, Japan Tobacco and Roche entered into a licensing agreement for the development and commercialization of dalcetrapib. Japan Tobacco was to retain rights in Japan and Korea, and receive milestone payments and royalties from Roche for exclusive rights in the rest of the world. It appears that the agreement was amended to list only Japan as the excluded territory.

1.2 Key Development Milestones

In April 2008, Roche began a phase III study to evaluate the potential of dalcetrapib to reduce cardiovascular morbidity and mortality in stable coronary heart disease patients with recent Acute Coronary Syndrome (ACS) and evaluate the long-term safety profile of the drug (NCT00658515). Enrollment of approximately 15,600 patients has been completed from sites around the world and patients are randomized to receive either dalcetrapib 600 mg or placebo daily, together with stable medication for ACS. Completion of this study is expected in April 2013. The company reported in March 2010 that enrollment in the phase III trial was continuing and that regulatory submissions for dalcetrapib for the treatment of atherosclerosis in high-risk patients with cardiovascular disorders are planned for 2013.

Favorable safety and efficacy results were reported from phase II trials of dalcetrapib in patients with dyslipidemia, coronary heart disease (CHD), or CHD risk equivalents with type 2 diabetes mellitus and/or metabolic syndrome.

A phase II trial (NCT00655473) is evaluating the effect of dalcetrapib on progression or regression of atherosclerotic plaque in patients with coronary heart disease and with other CHD risk factors. This study involves 100 patients in the US and Canada who are receiving dalcetrapib 600 mg or placebo daily for 24 months. Roche expects this study to reach completion in 2011.

Another phase II trial (NCT00655538) is assessing the safety, tolerability and effect on endothelial function of dalcetrapib in patients with CHD or CHD risk equivalents. Patients were randomized to receive dalcetrapib 600 mg or placebo for 36 weeks. Enrollment of 476 patients was completed in March 2010, in Europe. Completion of this study is anticipated in January 2011.
Roche initiated phase II US development of dalcetrapib in 100-500 patients with dyslipidemia in 2005. The double-blind, multicenter, parallel, randomized study examined the effect of dalcetrapib in combination with pravastatin on HDL-cholesterol levels in patients with low or average HDL-cholesterol levels (NCT00697203). The trial also examined apolipoprotein A1, LDL-cholesterol, total cholesterol and triglyceride levels. Roche has published positive phase II efficacy data.[6]

Dalcetrapib is in phase II development in Japan for the treatment of hyperlipidemia, according to the Japan Tobacco pipeline dated May 2009.

2. Scientific Summary

2.1 Adverse Events

2.1.1 Hyperlipidemia

**Phase II:** Data from phase II trials of dalcetrapib alone (at doses up to 900 mg/day) or in combination with HMG-CoA reductase inhibitors (statins) have shown that dalcetrapib was generally well tolerated in patients with type II hyperlipidemia, CHD or CHD risk equivalents, with a similar incidence of adverse events (AEs) and serious AEs seen in dalcetrapib and placebo recipients. Pooled data were analyzed from four, double-blind, placebo-controlled, phase IIa trials conducted in 546 patients who received dalcetrapib 300 mg, 600 mg or 900 mg monotherapy (one study) for 4 weeks, or combination treatment with dalcetrapib 300 mg or 600 mg in combination with a statin (three studies). In a separate analysis, safety data from a 12-week, phase IIb combination study of dalcetrapib 300 mg, 600 mg or 900 mg with pravastatin (n = 218) versus placebo treatment (n = 74) were evaluated. In the phase IIa trials, all AEs were mild to moderate in intensity with the most frequent AEs reported being gastrointestinal disorders (i.e. diarrhea [6.3–10%], flatulence [4–6.3%], nausea [1.4–6.6%]), headache (2.9–10.4%) and dizziness (4.2–6%). In the phase IIb trials, the most frequent AEs included diarrhea (6.6–10.3%), upper respiratory tract infection (2.6–5.4%), stomach discomfort (1.3–2.9%) and myalgia (muscle pain; 1.3–4.1%).[7,8]

Dalcetrapib at dosages of 300, 600 and 900 mg/day, was well tolerated in patients with hyperlipidemia. Digestive complaints occurred in 21%, 25% and 27% of 300, 600 and 900 mg/day recipients, and 12% of placebo recipients.[9]

Twenty-four-week treatment with dalcetrapib (900 mg daily) was well tolerated in patients with...
dyslipidemia, CHD or CHD risk equivalents with and without type 2 diabetes and/or metabolic syndrome (T2DM/MetSyn). In the study, 107 patients with T2DM/MetSyn received dalcetrapib (n = 74) or placebo (n = 33) and 28 patients without T2DM/MetSyn received dalcetrapib (n = 15) or placebo (n = 13) for 24 weeks. By week 24, 82% (n = 61) of dalcetrapib recipients and 82% (n = 27) of placebo recipients in the T2DM/MetSyn group reported AE. In patients without T2DM/MetSyn, AEs were reported in 87% (n = 13) and 77% (n = 10) of dalcetrapib and placebo recipients, respectively. Most AEs were mild to moderate in intensity and considered unrelated to dalcetrapib. The most common AEs, occurring in ≥10% of patients in those with T2DM/MetSyn, were upper respiratory tract infection (URTI [15%/9%]) and diarrhea (14%/12%), for dalcetrapib/placebo recipients, respectively. The most common AEs, occurring in ≥10% of patients in those without T2DM/MetSyn, were URTI (13%/23%), diarrhea (20%/8%), flatulence (7%/23%) and nasopharyngitis (7%/15%) for dalcetrapib/placebo recipients, respectively. No effect on blood pressure, fasting glucose or glycated hemoglobin (HbA1c) was observed. Serious AEs occurred in 8% (n = 6) and 6% (n = 2) of dalcetrapib and placebo recipients, respectively, in the T2DM/MetSyn group. Serious AEs were reported in 20% (n = 3) and 15% (n = 2) of patients in those without T2DM/MetSyn. No serious AE was considered related to treatment. The tolerability profile was sustained for up to 48 weeks.[4]

### 2.2 Pharmacodynamics

#### 2.2.1 Hyperlipidemia

**Clinical studies:** After 4 weeks, dalcetrapib at dosages of 300, 600 and 900 mg/day, had increased HDL-cholesterol levels (p ≤ 0.001), and decreased cholesteryl ester transfer protein activity (p ≤ 0.001) in patients with hyperlipidemia.[9]

**Preclinical studies:** Dalcetrapib attenuated atherosclerosis in cholesterol-fed rabbits according to the results of a study conducted in Japan. In this study, rabbits were given a cholesterol-containing diet alone to establish hyperlipidemia, then dalcetrapib or simvastatin was added.
to the diet for 6 months. Compared with untreated controls, dalcetrapib and simvastatin recipients had HDL-cholesterol levels, which were 90% and 28% higher, respectively, and non-HDL-cholesterol levels which were 40–50% and 50–70% lower, respectively. Compared with controls, the area of atherosclerotic lesions in the aortic arch was 70% lower in dalcetrapib recipients and 80% lower in simvastatin recipients.\[10\]

Dalcetrapib demonstrated 95% inhibition of cholesteryl ester transfer protein, a protein that transfers neutral lipids among lipoproteins, in JW rabbits.\[11\]

2.3 Therapeutic Trials

2.3.1 Hyperlipidemia

Post hoc analysis of data from four phase II trials in patients with dyslipidemia, CHD or CHD risk equivalents with and without type 2 diabetes mellitus and/or metabolic syndrome (T2DM/MetSyn) showed that dalcetrapib 600 mg had comparable efficacy in patients with and without T2DM and/or MetSyn. In the studies, 296 patients with T2DM/MetSyn received dalcetrapib 600 mg (n = 124) or placebo (n = 172) and 192 patients without T2DM/MetSyn received dalcetrapib 600 mg (n = 90) or placebo (n = 102) for 4 weeks. In the T2DM/MetSyn group, significant increases from baseline at 4 weeks in key parameters were reported with dalcetrapib versus placebo recipients (HDL-cholesterol [+24.0], apolipoprotein A-I [+10.2], apolipoprotein B [+4.4] and total cholesterol [+6.6]). A significant reduction in CETP activity was reported (–11.1) with dalcetrapib treatment in this group. In those without T2DM/MetSyn, significant increases from baseline at 4 weeks in HDL-cholesterol [+26.4] and apolipoprotein A-I [+10.7] were reported with dalcetrapib versus placebo recipients. Significant reductions in ApoB : ApoA-I (–11.8) and CETP activity (–10.0) were reported with dalcetrapib treatment in this group. In either patient group, no significant change in triglyceride level was observed.\[5\]

References

1. Japan Tobacco Inc, Roche, Roche and Japan Tobacco Enter Agreement for Novel Cholesterol Modifying Agent. www.rocheusa.com, 20 Oct 2004 Media Release
2. Roche F. Hoffmann-La Roche Announces First Quarter Sales 2008. www.roche.com, 17 Apr 2008 Media Release
3. Roche, Roche uniquely positioned to deliver long-term growth. www.roche.com, 18 Mar 2010 Media Release
4. Kallend D, Stalenhofen AH, Duttlinger-Madkour R, et al. Dalcetrapib safety and tolerability in high-risk patients with type 2 diabetes mellitus and/or metabolic syndrome. 45th Annual Meeting of the European Association for the Study of Diabetes: abstr. 1261, 29 Sep 2009. Available from URL: http://www.easd.org, Switzerland [English]
5. Stalenhofen AH, Davidson MH, Robinson JG, et al. Dalcetrapib in high-risk patients with type 2 diabetes mellitus and/or metabolic syndrome. 45th Annual Meeting of the European Association for the Study of Diabetes: abstr. 1262, 29 Sep 2009. Available from URL: http://www.easd.org, Netherlands [English]
6. Roche, Record operating results for Roche again in 2007. www.roche.com, 30 Jan 2008 Media Release
7. Steiner G, Kastelein JJ, Kallend D, et al. Cardiovascular safety of the cholesteryl ester transfer protein inhibitor R1658/JTT-705: results from phase 2 trials. Journal of the American College of Cardiology. 51 (Suppl. A): 333 (plus poster) abstr. 1028-166, No. 10, 11 Mar 2008, Canada [English]
8. Stein EA, Kallend D, Buckley B. Safety profile of the cholesteryl ester transfer protein inhibitor R1658/JTT-705 in patients with type II hyperlipidemia or coronary heart disease. Journal of the American College of Cardiology. 51 (Suppl. A): 333-334 (plus poster) abstr. 1028-167, No. 10, 11 Mar 2008, USA [English]
9. de Grooth GJ, Kuivenhoven JA, Stalenhof AH, et al. Efficacy and safety of a novel cholesteryl ester transfer protein inhibitor, JTT-705, in humans: a randomized phase II dose-response study. Circulation. 103: 2159-2165, 7 May 2002, Netherlands [English]. Clinical Trials Insight Journal Fulltext
10. Okamoto H, Yonemori F, Wakahara K, et al. A cholesteryl ester transfer protein inhibitor attenuates atherosclerosis in rabbits. Nature. 406: 203-207, 13 Jul 2000. Japan [English]. Journal Fulltext
11. Shinkai H, Maeda K, Yamasaki T, et al. Bis(2-(acylamino)phenyl) disulfides, 2-(acylamino)benzenethiols, and S-(2-(acylamino)phenyl) alkaneethioates as novel inhibitors of cholesteryl ester transfer protein. Journal of Medicinal Chemistry. 43: 3566-3572, 21 Sep 2000. Japan [English]. Journal Fulltext

© 2010 Adis Data Information BV. All rights reserved.