Drugs R D 2011; 11 (2): 207-213
1179-6901/11/0002-0207

RVX 208

Abstract

RVX 208 (RVX-208; RVX000222) is a first-in-class novel small molecule in development by Resverlogix Corporation for acute coronary syndromes, atherosclerosis and Alzheimer disease. It increases the levels of apolipoprotein A1 and high-density lipoprotein cholesterol, thereby potentially reducing the risk for cardiovascular disease. This review discusses the key development milestones and therapeutic trials of this drug.

1. Introduction

Resverlogix is developing RVX 208, an orally available, small-molecule therapeutic that increases apolipoprotein AI (ApoA-I) and high-density lipoprotein (HDL) cholesterol levels, to treat cardiovascular disorders, including atherosclerosis, cerebrovascular disease (i.e. stroke), and hypertension. The first-in-class compound could also be beneficial for the treatment of Alzheimer disease (AD). Clinical development is underway in the US for atherosclerosis, acute coronary syndromes and AD.

RVX 208 emerged from Resverlogix's cardiovascular research programme.

Reverse cholesterol transport (RCT) is a pathway by which cholesterol is transported from the artery wall to the liver for excretion, thereby reducing the progression of atherosclerosis. HDL and ApoA-I are major constituents of the RCT pathway; acting as acceptors for cholesterol molecules. A key component of RCT is cholesterol efflux, in which accumulated cholesterol is removed from macrophages. RVX 208 increases endogenous ApoA-I production, which raises HDL levels and enhances HDL functionality to augment RCT. Previous landmark trials supported the concept that ApoA-I enhancement in humans reversed atherosclerotic plaque volume in major coronary arteries. RVX 208 was discovered by Resverlogix using its NexVas™ technology.

Additionally, emerging evidence from large epidemiology studies, such as the Harvard Women's Study, the Honolulu-Asia Aging Study and the Whitehall II study, are building support for the relationship between poor HDL and ApoA-I levels, and decreased cognitive function and AD. Researchers investigating elective HMG-CoA reductase inhibitor (statin) use and fractionated cholesterol levels in the ADAPT cohort have identified a significant relationship between elevated HDL levels and better performance on the Mini Mental State Examination (MMSE), and a significant inverse relationship between increased total and low-density lipoprotein (LDL) cholesterol and learning and memory. Elevated cholesterol levels are thought to increase the production and accumulation of the putative AD neurotoxin,

amyloid-beta (Aβ), which is an important marker of cognitive function and AD.[1]

Resverlogix has entered into discussions with various leading life science organisations for the NexVax™ PR cardiovascular technology programme. At the 2009 European Society of Cardiology Congress meeting in Barcelona, Spain, Resverlogix communicated the results for the 28-day phase Ib/IIa trial of RVX 208 to potential partners under a confidentiality agreement.[2]

1.1 Company Agreements

In January 2005, Resverlogix began an international research collaboration with the Cedars-Sinai Medical Center and Dr PK Shah, Director of the Atherosclerosis Research Center.[3] The programme was expanded in July 2005 to include the acute as well as the chronic aspects of cardiovascular disorders, as a result of favorable preclinical testing.[4]

Resverlogix established RVX Therapeutics in July 2005, a wholly owned subsidiary for business and strategic objectives. Resverlogix retains its primary asset, the NexVas™ technology, while RVX Therapeutics holds non-core assets including TGF-Beta Shield™ technology.[5]

1.2 Key Development Milestones

1.2.1 Alzheimer Disease (AD)

Resverlogix has conducted an exploratory phase Ia trial to evaluate RVX 208 (2, 3, and 8 mg/kg) for the treatment of AD. This double-blind, dose-escalation, placebo-controlled trial enrolled 24 subjects in three separate dosing cohorts for a period of 7 days. Plasma levels of $A\beta_{40}$ were measured on days 1 and 7. *Post hoc* analysis revealed a 12–14% increase in plasma $A\beta_{40}$ levels at the highest dose of RVX 208 (8 mg/kg) after 7 days of dosing. Based on the study hypothesis, these results trended towards significance versus placebo, even with the minimal number of study subjects.[1,6]

RVX 208 has also demonstrated positive effects on plasma $A\beta_{40}$ levels in 299 patients with stable coronary artery disease (the phase II ASSERT trial population). After 12 weeks of treatment with RVX 208, 150 mg twice daily, a highly significant change from baseline and 13.4% change compared with placebo was observed in the quartile of patients with the lowest plasma $A\beta_{40}$ levels at baseline, which is known to increase the risk for developing AD. Resverlogix announced that the data further supports the previous phase I trial in AD and the hypothesis that RVX 208 can augment $A\beta_{40}$ transport from the brain.[7]

1.2.2 Cardiovascular Disorders (Acute Coronary Syndrome and Atherosclerosis)

In October 2010, Resverlogix and the Cleveland Clinic in the US completed a phase II, randomized, placebo-controlled, dose-ranging trial (ASSERT; NCT01058018) of RVX 208 for the treatment of atherosclerosis in 299 patients with stable coronary artery disease. The trial was initiated in December 2009. The primary endpoint was the change in ApoA-I levels after 3 months of dosing. Patient recruitment was completed in February 2010, and dosing was completed in May 2010 (5 months ahead of schedule, and without any dose alterations).[8] Results were presented in November 2010.[9-13]

Resverlogix announced in September 2010 that it had made important modifications to the design of its phase IIb trial of oral RVX 208 (RVX222-CS-007; ASSURE 1; NCT01067820). Primary changes to the trial included increasing the number of patients from 120 to over 230, making all patients undergo an intravascular ultrasound (IVUS) assessment, increasing the number of trial sites and opening recruitment to multiple countries, the inclusion of patients with low HDL-cholesterol levels and changing the primary endpoint to plaque regression. The trial was expected to begin dosing before the end of 2010.[14] However, Resverlogix temporarily suspended the trial in order to modify enrollment procedures to expedite recruitment.[10] The trial was underway in the US and was investigating the early effects of oral RVX 208 (100 or 150 mg twice daily for 2 weeks) on the changes in lipid and coronary plaque in patients with recent acute coronary syndrome. The ASSURE 1 study complements the ASSERT trial in patients with stable coronary artery disease.[15,16]

In August 2009, Resverlogix completed a double-blind, placebo-controlled, US-based, phase Ib/IIa

trial (RVX222-CS-003; NCT00768274) investigating the safety, pharmacokinetics and pharmacodynamics of three dosages of RVX 208 in 72 subjects with normal and low HDL levels. Positive results reported from this 28-day trial showed RVX-208 increased plasma levels of ApoA-I by 13.25% compared with placebo in patients with baseline HDL/ApoA-I.[2,17-21]

Resverlogix has completed two arms of a phase I trial investigating the bioequivalence of RVX 208 capsules and the original powder formulation. The final arm was expected to be completed by the end of the third quarter of 2009.[2]

A phase Ia safety, tolerability, and pharmacokinetics study has successfully met its objectives, being well tolerated and showing good oral absorption. The three-armed study comprised a single escalating dose portion, a food versus fasted effect on pharmacokinetics portion, and three cohorts with 7-day multiple dosing arms. The trial took place at a US contract research organisation and enrolled 80 healthy volunteers. Results concerning the effect of RVX 208 on levels of HDL-cholesterol have been reported.[22-26]

Data from the 80th and 81st Scientific Sessions of the American Heart Association demonstrated that oral administration of RVX 208 increased the production of serum ApoA-I levels and improved HDL-mediated cholesterol efflux in African Green Monkeys.[24,27,28]

As of April 2008, RVX 208 had undergone 126 preclinical trials comprising safety, toxicity, pharmacokinetics, and pharmacology studies.[25]

RVX 208 has shown efficacy in raising ApoA-I production and HDL levels in human trials and also reduced plaque numbers in a mouse model of atherosclerosis.[29]

The US FDA approved an IND (investigational new drug) for a phase I trial of RVX 208 for the treatment of cardiovascular disorders in December 2007.[30]

1.3 Patent Information

In November 2010, Resverlogix filed a patent application covering dosing combinations of RVX 208 and leading statin therapeutics. The patent includes data from the ASSERT trial showing that RVX 208 at certain doses in combination with statins markedly improved not only ApoA-I production, HDL, and large HDL particles, but also important properties of LDL and ApoB particles. The synergistic effect of RVX 208 was more pronounced with Pfizer's Lipitor® and AstraZeneca's Crestor®.[31]

Resverlogix, on behalf of RVX Therapeutics, announced the filing of a patent application covering NexVas™, its cardiovascular technology.

Table I. Features and properties

Alternate names	RVX 000222; RVX-208
Originator	Resverlogix Corporation
Highest development phase	II (USA)
Active development indications	Acute coronary syndromes, Alzheimer disease, Atherosclerosis
Class	Quinazolines, Small-molecules
Mechanism of action	Apolipoprotein A I stimulants
CAS Registry Number	1246400-89-4
Route of Administration	Oral
Pharmacodynamics	Significantly increases pre-beta high density lipoprotein (HDL), cholesterol efflux, and serum apolipoprotein A-I in healthy volunteers; significantly increases average serum apolipoprotein A-I (ApoA-I) and HDL-cholesterol levels in African Green monkeys; increases plasma levels of Apo-AI and HDL particles in humans
ATC Codes	
WHO ATC code	C (Cardiovascular System), C10 (Lipid Modifying Agents), N06D (Anti-Dementia Drugs)
EphMRA ATC code	C (Cardiovascular System), C10 (Lipid-Regulating/Anti-Atheroma Preparations), N7D (Anti-Alzheimer Products)

Table II. History

Event Date	Update Type	Comment	Update Date
2 February 2011	InThought Forecasts	inThought Analysis for atherosclerosis updated	2 February 2011
25 January 2011	Scientific Update	Pharmacodynamics data from a phase II trial in atherosclerosis/acute coronary syndromes that support ongoing development in Alzheimer disease released by Resverlogix[7]	28 January 2011
17 November 2010	Scientific Update	Pharmacodynamics data from the phase II ASSERT trial in atherosclerosis presented at the 83rd Annual Scientific Sessions of the American Heart Association (AHA-2010)[9]	22 November 2010
7 October 2010	Trial Update	Resverlogix completes the phase II ASSERT trial for atherosclerosis in the US (NCT01058018)	16 February 2011
23 June 2010	Scientific Update	Pharmacodynamics and adverse events data from a phase Ia/IIb trial in volunteers with normal or low HDL-cholesterol released by Resverlogix[17,32]	24 June 2010
12 May 2010	Trial Update	Resverlogix suspends enrolment in the phase II ASSURE 1 trial for acute coronary syndromes in the US[10]	14 May 2010
25 February 2010	Trial Update	Resverlogix initiates enrollment in the phase II ASSURE 1 trial for acute coronary syndromes in the US	15 March 2010
9 February 2010	Trial Update	Resverlogix completes enrollment in the ASSERT trial for atherosclerosis in the US (NCT01058018)	10 February 2010
22 December 2009	Phase Change	Phase II clinical trials in atherosclerosis in the US (PO)	15 March 2010
22 December 2009	Phase Change	Phase II clinical trials in acute coronary syndromes in the US (PO)	15 March 2010
29 September 2009	Scientific Update	Final pharmacodynamics, pharmacokinetic and adverse events data from a phase Ia/IIb trial in volunteers with normal or low HDL-cholesterol released by Resverlogix Corporation[18]	2 October 2009
25 August 2009	Scientific Update	Interim pharmacodynamics data from a phase Ib/IIa trial in volunteers with normal or low HDL-cholesterol released by Resverlogix[2]	31 August 2009
25 August 2009	Trial Update	Resverlogix completes a phase Ib/IIa trial in subjects with normal or low HDL-cholesterol levels in the US	31 August 2009
31 March 2009	Scientific Update	Interim pharmacodynamics data from a phase I trial in cardiovascular disorders presented at the 58th Annual Scientific Session of the American College of Cardiology (ACC-2009)[22]	1 April 2009
10 November 2008	Scientific Update	Pharmacodynamics data from a phase Ia and a preclinical trial in cardiovascular disorders presented at the 81st Annual Scientific Sessions of the American Heart Association (AHA-2008)[24]	14 November 2008
10 November 2008	Phase Change	Phase I clinical trials in Alzheimer disease in the US (PO)	13 November 2008
21 October 2008	Trial Update	Resverlogix advances RVX 208 to the second arm of a phase Ib/IIa trial in the US[21]	23 October 2008
30 September 2008	Phase Change	Phase-I/II clinical trials in cardiovascular disorders in the US (PO)	23 October 2008
18 June 2008	Scientific Update	Interim pharmacodynamics data from a phase I trial in cardiovascular disorders released by Resverlogix[33]	20 June 2008
22 April 2008	Trial Update	Resverlogix completes dosing in its phase Ia trial for cardiovascular disorders in the US	30 April 2008
14 January 2008	Phase Change	Phase I clinical trials in cardiovascular disorders in the US (PO)	16 January 2008
10 December 2007	Regulatory Status	The US FDA approves IND application to begin phase I trial of RVX 208 in cardiovascular disorders (PO)	1 May 2008
29 November 2006	Phase Change	Preclinical trials in cardiovascular disorders in the US (PO)	30 April 2008

2. Scientific Summary

2.1 Pharmacokinetics

Oral administration of RVX 208 resulted in dose dependant pharmacokinetic parameters; the drug was given at either low (2 mg/kg), dose-escalating (3–6 mg/kg), or high (6 mg/kg) doses for a 28 days.[18]

2.2 Adverse Events

RVX 208 was demonstrated to be safe and well tolerated in a phase Ib/IIa study.[17,18,32]

2.3 Pharmacodynamics

2.3.1 AD and Cognition Disorders

RVX 208 demonstrated positive effects on plasma $A\beta_{40}$ levels in 299 patients with stable coronary artery disease (the phase II ASSERT trial population). After 12 weeks of treatment with twice-daily RVX 208 150 mg, a highly significant 34.8 pg/mL change from baseline and 13.4% change compared with placebo was observed in the quartile of patients with the lowest plasma $A\beta_{40}$ levels at baseline, which is known to increase the risk for developing AD.[7]

2.3.2 Hyperlipidemia

***Clinical Studies*:** Results from the phase II ASSERT trial showed dose dependent increases in ApoA-I by 5.6%, statistically significant increases in HDL-cholesterol including alpha1 particles or functional HDL by 8.3%, and large HDL particles by 21.1%. ApoA-I and other HDL particles continued to increase at the end of the 12-week study.[9]

Results from a phase Ib/IIa study (NCT00768274) conducted in 72 patients with normal or low HDL-cholesterol levels demonstrated RVX 208 to be associated with a significant increase in ApoA-I levels. The primary endpoint, plasma ApoA-I increase compared to placebo, achieved a range of 5.1–10.4% in all patients at all doses at days 8 and 28, respectively. At the lowest dose of 1 mg/kg twice daily in patients with low levels of HDL-cholesterol, significantly increased plasma ApoA-I levels by 5.7% and 7.8% at days 8 and 28, respectively ($p < 0.05$). A critical RCT functionality marker, alpha-1 HDL particles, also demonstrated significance with an increase of 46.7% ($p < 0.004$) in all patients and 57.2% ($p < 0.02$) in the low dose arm over placebo at day 28. RVX 208 was shown to be compatible with simvastatin (40 mg).[2,17,18,32]

An interim analysis of 24 healthy volunteers who participated in a 7-day phase I trial of RVX 208 showed statistically significant improvements over placebo in three of the four key variables assessed. Significant improvements included increases in pre-beta HDL of 42%, cholesterol efflux of 11%, and serum ApoA-I of 11%. A fourth variable, HDL-cholesterol level, increased by 10% but the change was not significant. A rapid onset of action was observed, with the serum ApoA-I increases surpassing the previous 8%

Table III. Forecasts

InThought Probability of Approval[a]			
Indication	Approval Date Estimate	inThought Approvability Index	Last Update
Acute coronary syndromes	NE	24% (NYR)	21 May 2010
Alzheimer disease	NE	19% (NYR)	27 Jul 2009
Atherosclerosis	1 Apr 2014	15% (F)	2 Feb 2011

a The Wolters Kluwer Health Approvability Index is a dynamic tool that assesses the progress of a drug candidate through clinical development, evaluating strength of clinical data and trial design, benchmarked against historical parameters and likelihood to maintain forward momentum. Points are assigned for specific line items relating to safety, efficacy, and other factors in each phase of clinical development. Possible points total 100 upon drug approval, and are allocated in each phase according to the historical approval rate of similar drugs, such that the current points of a drug relate to its probability of approval. In addition, a letter grade is assigned and reflects the momentum of a drug candidate in its current phase, with 'A' indicating significantly above average/likely to progress, 'C' indicating average, and 'F' indicating significantly below average/unlikely to progress. 'NYR' stands for 'Not Yet Rated,' indicating that the probability of approval is based on historical approval rates for similar drugs according to indication, molecule type, novelty, and phase, but without analyses of clinical data, trial design, and other factors specific to the individual agent.

NE = no estimate.

5-week average benchmark totals displayed by the ApoA-I milano agent developed by Pfizer.[22,33] RVX 208 was dosed at 2, 3, or 8 mg/kg/day. Further analysis of the data revealed that after 7 days, RVX 208 increased the change for ApoA-I by 11% versus placebo ($p = 0.03$). The corresponding pre-beta HDL change was 42% ($p = 0.007$) versus placebo. This change correlated with ABCA1-dependent cholesterol efflux change, which increased by 10% ($p = 0.03$).[23,24]

***Preclinical Studies*:** Highly significant increases in average serum ApoA-I and HDL-cholesterol levels (57% and 92%, respectively) occurred in African Green monkeys that received RVX 208 (7.5, 15, and 30 mg/kg twice daily and 60 mg/kg once daily). The distribution of HDL particle size was also modified after drug administration; there was a significant increase in pre-beta and alpha HDL particles. In a cell culture model, RVX 208 significantly increased the ability of serum to promote cholesterol efflux via ABCA1, ABCG1, or SR-BI-dependent pathways.[23,24]

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