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MCRI Updates

Receptos' RPC1063 for Treating Multiple Sclerosis

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Summary

We recently hosted a conference call to discuss Receptos' (RCPT) RPC1063, which is in the phase II/III RADIANCE trial in patients with multiple sclerosis. RPC1063 is a sphingosine-1-phosphate receptor 1 (S1PR1) modulator and thus has some similarity to Novartis' (NVS) Gilenya, a non-specific sphingosine-1-phosphate receptor modulator approved for treating multiple sclerosis. Phase I data showed RPC1063 caused dose-dependent lymphocyte count reduction to target levels (-60%), and lymphocyte counts rapidly recovered to the normal range in 48-72 hours after dosing cessation. There were three patients in the phase I trial who developed arrhythmias. There is, however, little evidence that the agent will actually have a favorable risk/benefit in multiple sclerosis. Because of the difference in binding affinity for different subtypes of sphingosine-1-phosphate receptors, we do not believe it is predictable whether RPC1063 will mimic Gilenya's success in treating MS.

Stocks Impacted

- **Receptos (RCPT-$30.84-NR)**
- **Novartis (NVS-$88.41-NR)**

Background

- ***RPC1063 is in a phase II/III clinical trial for multiple sclerosis.*** Results of the phase II part are expected in 2H14.

Reasons for Research

- ***Investors are waiting to learn if the results are positive.***

The Impact

- ***RPC1063 is not a "me too" analog of Gilenya.*** Gilenya binds to multiple subtypes of sphingosine-1-phosphate receptors, while RPC1063 is much more specific to the sphingosine-1-phosphate receptor 1. Furthermore, the relative agonist-antagonist effect on the receptors may not be the same. Thus, the agents are likely to have noticeably different risk/benefit profiles.
- ***Phase I data shows RPC1063 caused a dose-dependent lymphocyte count reduction to target levels (-60%), and lymphocyte counts rapidly recovered to the normal range in 48-72 hours after dosing cessation.*** This biomarker result implies reversible efficacy — immune suppressive activity that can be reversed in the event of a life-threatening infection. However, this biomarker may not be a good predictor of outcomes.
- ***Potential cardiac arrhythmias are a concern.*** Gilenya causes an increased risk of cardiac arrhythmias and has a label warning about this. There were three patients who developed arrhythmias in the phase I trial of RPC1063 even though the company indicates the cardiac QT trial was uneventful.

MCRI Insights

- ***Because of the difference in binding affinity for different subtypes of sphingosine-1-phosphate receptors, we do not believe it is predictable whether RPC1063 will mimic Gilenya's success in treating MS.*** We believe the two drugs will have different risk/benefit profiles. It is possible RPC1063 could be used in those who fail Gilenya or even be used before Gilenya. However, at this time there is no evidence that RPC1063 is an approvable drug.

Tech Assessment: Receptos' (RCPT) RPC1063 for Treating Multiple Sclerosis

I. RPC1063
- Oral
- Small molecule
- Once daily
- Sphingosine-1-phosphate receptor 1 (S1PR1) modulator

II. Mechanism of RPC1063
- S1PR1 modulator
- Sphingosine-1-phosphate (S1P) is made from membrane-derived lipids at area of inflammation
- At least five different S1P receptors
- S1P receptors are ubiquitous; found on many different cell types
- S1PR1s found on endothelial cells and lymphocytes
- S1PR1s mediate migration of lymphocytes toward areas of inflammation

III. Multiple Sclerosis Pathophysiology
- Destruction of myelinated nerves in the central nervous system
- Immune mediated
- Unclear whether autoantigen or viral antigen in the nerve triggers response
- Relapsing-remitting MS, (85%)
- Primary-progressive MS (10%)
- Progressive-relapsing MS (5%)
- Secondary-progressive MS (50% of relapsing/remitting develop this)

IV. Market for Multiple Sclerosis
- MS prevalence: 50-100 per 100,000 in the US
- Approximately 225,000-400,000 people in US
- World sales of disease-modifying drugs is $13B (sales estimate from the company)

V. Current Diagnosis and Treatments of Multiple Sclerosis
- Imaging study: MRI
- Evoked potentials
- History and physical
- Treatments: Disease modifying drugs
- Injectables
- Betaseron, Avonex, Rebif: Beta interferon
- Copaxone
- Tysabri
- Oral Agents
- Gilenya (fingolimid): Sphingosine 1-phosphate receptor modulator
- Tecfidera (dimethyl fumarate): Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) activator

VI. Existing Data on RPC1063

Phase I Study
- Randomized, double-blind, placebo-controlled
- 88 healthy male and female subjects
- Aged 18-55 years
- Single ascending dose (SAD) portion
- Multiple ascending dose portions for 7 day (MAD-7) and 28 day(MAD-28)
- Cohorts included eight subjects assigned to RPC1063 (six) or placebo (two)
- Doses were 0.3-3 mg (SAD), 0.3-2 mg (MAD-7), and 0.3-1.5 mg (MAD-28)
- Dose-dependent lymphocyte count reduction to target levels (-60%)
- Lymphocytes rapidly recovered to the normal range upon dosing cessation in 48-72 hours
- Adverse events: Some EKG changes in three subjects, infections in four subjects, connective tissue diseases in two subjects

Cardiac/EKG: QT/QTc Study
- Enrolled 124 subjects
- 62 subjects randomized to receive RPC1063
- Dose of 1 mg/day and at a supra-therapeutic dose of 2 mg/day
- 62 subjects randomized to receive placebo

VII. Ongoing Phase II/III RADIANCE Trial in Multiple Sclerosis
- Double-blind, randomized, placebo-controlled trial
- Patients with relapsing MS
- n=258
- Receive 0.5 and 1.0 mg or placebo
- Once daily
- Duration: 24 weeks
- Primary outcome: Cumulative number of lesions by MRI
- Results expected 2H14

VIII. Our Prediction
- There are enough differences from Gilenya that our confidence is weak
- This is not a true “me too” drug
- Dose may cause too much immune suppression
- Safety: Possible serious adverse events based on small studies (cardiac)
- Efficacy: Likely efficacious, but risk of failing

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