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Control Medical Drug Spend

RJ Health Systems 2018 Drug Pipeline Review and Analysis

Volanesorsen sodium

General Drug Information:

Manufacturer:	**Akcea Therapeutics Inc. / Ionis Pharmaceuticals Inc.**
Drug Brand Name:	Waylivra ™
Drug Generic Name:	Volanesorsen sodium
Route of Administration:	Subcutaneous
Anticipated Approval:	August 30, 2018 (PDUFA)
Status:	Pipeline/Pre-Registration
FDA Indications:	Familial Chylomicronemia Syndrome (FCS)

Current Marketed Products:

Volanesorsen is under development for two rare genetic disorders: familial chylomicronemia syndrome (FCS) and familial partial lipodystrophy (FPL). FCS is characterized by the buildup of chylomicrons, which are lipoproteins that transport dietary cholesterol and fat in the body. The enzyme lipoprotein lipase (LPL), which normally breaks down chylomicrons in the blood, does not function correctly in FCS. A significant increase in triglyceride levels results from this inability to break down chylomicrons. Patients with FCS often experience abdominal pain and debilitating and potentially fatal episodes of pancreatitis. Currently, there are no approved therapies to treat FCS. Patients with FCS are currently managed with dietary restrictions such as reductions in levels of dietary fat.

Indication Under Review:

Indication	**Estimated Global Prevalence (Number of individuals affected)**
Familial Chylomicronemia Syndrome (FCS)	1 in 1,000,000[+]

[+] Source: "About FCS". *The FCS Foundation*. https://www.livingwithfcs.org/What-is-FCS/About-FCS Accessed: July 12, 2018.

Clinical Trial Data:

Ionis Pharmaceuticals Inc; Akcea Therapeutics Studies				
Study Name	**Purpose**	**Intervention**	**Results**	**Simplified Key Takeaway**
The COMPASS Study: A Study of Volanesorsen (Formally ISIS-APOCIIIRx) in Patients With Hypertriglyceridemia (NCT02300233 | Phase 3)	The purpose of this study was to evaluate the efficacy and safety of volanesorsen given for 26 weeks in 113 patients with Hypertriglyceridemia.	Active Comparator: Volanesorsen 300 mg administered subcutaneously once-weekly for 26 weeks Placebo Comparator: Placebo administered subcutaneously once-weekly for 26 weeks	Study met its primary endpoint of reducing triglyceride levels in patients with hypertriglyceridemia. Volanesorsen-treated patients (n=75) achieved a statistically significant mean reduction in triglycerides of 71.2% from baseline, compared with a mean reduction of 0.9% in placebo-treated patients (n=38) after 13 weeks of treatment; this represented a mean absolute reduction of 869 mg/dL in volanesorsen-treated patients. This treatment effect observed was sustained through all 26 weeks of treatment. In a subset of 7 patients with FCS: Volanesorsen-treated patients (n=5) achieved a mean reduction in triglycerides of 73% from baseline after 13 weeks of treatment, compared with a mean increase of 70% in placebo-treated patients (n=2). This represented a mean absolute reduction of 1,511 mg/dL in volanesorsen-treated patients. This treatment effect was sustained through all 26 weeks of treatment. 82% of patients treated with volanesorsen, including 3 of the patients with FCS, achieved triglyceride levels < 500 mg/dL after 13 weeks of treatment, compared to 14% of placebo-treated patients. ***Sources***: Pharma Intelligence Center https://pharma.globaldata.com Accessed: June 26, 2018. Gouni-Berthold I, Alexander V, Digenio A, DuFour R, Steinhagen-Thiessen E, *et al*. COMPASS Study. *Journal of Clinical Lipidology*. 2017 May;11(3):794-95.	Based on results reported, treatment with volanesorsen resulted in greater than 70% reduction in triglyceride levels in patients with hypertriglyceridemia (with or without FCS), as compared to placebo.

Study Name	Purpose	Intervention	Results	Simplified Key Takeaway
The APPROACH Study: A Study of Volanesorsen (Formerly IONIS-APOCIIIRx) in Patients With Familial Chylomicronemia Syndrome (NCT02211209 | Phase 3)	The purpose of this study was to evaluate the efficacy and safety of volanesorsen given for 52 weeks in 66 patients with Familial Chylomicronemia Syndrome.	Active Comparator: Volanesorsen 300 mg administered subcutaneously once-weekly for 52 weeks Placebo Comparator: Placebo administered subcutaneously once-weekly for 52 weeks	Study met its primary endpoint of reducing triglyceride levels in patients with FCS. Primary Endpoint: Volanesorsen-treated patients (n=33) achieved a statistically significant mean reduction in triglycerides of 77% from baseline after 3 months of treatment, compared to a mean increase of 18% in placebo-treated patients (n=33) ($p<0.0001$). Secondary Endpoint: This represented a mean absolute reduction of 1,712 mg/dL in volanesorsen-treated patients. This effect observed was sustained over the 52-week treatment period. Other Results: 50% of the volanesorsen-treated patients who had triglycerides $\geq$ 750 mg/dL at baseline achieved triglyceride levels < 500 mg/dL after 3 months of treatment; in comparison, none of the placebo-treated patients achieved this level ($p<0.003$). Volanesorsen-treated patients with the highest documented frequency of pancreatitis attacks suffered no attacks during the 52-week treatment period ($p=0.02$). A reduction in self-reported abdominal pain intensity was observed in volanesorsen-treated patients compared to placebo ($p=0.03$). Declines in platelet counts led to 5 discontinuations in patients receiving volanesorsen; no patients discontinued in the last 6 months of study after platelet monitoring was fully implemented. Declines in platelet counts were managed with dose adjustment. ***Sources***: Pharma Intelligence Center https://pharma.globaldata.com Accessed: June 26, 2018. Gaudet D, Digenio A, Alexander VJ, Arca M, Jones AF, *et al*. The APPROACH Study. *Journal of Clinical Lipidology*. 2017 May;11(3):814-15.	Based on results reported, treatment with volanesorsen resulted in reduced triglyceride levels, as well as reductions in abdominal pain and recurrence of pancreatitis in patients with FCS, as compared to placebo. Changes (declines) in platelet count are manageable with frequent monitoring.

Study Name	Purpose	Intervention	Results	Simplified Key Takeaway
The Approach Open Label Study: A Study of Volanesorsen (Formerly IONIS-APOCIIIRx) in Patients With Familial Chylomicronemia Syndrome (NCT02658175 | Phase 3)	An Open-Label Study of Volanesorsen (IONIS 304801) Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS). A multi-center, open-label study for: Group 1: APPROACH study roll-over FCS patients, Group 2: COMPASS study roll-over FCS patients, and Group 3: FCS patients who did not participate in the APPROACH or COMPASS studies.	All patients receive volanesorsen 300 mg administered subcutaneously once per week for 52 weeks. Patients have the option of continuing dosing for an additional 52 weeks until an expanded access program is approved and available in their country.	Estimated Study Completion Date: September 30, 2018 Estimated Primary Completion Date: June 30, 2018	None at this time
Akcea Therapeutics; CaligorRx, Inc. Studies				
Study Name	**Purpose**	**Intervention**	**Results**	**Simplified Key Takeaway**
Volanesorsen Early Access Program for Patients With Familial Chylomicronemia Syndrome (FCS) (NCT03544060 | Phase 3)	The purpose of this program is to provide expanded access to volanesorsen for up to 100 eligible patients with Familial Chylomicronemia Syndrome (FCS) who have limited or no available treatment options.	Drug: Volanesorsen (Waylivra™) administered by subcutaneous (SC) injections	Estimated Study Completion Date: not listed Estimated Primary Completion Date: not listed	None at this time

Clinical Trial data obtained at https://clinicaltrials.gov/ct2/home Accessed: July 9, 2018.

Sales Forecast:

	Sales in Millions						
	2018(F)	**2019(F)**	**2020(F)**	**2021(F)**	**2022(F)**	**2023(F)**	**2024 (F)**
Volanesorsen Sodium (Ionis Pharmaceuticals Inc) – Global	$10	$65	$139	$227	$317	$381	$440
Source: Pharma Intelligence Center https://pharma.globaldata.com Accessed: July 25, 2018							

Conclusion:

Familial chylomicronemia Syndrome (FCS) is a genetic disorder characterized by impaired function of the enzyme lipoprotein lipase (LPL), leading to the inability to break down chylomicrons and the buildup of chylomicrons in the blood. Chylomicrons are lipoprotein particles primarily made up of triglycerides. This buildup results in a significant increase in triglyceride levels, severe abdominal pain, and potentially fatal episodes of pancreatitis. Currently, there are no approved drug therapies to treat FCS. Patients are managed with dietary restrictions such as reductions in the consumption of dietary fat.

Volanesorsen (Waylivra™), an investigational antisense lipid-modifying agent, is being developed by Akcea Therapeutics in collaboration with Ionis Pharmaceuticals for the treatment of familial chylomicronemia syndrome (FCS), familial partial lipodystrophy (FPL), and hypertriglyceridemia. Apolipoprotein C-III (ApoC-III) is a glycoprotein synthesized in the liver that normally inhibits LPL and hepatic lipase, delays the breakdown of triglyceride-containing particles, and plays a role in the regulation of serum triglycerides. Volanesorsen inhibits and reduces the production of ApoC-III, resulting in decreased triglyceride levels.

Volanesorsen has been studied in two Phase 3 trials. The COMPASS study evaluated the efficacy and safety of volanesorsen 300 mg given subcutaneously once weekly for 26 weeks in patients with hypertriglyceridemia. Treatment with volanesorsen resulted in greater than 70% reduction in triglyceride levels as compared to placebo. A second phase 3 trial, the APPROACH study, evaluated the efficacy and safety of volanesorsen 300 mg given subcutaneously once weekly for 52 weeks in patients with familial chylomicronemia syndrome (FCS). Patients treated with volanesorsen achieved a statistically significant mean reduction in triglycerides of 77% from baseline compared to a mean increase of 18% in placebo-treated patients. Treatment with volanesorsen resulted in reduced triglyceride levels, as well as reductions in abdominal pain and recurrence of pancreatitis in patients with FCS, as compared to placebo.

A serious safety concern of drops in platelet counts was identified in the Phase 3 trials. Five patients in the APPROACH study discontinued due to declines in platelet counts. The study also reported three cases of grade 4 thrombocytopenia, which were resolved by discontinuing the medication. The studies ultimately concluded that declines in platelet counts were manageable with dose adjustments and increased monitoring. These safety concerns caused some members of the FDA advisory committee to reject Waylivra™; however, the committee's majority vote of 12-8 resulted in the support of approval for the drug candidate.

According to the FDA advisory committee, the safety concerns and risk of thrombocytopenia associated with volanesorsen treatment may require a risk evaluation and mitigation strategy (REMS) program if the drug were to be approved to ensure that the benefits of therapy outweigh its risks. Despite this, Waylivra™ has the potential to be the first and only treatment available for individuals suffering from FCS. In May of 2018, Akcea Therapeutics announced the expansion of its Global Early Access Program to provide volanesorsen to patients with FCS who have limited or no treatment options available to them. Volanesorsen received Orphan Drug Designation in June of 2015 for its familial chylomicronemia syndrome (FCS) indication and has a current PDUFA action date of August 30, 2018.

References:

"About FCS". *The FCS Foundation*. https://www.livingwithfcs.org/What-is-FCS/About-FCS . Accessed: July 12, 2018.

Clinical Trial data obtained at https://clinicaltrials.gov/ct2/home Accessed: July 9, 2018.

"FDA Briefing Document: Endocrinologic and Metabolic Drugs Advisory Committee Meeting, May 10, 2018". *U.S. Food and Drug Administration*. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM606857.pdf. Accessed: July 16, 2018.

Gaudet D, Digenio A, Alexander VJ, Arca M, Jones AF, *et al*. The APPROACH Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Volanesorsen Administered Subcutaneously to Patients with Familial Chylomicronemia Syndrome (FCS). *Journal of Clinical Lipidology*. 2017 May;11(3):814-15.

Global Data, Pharma Intelligence Center https://pharma.globaldata.com Accessed: July 25, 2018.

Gouni-Berthold I, Alexander V, Digenio A, DuFour R, Steinhagen-Thiessen E, *et al*. Apolipoprotein C-III Inhibition With Volanesorsen in Patients With Hypertriglyceridemia (COMPASS): A Randomized, Double-Blind, Placebo-Controlled Trial. *Journal of Clinical Lipidology*. 2017 May;11(3):794-95.

"Understanding Familial Chylomicronemia Syndrome". *Rare Disease Report*. http://fcs.raredr.com. Accessed: July 17, 2018.

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