Evaluate Vantage

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Upcoming events – Gilead’s Nash refocus and an early chance for Ionis and Roche

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Data from Gilead's Atlas combination trial in Nash could point to a way forward, while Roche and Ionis are hoping to confirm earlier signals seen with a Huntington's disease project.

Welcome to your weekly roundup of approaching clinical readouts. Gilead’s focus on Nash turned to a combination approach after its ASK1 inhibitor selonsertib flunked two phase III trials when used as monotherapy. Data from the phase II Atlas trial, which tests seven different combinations of selonsertib with two other Gilead agents – the ACC inhibitor firsocostat and cilofexor, an FXR agonist – are due before year-end.

The company noted at its third quarter results that Atlas will “allow us to think about how we pivot our Nash strategy moving forward”. Given that selonsertib is essentially a failed asset, little will be expected from the arms that contain this project.

Atlas recruited advanced patients, many with compensated cirrhosis and stage 3-4 fibrosis. Alongside safety the trial is evaluating the proportion of patients achieving at least a one-point improvement in fibrosis score, without worsening of Nash, at 48 weeks. This is the endpoint selonsertib missed as a monotherapy.

Data from a proof-of-concept trial have hinted at the efficacy of the combos. The first batch was released at EASL in 2018 and the second came earlier this year; the trial showed that a combination of firsocostat plus cilofexor produced the largest median decline in liver fat fraction. Patients had stage 2-3 fibrosis and were treated for 12 weeks.

Combination data from proof-of-concept study						
	EASL 2018 data					EASL 2 data
	Selonsertib 18mg	Firsocostat 20mg	Cilofexor 30mg	Selonsertib+ Firsocostat	Selonsertib+ Cilofexor	Firsoco Cilofex
Number of patients	10	10	10	20	20	20
MRI-PDFF reduction at 12 wks	7.1%	-42.7%*	-15.6%*	-32.0%*	-9.4%	-45.3%
No of pats w ≥30% reduction in MRI-PDFF	10%	70%	0%	50%	15%	74%
ALT reduction at 12 wks	-1.2%	-33.5%	29.7%	-27.2%*	-3.0%	-37.0%*

**p<0.05 vs. baseline. MRI-PDFF=magnetic resonance imaging-proton density fat fraction; ALT=alanine aminotransferase, a marker of liver inflammation and damage. Source: EASL 201 EASL 2019.*

The issue with ACC inhibitors such as firsocostat is that they are known to increase triglycerides. Notably, early this month Gilead added another arm to this proof of concept study, adding Vascepa to firsocostat plus cilofexor. Another new cohort includes fenofibrate, a generic lipid-lowering drug, with the same combination. The study has a primary completion date of May next year.

This seems to hint at the way Gilead is moving forward here. The Atlas does not have patients taking anti-hyperlipidaemics, so will clarify firsocostat's lipid impact, but the expanded proof-of-concept trial is also one to watch now.

Gilead had been the front-runner in Nash until its failure with selonsertib. Intercept's FXR agonist Ocaliva now leads the space with a PDUFA in March next year despite having shown modest effects on fibrosis. Readouts are also due from Genfit's phase III Resolve-It trial of elafibranor.

Biggest selling Nash products by 2024			
Product	**Company**	**Annual Nash sales, 2024e ($m)**	**Phase**
Ocaliva	Intercept Pharmaceuticals	923	Marketed
MGL-3196	Madrigal Pharmaceuticals	811	Phase III
Elafibranor	Genfit	508	Phase III
Source: EvaluatePharma.			

Going hunting

The Huntington's disease project being developed by Roche and Ionis Pharmaceuticals is in a pivotal phase III trial, due to report fully in 2022. But it is possible that the groups could obtain accelerated FDA approval of RG6042 next year, based on a combination of several trials. One key readout contributing to this is the data from a small extension study, due in the next few months.

The 46 patients enrolled in Roche and Ionis's placebo-controlled phase I/II trial are being followed for another 14 months on an open-label basis. Data from both these studies are expected to be used in an FDA submission, along with interim biomarker data from the pivotal trial, Generation-HD1 (*Readouts approach for biggest Huntington's hopes, March 26, 2019*).

RG6042, which is also known as Ionis-HTTrx, is an antisense agent which blocks production of the mutant protein that causes Huntington's. Achieving accelerated approval for the asset will be crucial for Roche and Ionis if they are to get the drop on rivals Wave Life Sciences and Takeda. These partners are collaborating on two antisense projects, one of which, WVE-120101, is forecast to launch in 2022.

Trials of RG6042/IONIS-HTT-Rx		
Trial details	**N**	**Data**
Placebo-controlled phase I/II trial	46	Post-hoc analysis reported April 2018
Open-label extension trial	46	Expected by end Q1 2020
Pivotal, placebo-controlled phase III trial (Generation-HD1)	909	Expected 2H 2022
Source: EvaluatePharma.		

Half the patients in the extension trial will receive RG6042 intrathecally once a month, with the other subjects being treated every two months. The study is focused on the agent's safety, with the primary endpoint being incidence of treatment-emergent adverse events. Secondaries include the concentration of Huntingtin protein in the cerebrospinal fluid and assessments of patients' cognition.

The earlier trial showed significant, dose-dependent reductions in mutant huntingtin protein of up to 60%, and mean reductions of around 40% at the two highest doses, 90mg and 120mg. But a definitive link between reduction in mutant huntingtin and improvement in symptoms has yet to be proven. The closest Ionis has come is an exploratory post-hoc analysis of the phase I/II trial that suggested a correlation.

The extension will have to confirm RG6042's safety – the earlier study threw up no serious adverse events with the drug and no discontinuations – over a longer period. Any signs of improving patient symptoms would be a major bonus, but this kind of proof is not expected until the full pivotal readout two years hence, if indeed it comes at all.

Forecast WW sales of RG6042/Ionis-HTTrx ($m)				
Company	**2021e**	**2022e**	**2023e**	**2024e**
Roche (in-licensed)	25	70	219	398
Ionis Pharmaceuticals (originator)	15-19% royalties on WW sales			
Source: EvaluatePharma.				