Evaluate Vantage

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EU thumbs-up sets the stage for burosumab's more important test

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Today's EU approval for Ultragenyx's burosumab marks the first green light for this rare disease drug and sets the stage for a more important event: a US FDA decision, due in April, that should bring with it the company's second priority review voucher.

Given the mixed data burosumab had generated, a positive verdict by the EMA – albeit on a conditional basis – bodes well given the US FDA's arguably less stringent stance. While orphan drug pricing remains a contentious issue the EU regulator is showing itself to be favourably disposed; today also saw two other rare disease drugs recommended for approval.

These were Swedish Orphan Biovitrum's aging rheumatoid arthritis drug Kineret, recommended for Still's disease, and the established, off-patent diabetes drug glibenclamide, whose indication the EU's CHMP is proposing to extend to neonatal diabetes mellitus, an extremely rare form of the disease that is diagnosed in the first six months of life.

Second approval

Burosumab, trademarked Crysvita in the EU, has become Ultragenyx's second approved product, after the US green-lit the enzyme-replacement therapy Mepsevii for Sly syndrome last November.

That came with a priority review voucher that the group swiftly sold to Novartis for $130m. US approval of burosumab, a drug for treating X-linked hypophosphataemia, should yield another such voucher, and the expectation must be that the company will also seek to turn this into hard cash.

Today's approval could yet be revoked: it is conditional on the outcome of three ongoing studies, whose results are to be submitted by 2020. Conditional approvals are granted where there is an overriding public health interest but insufficient clinical backing.

For Ultragenyx this is just as well: burosumab's adult trial hit its primary efficacy measure but missed an important secondary endpoint looking at pain. The US burosumab filing seeks approval in adults as well as children, whereas the EU go-ahead is for children and adolescents only.

The EU approval is based on efficacy seen in a trial in 5-12 year-olds being extrapolated to children between the ages of one and four.

Ultragenyx's upcoming catalysts				
Project	**Indication**	**Event**	**Timing**	**2022e sales ($m)**
Burosumab	X-linked hypophosphataemia	US approval decision	Apr 17, 2018	240
		Data from phase III paediatric study*	H2 2018	
Mepsevii	Sly syndrome	EU approval decision	CHMP opinion due H1 2018	54
Triheptanoin	Long-chain fatty acid disorder	Filing based on phase II data?	Update in mid-2018	159
		Phase III study initiation**	H2 2018	
	Glut1 deficiency syndrome	Phase III data	H2 2018	

**Not required to support US approval, confirmatory in EU; **could be registrational or confirmatory. Source: company releases.*

Meanwhile, the EU's two positive recommendations will result in full approval extensions if they are adopted by the European commission.

Swedish Orphan's Kineret is proposed for use in infants, children, adolescents and adults with Still's disease, a rare condition that in the young includes systemic juvenile idiopathic arthritis.

Glibenclamide's recommendation concerns a new formulation, trademarked Amglidia, put forward by the private French speciality pharma company Ammtek. Crushed up glibenclamide tablets are apparently already used off label to treat neonatal diabetes, a condition thought to involve distinct genetic mutations.

The EU's positive stance might signal a turnaround for Ultragenyx after several clinical setbacks. And another project could also see a reversal of fortune: there had been doubts about triheptanoin, which failed in Glut1 deficiency syndrome, but hopes now rest on an early filing in another condition, long-chain fatty acid disorder.

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