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Pharming bets the house on Ruconest

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Pharming is gathering all the cash it can to get back North American rights to its hereditary angioedema therapy Ruconest from Valeant. But in the meantime the product risks being increasingly overshadowed by more convenient subcutaneous and oral candidates, which is a risk to Pharming and its bankers alike (see table below).

Shire has two subcutaneous projects in phase III development: lanadelumab, which is already forecast to become the biggest HAE drug in 2022, and a subcutaneous version of Cinryze. Meanwhile, Biocryst Pharmaceuticals has an oral contender, BCX7353, in phase II. Data with lanadelumab are due in the second quarter of 2017, which should give a clue whether it can live up to the lofty expectations.

All three of the new candidates are being studied for HAE prophylaxis, where Shire's original intravenous Cinryze is the only approved product. More options for prophylaxis could expand the market as Shire estimates that around 40% of patients still treat their attacks on an as-needed basis

This is another measure where Ruconest falls short – it is currently only approved for acute HAE attacks. Pharming is moving it into prophylactic use, but presumably this would require more trials and, crucially, more expense.

Best in class?

Pharming booked revenues of €8.6m ($9.1m) on product sales last year; based on its supply agreement with Valeant this implies in-market sales of about €20m. While Ruconest has struggled to make headway, Shire is set to dominate the HAE market with four of the top five products in 2022, according to *EvaluatePharma* sellside consensus forecasts.

Top-five HAE drugs in 2022

Product	Company	Details	Status	2022e sales ($m)
Lanadelumab	Shire	Subcutaneous anti-plasma kallikrein MAb; prophylactic use	Phase III	1,070
Cinryze	Shire	Intravenous C1 esterase inhibitor; prophylactic use	Marketed	542
Firazyr	Shire	Subcutaneous bradykinin B2 antagonist; acute use	Marketed	296
BCX7353	Biocryst Pharmaceuticals	Oral kallikrein inhibitor; prophylactic use	Phase II	158
Kalbitor	Shire	Subcutaneous kallikrein inhibitor; acute use	Marketed	79

Source: EvaluatePharma.

Lanadelumab – also known as SHP643 and gained through Shire's acquisition of Dyax – should become the best-in-class HAE drug if it is successful in phase III, Jefferies analysts believe.

"It can improve on efficacy and convenience versus current therapies and, most importantly, there have not been any safety signals to date," they wrote after Shire's November analyst day. Safety will no doubt be closely watched as the group's older kallikrein inhibitor, Kalbitor, carries a black box warning of anaphylaxis.

The primary endpoint of the phase III Help study of lanadelumab is the number of HAE attacks per week versus placebo, while secondary endpoints include time to first HAE attack. The project is being administered every two or four weeks.

If approved, the new therapy is forecast to overtake Cinryze in 2021, but Credit Suisse analysts believe that it will not completely cannibalise the older product. They noted that Cinryze could continue to grow outside the US, where pricing pressure is greater, while in the US “where the market will take a higher price” Shire will push lanadelumab.

Fund raising

With such fierce competition it is a wonder that Pharming is persevering in the US rather than concentrating on smaller markets – it also regained Ruconest rights from Swedish Orphan Biovitrum in 21 European, African and Middle Eastern countries in July.

But the launch of a rights issue today to raise €12.1m shows its commitment to the current plan. This also involves raising €37.7m in debt – at an interest rate of 8% – from Silicon Valley Bank and Kreos Capital, and €62m in two new convertible bonds, one at zero interest and one at 8.5%.

The net total of €85m will cover the $60m up-front fee agreed with Valeant and leave some extra cash for investment in sales and marketing in the US and EU.

The deal represent a decent return for Silicon and Kreos in the current low-interest era, perhaps going some way to explain why they would take the risky move of lending this amount of cash to Pharming in spite of the obstacles ahead. Whatever the reason, the company has managed to buy itself some more time.

Project	Study	Primary completion	Trial ID
Lanadelumab	Help	Dec 2016	NCT02586805
Lanadelumab	Help extension	Dec 2017	NCT02741596
Cinryze SC	Phase III trial	Dec 2017	NCT02584959
BCX7353	Apex-1	Apr 2017	NCT02870972