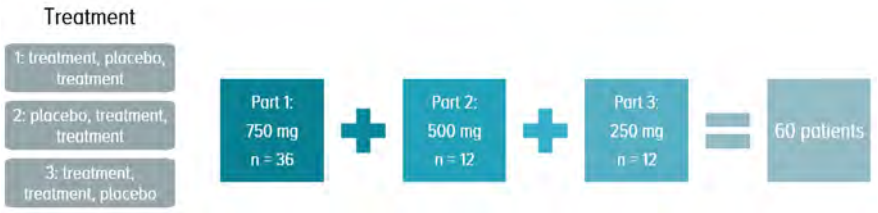
Liquid 750mg BCX7353 phase II results supportive for acute use

BioCryst initiated ZENITH-1, a randomized, placebo-controlled, dose ranging phase II study (NCT03240133), which has completed enrollment of 60 HAE patients. The trial is evaluating three doses of liquid BCX7353: 750mg (part 1), 500mg (part 2), and 250mg (part 3). Starting with the 750mg dose, patients will be randomized to three treatment arms, each consisting of two times treatment of the attack with BCX7353 and one time with placebo, in different orders (figure 17). If this proves effective, part 2 and part 3 will follow until the minimum effective dose is identified. Given the variability in historical acute trial endpoints, ZENITH-1 has no single primary endpoint rather BioCryst will be looking across multiple efficacy measures to identify the most appropriate primary endpoint to be used in the pivotal study. Part 1 results were reported the beginning of September 2018, and part 2 and 3 are expected in Q1'19. Though the 750 mg dose showed interesting results, we can't deduce a superior profile compared to currently available acute treatments and believe further readouts on parts 2 and 3 present rather clearing events.

Figure 18 - ZENITH-1: phase II BCX7353 acute trial



Source: BioCryst presentation, 2018

- **Self-administration and self-assessment add risk to the readout.** In ZENITH-1, patients will be self-administering the treatment at home within 1 hour of symptom onset, in contrast to comparative historic trials which used clinic administration within 4-12 hr of symptoms onset. Another confounding factor is that patients can use rescue medication. Naturally, it is also up to the patient whether to use rescue medication and when, although they are instructed to wait at least 4 hr. Cross trial efficacy comparison is also made difficult by the slight variations in endpoints in other trials, though generally, the range of efficacy at 4 hr with approved acute treatments has been between 16-43% vs placebo, with highest with Firazyr (see table 2).

Table 2 - Efficacy comparison acute trials

Trial / Drug	Dose / Administration	Subjects Receiving Rescue Therapy or Medical Intervention			Proportion meeting primary endpoint at 4 hours		
		Active	Placebo	% difference active vs placebo	Active	Placebo	% difference active vs placebo
CHANGE **Cinryze** (Shire)	1000 U IV infusion	23 / 35 66%	28/ 33 85%	**- 19%**	21 / 35 60%	14 / 33 42%	**18%**
IMPACT-1 **Berinert** (CSL)	20 U/kg IV infusion	8 / 43 19%	24 / 42 57%	**-** 38%	~86%	~59%	**~27%**
EDEMA-3 **Kalbitor** (Shire)	30 mg SC injection	5 / 36 14%	13 / 36* 36%	**- 22%**	~51%	~35%	**~16%**
FAST-3 **Firazyr** (Shire)	30 mg SC injection	3 / 43* 7%	18 / 45* 10%	**- 33%**	32 / 43* 74%	14 / 45* 31%	**~43%**
C-1310 **Ruconest** (Pharming)	50 U/kg IV infusion	5 / 44* 13%	13 / 31* 43%	**- 30%**	~80%	~53%	**~27%**

* FDA analysis

Source: BioCryst's Q2'18 presentation

- **750 mg cohort results were a good start.** In the 750 mg cohort, 33 patients treated 64 attacks with BCX7353 and 31 attacks with placebo, in line with the treatment sequence of the cohort. The results showed a 16 hours improvement (p=0.0671) in the time to >50% reduction in VAS score at 24 hr (8 hr with BCX7353 vs 24 hr placebo), while with Firazyr we saw 2 hr >50% reduction. The median time to initial symptom relief was 5.1 hr vs 19.4 hr with placebo (p=0.0978), while the median time to almost complete symptom relief was almost equal at around 23 hr with BCX7353 and placebo (p=0.06767). With Berinert and Ruconest, initial symptom relief is quick given IV administration at 50 min and 90 min respectively, while with Firaryz and Cinryzre complete/ unequivocal relief is achieved at 8 hr and 2 hr respectively. See table 3 for all results. Generally, it seems that current treatments provide faster and better symptom relief compared to BCX7353, though this could be masked by the different timing of treatment administration once symptoms appear (1 hr with BCX7353 vs 4-12 hr with others).

Table 3 - ZENITH-1 750 mg cohort results

Efficacy Endpoint	BCX7353 Treated Attacks (N=64)	Placebo Treated Attacks (N=31)	Difference	p-value
Change from baseline in VAS score through 4 hours	-3.9%	3.1%	-6.98	0.0024
Proportion of attacks requiring standard of care treatment through 24 hours	29.7%	61.3%	-31.6%	0.0029
Proportion of attacks with no or mild symptoms through 24 hours	64.1%	32.3%	31.8%	0.0038
Time to standard of care acute attack treatment (median)	>24 hours	14 hours	>+10 hours	0.0043
Proportion of attacks with improved or stable symptoms through 24 hours	64.1%	35.5%	28.6%	0.0092
Proportion of attacks with improved or stable VAS score through 24 hours	62.5%	35.5%	27.0%	0.0125
Proportion of attacks with improved or stable symptoms through 4 hours	82.3%	60.0%	22.3%	0.0192
Proportion of attacks with improved or stable VAS score through 4 hours	67.7%	46.7%	21.0%	0.0387
Time to stable or improved VAS (median)	1 hour	2 hours	-1 hour	0.0452
Proportion of attacks with no or mild symptoms through 4 hours	69.4%	50.0%	19.4%	0.0552
Time to ≥ 50% reduction in VAS through 24 hours (median)	8 hours	24 hours	-16 hours	0.0671
Time to initial symptom relief (median)	5.1 hours	19.4 hours	-14.3 hours	0.0978
Time to almost complete symptom relief (median)	23.1 hours	23.6 hours	-0.5 hours	0.6767
Time to complete symptom relief (median)	35.1 hours	41.3 hour	-6.2 hours	0.89

* Mean baseline composite VAS scores were 14.0 in BCX7353 treated attacks and 15.0 in placebo treated attacks

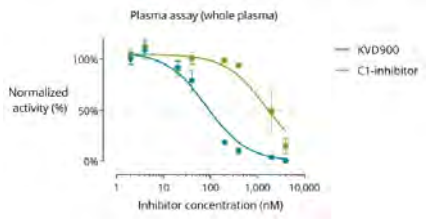
Source: BioCryst

- **Minimal GI AEs, though waiting for more data.** The most commonly reported adverse events were nasopharyngitis (4/64 attacks treated with BCX7353 vs 1/31 for placebo), diarrhea (3/64 with BCX7353 vs 0/31 for placebo) and headache (3/64 with BCX7353 vs 0/31 for placebo). Though we would need to see the results of the other cohorts to understand whether there were any confounding GI events recorded as HAE attacks, as in the prophylaxis phase II.

BioCryst or not, other orals are not far behind

Further in the oral pipeline, we identified five other companies following BioCryst's footsteps. KalVista (KALV US), Attune, Pharvaris, Rezolute, and Verseon are bringing at least another 7 oral candidates into development, for both acute and prophylaxis. We believe that, in the (unlikely) scenario of BCX7353 failing development, at least a few other oral options will reach the market in the coming 4-5 years.

Figure 19 - KVD900 Potency Compares Favorably to Berinert



Source: KalVista

KalVista to report acute phase II data mid-2019

KalVista is working on a portfolio of oral plasma kallikrein targeting HAE candidates, in both acute and prophylactic settings. KVD900 is expected to enter a proof-of-concept phase II in Q4'18 for acute treatment, with readout expected mid-19, while KVD818 completed phase I. The company is guiding for one more molecule to enter the clinic in 2018 and potentially more in 2019. The company is well funded to bring KVD900 to market.

Double-blind, randomized phase I data in healthy volunteers suggests that KDV900 displays a rapid uptake into the plasma and reach high plasma concentrations. At doses up to 600 mg, exposure increased proportionally and reached effective concentrations within 30 minutes or less, and a PK/PD correlation with inhibition of plasma kallikrein for up to 10 hours following a single dose. In addition, KVD900 is so far well tolerated with the most common adverse events being back pain, flu symptoms, and pyrexia, with no GI adverse events reported at any dose.

Attune is enrolling for the phase I

In Q2'17, the privately owned US-based Attune Pharmaceuticals announced results from preclinical safety studies evaluating ATN-249, an orally administered plasma kallikrein inhibitor for the treatment of HAE, suggesting strong safety, high potency, and high selectivity. According to the Australian/New Zealand clinical trials registry, a trial in healthy volunteers was registered in Q1'18 (here).

Pharvaris developing an oral Firazyr, to enter the clinic in late 2018

Unlike the competition, Pharvaris is working on bringing an oral bradykinin B2 receptor antagonist to the market. The Dutch private company was founded by former executives of Jerini, who were behind the development of Firazyr. The company has selected a potent and specific candidate, PHA121, expected to enter the clinic later in 2018.

Rezolute and Verseon are on the oral inhibition of plasma kallikrein trail

In addition, oral HAE potential candidates are being explored by Rezolute (RZLT US, formerly AntriaBio), with an IND filling planned for Q1'19, and by Verseon (VSN LN), with a candidate expect to enter phase I in the near term.

Gene therapy, antisense RNA drugs, and more

Further in the HAE pipeline companies are pursuing candidates with various mechanisms of action. Adverum (ADVM US) is developing a gene therapy while Ionis is working on antisense RNA drug candidate. In addition, CSL is investing in its HAE franchise with the development of an anti-factor XIIa antibody and a recombinant version of C1-INH (i.e. generic Ruconest).

Adverum intends to file IND for gene therapy in Q4'18

One-time administration of a gene therapy could provide a curative solution for HAE patients. Adverum's (ADVM US) ADVM-053 (AAVrh.10-C1EI) is designed as a potential single-administration treatment to provide sustained release C1-INH, and preclinical studies demonstrated a protein expression above therapeutic levels and

a decreased vascular permeability after treatment. The company announced the intention to file an IND in Q4'18.

Ionis brings on RNA-targeted antisense drugs

Ionis is focusing on the development of RNA-targeted antisense drugs designed to reduce the production of prekallikrein. The SC compounds IONIS-PKKRx and IONIS-PKK-LRx are currently in early-stage development for a potential application in prophylaxis. The company has completed a phase I study evaluating IONIS-PKKRx in healthy volunteers and is exploring potential development options, and IONIS-PKK-LRx is currently in a phase I study in healthy volunteers.

CSL looking to beef-up franchise with non-plasma derived products

- **An anti-factor XIIa monoclonal antibody completed phase I.** CSL is developing CSL312, a humanized anti-factor XIIa monoclonal antibody, potentially for an SC prophylaxis therapy for HAE and thrombosis. In December 2017, the company gave an update on its R&D day confirming the completion of the dosing on a phase I study in healthy volunteers, followed by a second part on which bioavailability favored a similar dosage to the one observed with lanadelumab.

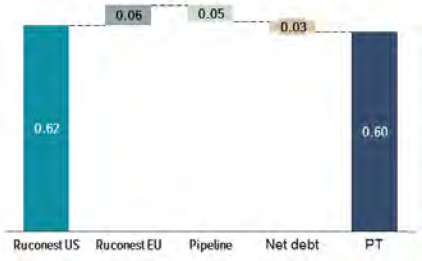
- **CSL licenses generic Ruconest.** In May 2018, CSL signed a licensing agreement with Cevec Pharmaceuticals (private) for the development, manufacture, and commercialization of a recombinant C1-INH for HAE and other potential indications, using Cevec's proprietary CAP(R)Go technology. The CAP-Go expression platform comprises a portfolio of glyco-optimized human suspension cell lines for the production of difficult to express recombinant proteins. The licensing was the result of an ongoing collaboration that showed initial data on the potential of the technology to develop CAP(R)Go-derived C1-INH proteins with tailored glycosylation, leading to an improved half-life and more convenient application. The companies reported in 2015 that the platform produced a recombinant protein that matches plasma C1-INH in activity, serum half-life, and glycosylation patterns and, additionally, is producible at large scales on a safe platform (Wissing 2015).

Overview upcoming HAE newsflow

Table 4 - Upcoming HAE candidates newsflow

2018			
	Q3	**Pharming**	**Ruconest BLA for prophylaxis, PDUFA Sep 21**
		Adverum	IND submission for ADVM-053
		Pharvaris	To Initiate phase I with PHA121
		CSL	To Initiate phase II prophylaxis trial with CSL312
	Q4	KalVista	To Initiate phase II acute trial with KDV900
		KalVista	To Initiate phase I trials with new candidate
		Pharming	To initiate phase II with Ruconest SC, IM, ID
		Conference	Annual Meeting of the American College of Allergy, Asthma, and Immunology (Nov 15-19)
2019			
	Q1	Rezolute	IND submission for oral candidate
		Conference	American Academy of Allergy, Asthma and Immunology Annual Meeting (Feb 22-25)
		BioCryst	Readout phase II acute second (500 mg) and third cohort (250mg) with liquid BCX7353
	Q2	**KalVista**	**Readout phase II acute with KDV900 (mid 2019)**
		BioCryst	**Readout BCX7353 phase III prophylaxis with BCX7353**
	Q3	BioCryst	BCX7353 BLA filling prophylaxis
		Conference	European Academy of Allergy and Clinical Immunology Congress (Jun 01-05)

Figure 20 - Sum-of-the-parts PT



Initiate with a SELL and €0.6 PT

Our DCF valuation results in a PT of €0.60, with €0.62 attributed to Ruconest in HAE in the US, €0.06 to Ruconest in HAE in Europe, - €0.05 for near-term R&D pipeline expenses, and -€0.03 to the net debt position (see figure 20). Given the exploratory and early nature of Pharming's pipeline, we currently do not value any upside from these programs. However, we appreciate the preeclampsia and Pompe programs as most promising, which could add ~17% (€0.10) and ~8% (€0.05) to our valuation. Foreseeing further competitive pressure on Ruconest in the US from the changing treatment paradigm in HAE, we consider the share price overvalued and initiate coverage with a SELL.

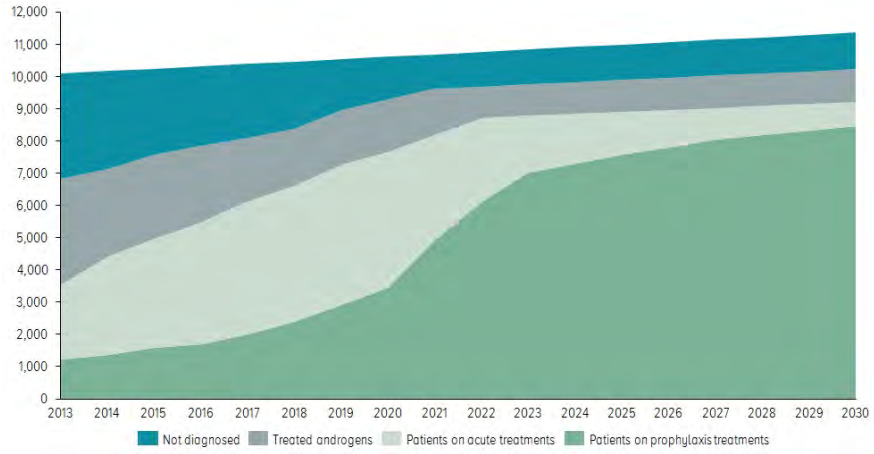
We forecast an acceleration in patients on prophylaxis

We estimate that there are currently about 10,000 HAE patients in the US with the prevalence rising mainly with population increase. However, the HAE market has more than doubled in the last 6 years driven by an increase in the diagnosis rate and patients switching from androgens to newer treatments due to increased awareness and improved drugs accessibility. Currently, we estimate that 80% of patients are being correctly diagnosed of which about 20% are on androgens, resulting in an effective market of 6.6k US HAE patients. We expect the market to further increase to about 8.8k patients by 2023 (see figure 20), driven primarily by an increase in drugs with an easier mode of administration (e.g. orals and SC). This will effectively also accelerate sales of HAE drugs as patients will be more likely to switch from on-demand to prophylactic treatments.

We forecast 80% of patients on prophylaxis treatments by 2023

According to market research by Shire and BioCryst, in 2017, approximately 50-60% of patients were on prophylaxis or on acute + prophylaxis treatments. Given plasma-derived C1-INH supply issues in 2017, we estimate that currently, about 30-40% of patients are only on prophylaxis treatment. With better formulations and additional treatments entering the market in the coming years, we expect the ratio of patients on prophylaxis treatments to reach 80% by 2023, continuing to accelerate as more orals therapies are approved (see figure 21).

Figure 21 - Forecast US HAE patients



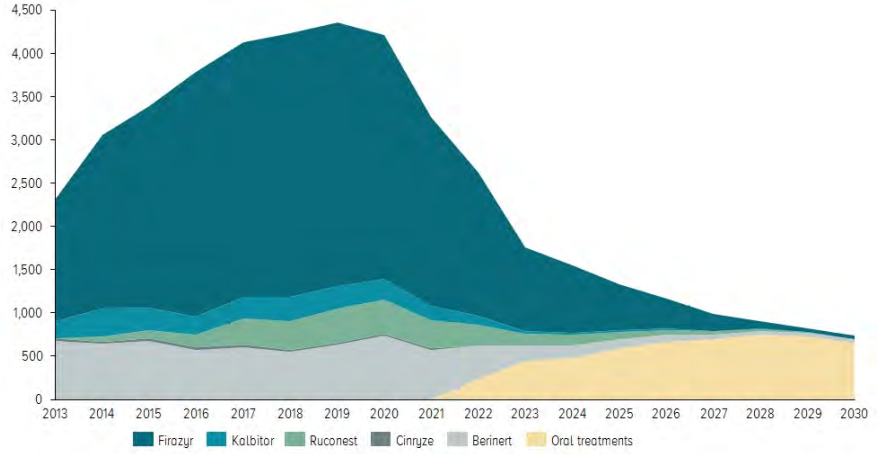
Source: Shire, BioCryst, Pharming, Kempen estimates

In the acute setting, Firazyr to hold >60% of the market until orals launch

In the acute treatments market, we believe Firazyr will continue to dominate in the mid-term, given its ease of use and efficacy. Notably, we could expect to see Firazyr generics coming to the market after patent expiration in July 2019, particularly

as Fresenius and Sandoz have already tried (unsuccessfully) to challenge Shire's exclusivity. From 2022 onwards, we expect oral treatments (most likely from BioCryst and KalVista) to gain the majority market share in the shrinking acute market. We forecast gradual Ruconest adoption with 10% peak market share in 2021, declining from 2022 onwards as oral treatments sales ramp up (see figure 22).

Figure 22 - Forecast US HAE patients on acute treatments

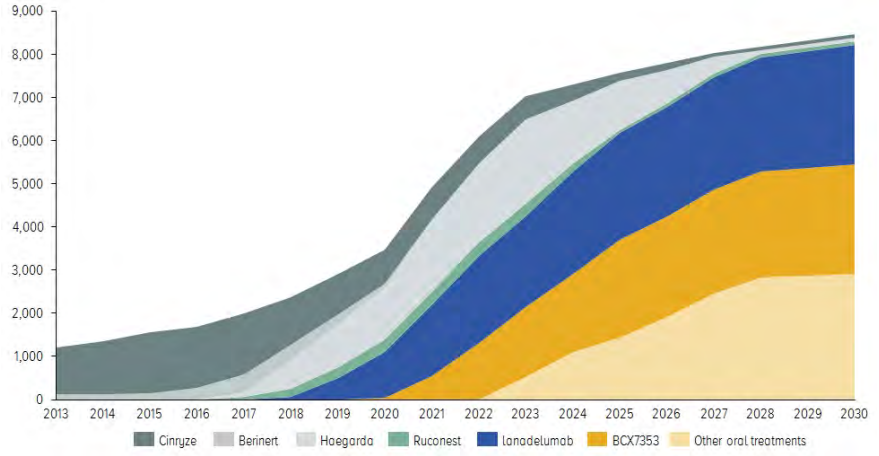


Source: Shire, CSL, Pharming, Kempen estimates

Prophylactic market to be split by lanadelumab, BCX7353 and other orals

We believe that the launch of lanadelumab in 2018 will be transformational for the HAE market, capturing patients currently using acute treatments. Additionally, we expect BCX7353 to deliver positive results from its phase III trial in H1'19, followed by a launch in 2020. Given both drugs advantage in terms of ease of use, we expect them to represent the majority of usage in 2023. Although we foresee Ruconest getting approval in prophylaxis in September 2018, we expect Haegarda to lead the C1-INH class in the mid-term given its superior efficacy, cheaper price point and easier mode of administration compared to Cinryze or Ruconest. Although Pharming is working on easier to administer new formulations expected in 2021, we believe that the window to gain market share will be closing with the launch of lanadelumab and BCX73531. Thus, we forecast Ruconest to reach an 8% peak market share in 2019, starting to decline as BCX7353 sales ramp up. Beyond 2023, we expect companies such as KalVista, Pharvaris and Attune to launch one or more oral therapies (see figure 23).

Figure 23 - Forecast HAE patients on prophylactic treatments



Source: Shire, CSL, Pharming, Kempen estimates

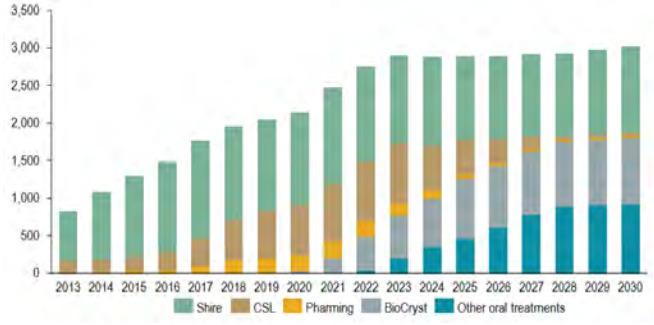
We estimate a $3b US HAE market in 2023

For both Shire and CSL, HAE is a highly profitable niche business with both companies investing over the year to maintain their lead market share.

- With 4 out of the 7 approved HAE treatments, we expect Shire to maintain its lead market share, with Cinryze sales erosion, due to Haegarda and Ruconest, to be made up by lanadelumab from 2019 onwards. We forecast Shire's HAE sales reach 2017 $1.3b in sales in 2021, remaining relatively flat until 2023 and declining after.
- We forecast CSL HAE sales to be primarily driven by Haegarda gaining market share in the prophylactic setting, mainly by switching patients from Berinert, with a total peak of $800m in 2023. CSL HAE pipeline includes an antibody in phase I as well as a recombinant C1-INH in pre-clinical stages, recently licensed from German Cevec.
- For Pharming, with the approval of Ruconest in prophylaxis, we expect sales to accelerate to a peak of $223m in 2021 and gradually decline as lanadelumab and BCX7353 gain market share in the prophylaxis market.

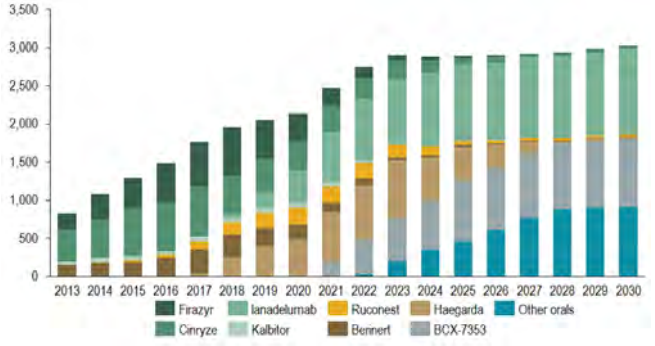
Overall, we project the US HAE market to be worth approximately $3b in 2023. We believe further sales expansion will be difficult given the almost perfect diagnosis rate and the increasing number of oral treatments and price competition (see figures 24 and 25).

Figure 24 - Forecast US HAE market by company (USDm)



Source: Shire, CSL, Pharming, Kempen estimates

Figure 25 - Forecast US HAE market by drug (USDm)



Source: Shire, CSL, Pharming, Kempen estimates

We expect Shire to continue buying its way to the top

Shire built its HAE franchise via three acquisitions starting with the $521m takeover of Jereni in 2008, acquiring Firazyr. Since Firazyr could never work in prophylaxis due to its short half-life, Shire added Cinryze via the $4.2b acquisition of Viro Pharma in 2013. Next, Shire acquired Dyax in 2015 for $5.9bn for lanadelumab (and Kalbitor) after it showed great efficacy (>90% reduction in attacks) in a phase Ib proof of concept study. Although the ongoing merger with Takeda is a confounding variable, we think it makes strategic sense for Shire to look at complementary oral treatments to its antibody to further the growth of its HAE franchise. BioCryst is, of course, the most obvious takeout candidate once the phase III trial of BCX7353 reads-out in Q2'19. Another logical take-out candidate is Pharvaris (private) given its developing essentially an oral Firazyr, which comes off patent in 2019. We would expect Shire to wait for phase Ib data which could come as early as H2'19 as the company plans to start the trial in Q4'18. Furthermore, the CEO of Pharvaris has previously been the CFO of Jereni during the sale to Shire.