Pharming

# Down the rabbit hole

European Life Sciences | 14 September 2018, 15:15

**We initiate coverage on Pharming with a SELL (€0.60 PT) expecting the downside to materialize in the next 6-12 months as the company's hereditary angioedema (HAE) drug Ruconest fails to gain market share in light of the upcoming launch of lanadelumab, a superior treatment from Shire. While we appreciate the company's commercialization strategy in the US, we believe the market's expectation for Ruconest peak sales is grossly missing the quickly changing dynamics of the HAE market. We see in the mid-term increasing competition from oral treatments in development, particularly from BioCryst and KalVista.**

## Ruconest was destined for niche market share

Due to US regulatory delays, Ruconest was launched in 2014 in a market dominated by Shire and CSL. Apart from a rather theoretically safer profile, Ruconest as acute HAE treatment had on par efficacy data and no administration advantage. Moreover, repeated change in ownership never allowed Ruconest to ramp-up meaningful sales. Ruconest recently caught a break due to competitor shortages and sales tripled in 2017. With such issue resolved, Ruconest sales in the last two quarters were flat, which we believe is a return to normal and forecast only modest growth in the shrinking acute market with peak sales of $88m.

## We think prophylaxis sales expectations are unrealistic

We expect that the upcoming approval for Ruconest for prophylaxis use will reignite high sales expectations. However, compared to competing therapies lanadelumab (Shire) and Haegarda (CSL), Ruconest scores last on efficacy, convenience in dosing schedule, and mode of administration or price. Giving the benefit of the doubt to Pharming's large HAE sales force, we estimate prophylaxis sales to grow to just above $150m at peak.

## BioCryst is likely to launch the first oral treatment in 2020

BioCryst's prophylaxis oral treatment is on track to report phase III data in Q2'19. We believe the probability of success is high, with a launch in 2020. We think this will accelerate the shift of patients towards prophylaxis as the convenience of a daily pill simply outweighs treating attacks as they come.

## Pipeline is early and exploratory

We see little downside cushion in the pipeline as Ruconest indication expansion is investigator-driven in indications with unclear pathogenesis. In addition, candidates for Pompe and Fabry have yet to enter the clinic, while multiple gene therapies are already in late stages of development.

## Initiate with a SELL and €0.60 PT

Our valuation points to ~50% downside to current share price levels, where Ruconest for US HAE represents 90% of the value. Our 2021 Ruconest sales estimates are ~50% below consensus, with the difference primarily due to an overvaluation of Ruconest's prophylaxis sales.


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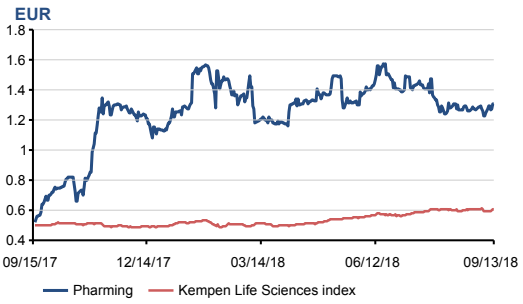
|---|---|
| Rating | SELL |
| Price Target | €0.60 |
| Closing price (13 Sep 2018) | €1.30 |

**Company data**

| | |
|---|---|
| Market capitalization | $1,098.9m |
| 52-week range | €0.47 - €1.62 |
| Number of shares | 616.7m |
| Free float | 91.6% |
| Avg. daily volume (20d) | 6,918,458 |
| Avg. daily turnover (20d) | €8,783,637 |
| Daily turnover | €11,462,450 |
| Next announcement date | 25 October 2018 |
| Reporting Period | Q4 2018 Results |




Source: Bloomberg

*DISCLOSURES AND ANALYST CERTIFICATIONS START ON PAGE 43*

**pharming**

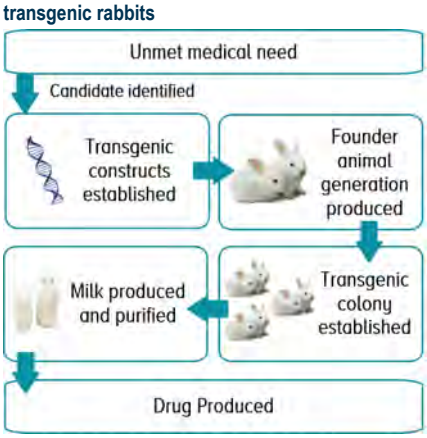
NOUN

1 The process of genetically modifying plants and animals so that they can produce substances which may be used as pharmaceuticals

# The trials and tribulations of Ruconest

Pharming spun-off in 1995 from GenPharm focusing on the production of recombinant proteins in the milk of transgenic cows. The company later switched its focus to a more easily scalable rabbit milk platform. In 1998, Pharming listed on the Amsterdam stock exchange and in collaboration with Genzyme was developing a recombinant human alpha-glucosidase candidate for the treatment of Pompe disease. On the back of financial difficulties in 2001, Pharming handed the Pompe research assets to Genzyme, focusing its operations towards the development of a recombinant version of the human C1 inhibitor (C1-INH) for the treatment of hereditary angioedema (HAE), which is now known as Ruconest.

**Figure 1 - Producing human proteins in the milk of transgenic rabbits**




Source: Pharming

## Ruconest, from (transgenic) rabbits with love

Pharming's core technology is based on the production of therapeutic recombinant proteins in transgenic rabbits. To produce the desired protein, a DNA sequence containing the human gene that codes for certain proteins is integrated into the genome of rabbit cells producing transgenic embryos. These (transgenic) rabbits are able to produce a recombinant version of the desired protein in their mammary glands (i.e. milk) which is highly similar to the human equivalent (see figure 1). Pharming out-sourced to Sanofi in 2010 an industrialized version of this process for the production of Ruconest (recombinant C1-INH). The company has intellectual protection for recombinant proteins produced in rabbit milk as well as for methods of generating transgenic animals last largely until 2020.

## Ruconest gained European approval on the second try in 2010

Pharming filed in 2006 for European approval of Ruconest for the treatment of acute (on demand) HAE attacks. After a negative CHMP opinion, primarily due to insufficient evidence confirming benefits of repeated use, the development progressed into extension studies. Pharming refiled the MAA in Q3'09 and gained approval by the end of 2010, launching Ruconest in Europe in partnership with Swedish Orphan Biovitrum (Sobi).

## US approval came in 2014 but the launch was hampered by M&A

In 2009, Pharming entered a US partnership with Santarus and filed for market approval. In early 2011, the FDA refused the filing due to insufficient data supporting the proposed dose and the need for the validation of a visual analog scale used to measure the treatment effect. The agency provided feedback for the amendment of an ongoing phase III trial that was initiated based on previous discussions. Finally, US approval came in 2014, however, around the same time Santarus was acquired by Salix, which launched Ruconest in Q4'14. Shortly after, in 2015, Salix was acquired by Valeant. The constant change of partners resulted in an unfocused launch in a highly competing and dynamic HAE market.

## Taking back US rights breathed new life into Ruconest

In Q3'16 when Pharming announced the acquisition of the North American rights from Valeant for a $60m upfront payment (plus $65m in potential milestones), with the intention to build its own focused commercial operation. In 2017, in order to broaden the addressable market, Pharming expanded the EU label of Ruconest with self-administration. In the same year, the company reported positive results with Ruconest as prophylaxis treatment for HAE. In Q1'18, the company applied for FDA label extension into prophylaxis use for Ruconest, with the PDUFA date scheduled for 21 September 2018.

## Doubling down on Ruconest

Pharming's clinical activities (see figure 2) are currently focused on developing more convenient modes of administration for Ruconest in HAE.

- **Ruconest subcutaneous (SC), intramuscular (IM) and intradermal (ID)** phase II studies are expected to start in Q4'18, with phase III studies expected in 2019. As we will detail further, improving patients' convenience has long been a driver for innovation in HAE, with a number of competing therapies already available in SC versions and with improved dosing regime. In addition, next generation, oral therapies are in late-stage clinical development.

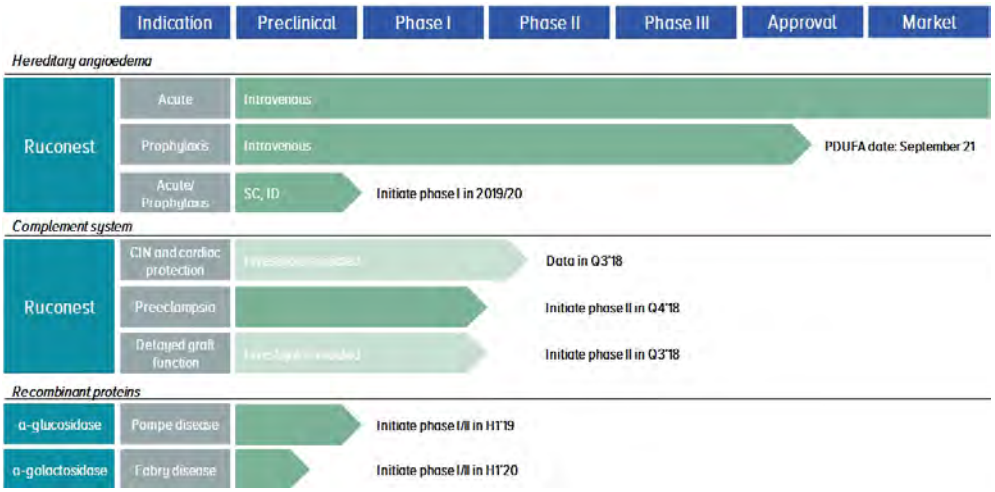
Considering competing forces in HAE, Pharming is focusing on expanding Ruconest's use into new indications. Due to its benign safety profile, Ruconest is being considered for a number of diseases were the complement system appears to be playing a role. Given the, mostly, investigator-driven nature of these trials (see below) we believe the data is likely to be more relevant for academic purposes and see limited commercial value for Pharming.

- **contrast-induced nephropathy** (CIN) investigator-initiated proof-of-concept phase II study with results expected in Q3'18.
- **delayed-graft function** (DGF) in kidney transplantation investigator-initiated proof-of-concept phase II trial expected to start in Q3'18.
- **preeclampsia** investigator-initiated but Pharming sponsored proof-of-concept phase II trial in pregnant women expected to start in Q4'18.

Lastly, Pharming is planning to leverage the transgenic rabbit platform into lysosomal storage disorders, Pompe and Fabry. Though the programs make sense, as they did at the beginning of 2000, we detail in the appendix the increasingly competitive landscape with a number of promising, potentially curative gene therapies already in the clinic. Thus we see limited value in the Pharming programs.

- **Pompe** (α-glucosidase) phase I/II study expected to start in H1'19
- **Fabry** (α-galactosidase) phase I/II study expected to start in H1'20

**Figure 2 - Pharming pipeline**

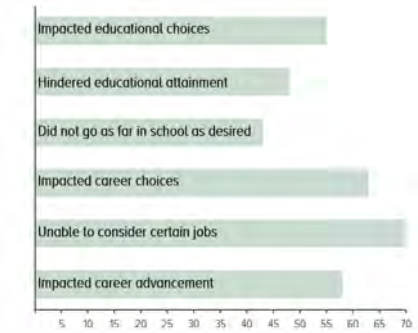



Source: Pharming

# HAE is an orphan but mature indication

Hereditary angioedema (HAE) is a rare genetic disorder caused mainly by one or more mutations in the SERPING1 gene, which codes the C1-inhibitor protein (C1-esterase inhibitor, C1-INH). In about 85% of patients, HAE is caused by C1-INH deficiency (type I) and in 15% of patients, HAE is caused by a dysfunctional C1-INH protein (type II) (Zuraw 2008). Additional HAE manifestations characterized by normal plasma levels of functional C1-INH have been identified, although those are extremely rare. Overall, it is estimated that HAE affects 1 in 50,000 people, though reported values vary between 1:10,000 to 1:150,000 people (Roche 2005; Bowen 2010; Zanichelli 2015), with about 10,000 patients in the US and 15,000 in Europe.

**Figure 3 - Patient reported impact on QoL due to HAE (% patients)**

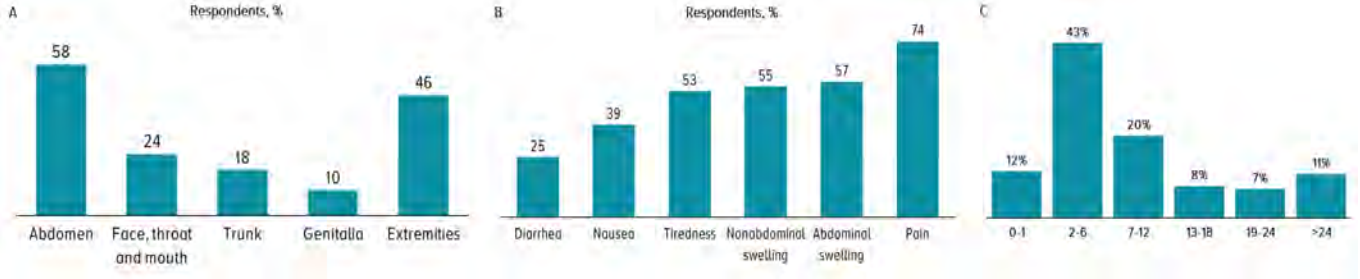



Source: HAEi patient survey 2011

## HAE attacks are unpredictable, severely limiting the quality of life

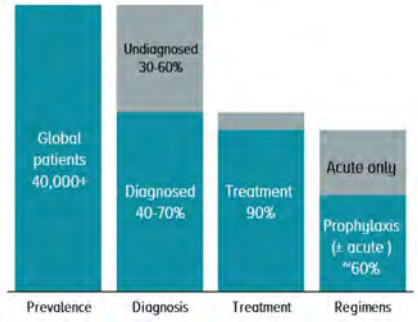
The disease manifests in the form of swelling (edema) attacks most commonly in the limbs, face, intestinal tract, and airway (see figure 4A). Attacks often lead to discomfort, pain, nausea, and, more seriously, to airway obstruction (see figure 4B), with a 30% risk of asphyxiation if the attack goes untreated (Zuraw, 2008). The amount and severity of attacks are highly variable between different patients and also throughout patients own lifetime. In general, HAE manifests ~2-24 attacks per year (see figure 4C) and lasts about 2 to 5 days (Cicardi 2018), with the most severe patients experiencing attacks every three days. A few factors, like trauma, stress and medical/dental procedures are known triggers, however, most attacks occur unexpectedly, resulting in the recurrent and prolonged disruption of normal activities, often precipitating anxiety and depression (see figure 3).

**Figure 4 - A) Location of most recent HAE attack B) Symptoms reported by ≥25% of patients C) patients' (%) attacks frequency in the past 6 months**




Source: Banerji 2017

**Figure 5 - HAE patients dynamics**




Source: Shire's presentation, 2017

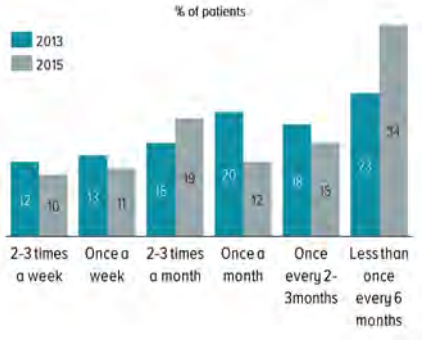
## HAE is often misdiagnosed as an allergic reaction

The diagnosis procedure starts by ruling out other disorders when the attacks do not respond to standard antihistaminic treatments. Once there is a suspicion of HAE, the confirmation is done by clinical chemistry testing (typically for low C4 levels). In the absence of a recognized family history and due to the rarity and similarity to other conditions, HAE is often not correctly diagnosed for several years. In a patient survey (Banerji 2015) only 25% of patients were diagnosed within 1 year of symptoms onset, while ~47% experienced a delay of 10 years or more. In 2011, the HAE international patient organization recognized a diagnosis rate in Europe varying between 20% to 60% while corporate market research points towards a global diagnosis rate of about 50% (see figure 5). Nevertheless, we estimate in the US based on sales figure that the diagnosis rate is closer to 80% nowadays.

## Patients can receive either on demand or prophylactic treatment

Upon a definitive diagnosis, patients are assigned to an acute (on demand) or a prophylactic treatment. Acute treatments are (mostly self) administered as soon as an attack is recognized, while prophylactic treatments are administered on a regular basis, in order to prevent or reduce the frequency of attacks. International guidelines recommend that all attacks are to be treated and that prophylaxis treatment can be considered for patients which do not minimize disease burden with acute therapy. In both options, guidelines strongly recommend patients to always have at least two doses of acute treatment at hand, at all times, as attacks might occur unpredictably and breakthroughs are common during a prophylaxis treatment. A short-term prophylaxis can also be initiated in the anticipation of a planned exposure to a situation likely to trigger an attack, such as dental, medical and surgical procedures (Longhurst, 2015, 2018)

**Figure 6 - Frequency of HAE breakthrough attacks after prophylactic therapy**




Source: Banerji 2018

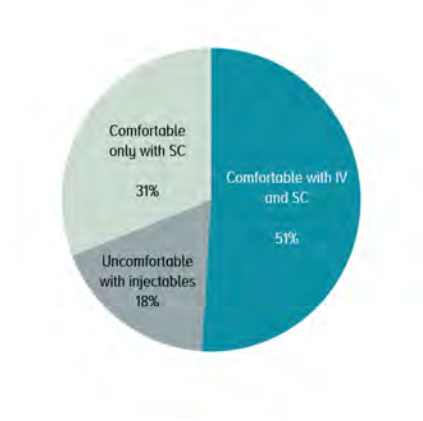
## The choice for prophylaxis is on a case by case basis

The choice to opt for acute or prophylactic treatment is particular to each patient and is not definitive throughout their lives, especially since past and current attack patterns do not necessarily reflect the future course of the disease. HAE guidelines recommend that physicians take into account comorbidities, drug interactions, side effects, patient preference, patients living situation, ease of intravenous access, and frequency and location of attacks (Longhurst 2017). In a patient survey conducted in 2015, Banerji reported that patients often overlap treatment modes, with 55% opting to use on-demand medication to treat attacks more than 90% of the time. Between 60% to 70% of patients opt for a prophylactic therapy, however, around 51% of those patients continue to experience breakthroughs attacks at least once a month (see figure 6).

## Patients can choose between IV and SC routes for administration

On top of the therapy approach, patients can also choose for treatments that are delivered intravenously (IV) or subcutaneously (SC). Regardless of their choice, most recent guidelines recommend physicians to encourage patients to perform home-based self-administration (SA), which is considered safe, leads to earlier treatment, earlier resolution of symptoms, decrease hospital visits, and improved overall QoL. Most patients that choose for IV treatments use peripheral veins for the administration, however, a few opt/need to use a central venous port, which is strongly discouraged in HAE due to higher risks of acquiring bloodstream infections and thrombosis (Riedl 2017; Wang 2015)

**Figure 7 - Patients perception of self-administrated treatments**




Source: Wang 2015

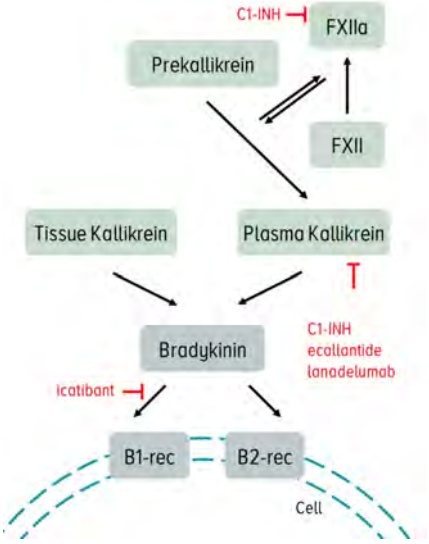
## Self-administered IV is good but SC is even better

In a patient survey (Wang 2015) looking at the satisfaction of self-administration medication in 59 HAE responders, about half reported not being comfortable with IV administration (see figure 7). Even though training for SA has become more common, in another study 79% of patients using peripheral veins reported dissatisfaction with IV administration due to vein access issues (29%), needing help from others (12%) or treatment difficulty during travel (8%) (Riedl 2017)

# Treatment paradigm is shifting from acute to prophylaxis

Historically treatment of HAE relied on the (prophylactic) use of oral attenuated androgens, which are inexpensive but associated with undesirable long-term side effects (hepatotoxicity, virilisation, psychiatric and behavioral effects, etc). In the past decade, a number of novel treatments were approved significantly improving disease management for both acute and prophylaxis setting. With near perfect effectiveness of drugs in IV form, most recent approvals were of SC drugs for the prophylaxis setting, aiming to improve patients' QoL through better and more convenient administration.

Figure 8 - HAE molecular pathway




Source: Adapted from Pharvaris' website 2018

## Lack of C1-INH triggers a cascade leading to an edema attack

The characteristic HAE swelling is formed due to a movement of liquid into the subcutaneous and/or submucosal tissues, primarily due to the lack of C1-INH and ultimately due to vasodilatory properties of bradykinin. The decreased functional activity of C1-INH ultimately results in the activation of the kinin-kallikrein system. In the absence of inhibition, factor XIIa activates prekallikrein, converting it into plasma kallikrein, which cleaves high-molecular-weight kininogen to release bradykinin. Bradykinin binds and activates the bradykinin B2 receptor, found on endothelial cells in the inner layer of the vascular space. In response, these cells will lose their attachment to each other and allow fluids and proteins to diffuse out into the local tissues causing the swelling (see figure 8).

## For acute therapy, treatments fall into three categories

- **Bradykinin receptor antagonist: Firazyr** (icatibant, Shire), mainstay acute therapy due to its quick onset and easy one-shot SC administration
- **Kallikrein inhibitor: Kalbitor** (ecallantide, Shire), requires hospital administration due to anaphylaxis side effects
- **C1-INH concentrates:**
  - **plasma-derived Berinert** (CSL) effective but inconvenient IV administration. In the EU plasma-derived, SC Cinryze (Shire) is also approved.
  - **recombinant Ruconest** (Pharming) effective but inconvenient IV administration.

## For prophylaxis, treatments fall into two categories

- **C1-INH concentrates:**
  - **plasma-derived Cinryze** (Shire) and **Haegarda** (CSL). Due to its higher concentration, Haegarda is more effective than Cinryze, ensuring almost >80% effectiveness.
  - **recombinant Ruconest.** Effectiveness in line with Cinryze but less-convenient IV administration. Approval pending.
- **Kallikrein inhibitor:** Takhzyro (lanadelumab, Shire). SC delivered antibody with once or twice a month administration, compared to twice a week for C1-INH concentrates. We expect this to become standard of care as well as accelerate patients moving from acute to prophylaxis setting.

**Table 1 - Overview of currently approved HAE treatments**

**Acute**

| Drug | Firazyr (Icatibant) | | Kalbitor (Ecallantide) | | Cinryze | | Berinert | | Ruconest | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Company** | Shire | | Shire | | Shire | | CSL | | Pharming | |
| **Mode of action** | Bradykinin B2 receptor antagonist | | Kallikrein antagonist | | Plasma-derived C1-INH | | Plasma-derived C1-INH | | Recombinant C1-INH | |
| **Adm. Route** | SC | | SC | | IV | | IV | | IV | |
| **Self-adm.** | Yes | | No (healthcare professional) | | Yes | | Yes | | Yes | |
| **Dose** | 30mg | | 30 mg (divided in 3 injections) | | 1,000 - 2500 IU | | 20 IU/kg | | 50 U/kg or 4,200 U if >84 kg | |
| **Approval** | **EU** | **US** | **EU** | **US** | **EU** | **US** | **EU** | **US** | **EU** | **US** |
| **Year** | 2008 | 2011 | - | 2009 | 2011 | - | 2008 | 2009 | 2010 | 2014 |
| **Clinical outcome for symptoms (vs. placebo)** | - 50% symptom reduction: ~2 vs. 20h<br>- Almost complete relief: 8 vs. 36h<br>- Rescue medication: 7% | | At 4h:<br>- Decrease of MSCS score : 0.8 vs. 0.4<br>- Improved TOS score: 53 vs. 8<br>* | | Unequivocal relief: 2 vs. 4h | | Onset of relief: 50 vs. 240 min | | Beginning of symptom relief: 90 vs.150 min | |
| **Safety concerns** | Erythema / swelling / pain at the injection site | | ~ 4% experience anaphylaxis | | Thromboembolic events | | Thromboembolic events | | Contraindicated for patients with rabbit allergy | |

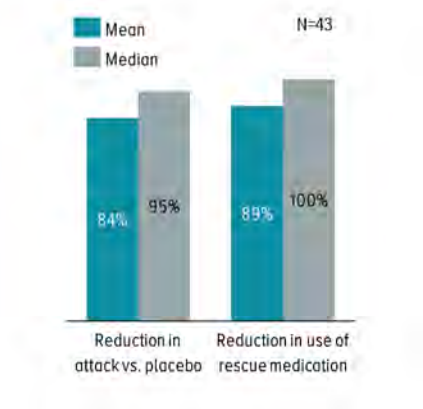
**Prophylaxis**

| Drug | Cinryze | | Haegarda | | Lanadelumab | | Ruconest | |
|---|---|---|---|---|---|---|---|---|
| **Company** | Shire | | CSL | | Shire | | Pharming | |
| **Mode of action** | Plasma-derived C1-INH | | Plasma-derived C1-INH | | Antibody targeting plasma kallikrein | | Recombinant C1-INH | |
| **Adm. Route** | IV | | SC | | SC | | IV | |
| **Self-administration** | Yes | | Yes | | Yes | | Yes | |
| **Dose** | 1,000 - 2500 IU | | 60 IU/kg | | 300mg | | 50IU/kg | |
| **Frequency** | Every 3 or 4 days | | 2X per week | | Every 2 weeks | | 2X per week | |
| **Approval** | **EU** | **US** | **EU** | **US** | **EU** | **US** | **EU** | **US** |
| **Year** | 2011 | 2008 | - | 2017 | - | 2018 | - | **2018 |
| **Clinical outcome for symptoms (vs. placebo)** | -No of attacks: 6.1 vs. 12.7<br>- Rescue medication: 5x in 12 weeks | | - Mean reduction of attacks : ~84% (ITT)<br>- Decrease in need for rescue medication: ~89% (ITT) | | - Attack rate reduction (ITT): 87% (2w) and 73% (4w)<br>- Steady state attack reduction (ITT): 91% | | - Mean attack reduction: 72% (PP), 63% (ITT)<br>- Clinical response: 96% (PP), 74% (ITT) | |
| **Safety concerns** | Thromboembolic events | | Thromboembolic events | | Pain at the injection site | | Contraindicated for patients with rabbit allergy | |

*MSCS: Mean Symptom Complex Severity score, TOS: Treatment Outcome Score - Developed by Dyax

**PDUFA date in September 2018

**Figure 9 - Haegarda: attacks and rescue medication reduction**




Source: Longhurst 2017

## Firazyr is the mainstay acute treatment

Firazyr (icatibant, Shire) is sold as a pre-filled syringe to be administered SC, upon patient's own recognition of an acute attack. Clinical trials performed prior to approval showed that a 50% decrease in symptoms was achieved ~2h after injection, vs ~20h for placebo, with a median time to almost complete relief of ~8h vs. 36h for placebo. According to the US label, 40% of patients on the placebo arm used rescue medication, versus 7% of patients that received Firazyr. Nevertheless, post-marketing experience indicates that a larger number of patients on Firazyr requires further intervention. No antibody formation has been reported, and patients often experience a temporary local erythema and swelling at the injection site, related to the locally high concentration. With a relatively quick and efficacious action as well as the most convenient administration mode among acute treatments, Firazyr is the mainstay therapy for the majority of patients treated acutely.

## Kalbitor's usage is limited due to possible anaphylaxis side effect

Kalbitor's (ecallantide, Shire) approval was based on the measurement of clinical outcome by specially developed scales: Treatment Outcome Score (TOS) for the response, and Mean Symptom Complex Severity (MSCS), for attack severity. Clinical data demonstrated a decrease in MSCS of -0.8 vs. -0.4 in placebo (reflecting an improvement in symptom severity), and a greater TOS of 53 vs. 8 for placebo (reflecting an improvement in symptoms). Attack relapse was observed in 2.5 – 10.1% of patients, with 9.6 – 11% requiring a second dose of treatment. Kalbitor is administered subcutaneously via three injections, however, patients must receive treatment in a hospital setting, due to its association with antibody induction and anaphylaxis reactions reported in ~3.5% of patients (for which it has a black-box warning, and was denied EU approval).

## Among plasma-derived C1-INHs, SC Haegarda beats IV Cinryze

Even though plasma-derived C1-INH has been used off-label for more than 30 years, the first approval came with Cinryze in 2008 (in the US) for prophylaxis, and with Berinert in 2009 for the acute treatment of HAE. Cinryze had a monopolistic position until CSL launched Haegarda in 2017, the first SC prophylaxis treatment showing a best-in-class reduction of attacks and incidence of breakthrough attacks.

- **Cinryze was the first plasma-derived C1-INH approved for prophylaxis.** A routine prophylaxis trial was conducted to assess the safety and efficacy of a twice-weekly regimen, with an IV dosing of 1000 IU. Over 12 weeks of treatment, the average number of attacks experienced in patients treated was 50% lower with Cinryze vs placebo (6.1 vs 12.7). The mean number of rescue treatment required was 4.7 for patients on Cinryze vs 15.4 for placebo. Based on post-approval studies showing that not all patients responded adequately to the recommended dose, Cinryze's label allows for an escalation up to 2500 IU when necessary, with ~50% of patients adopting a higher dose. In addition, the label includes a warning for thromboembolic events, based on five cases involving subjects with underlying risk factors (Henri Li 2018).

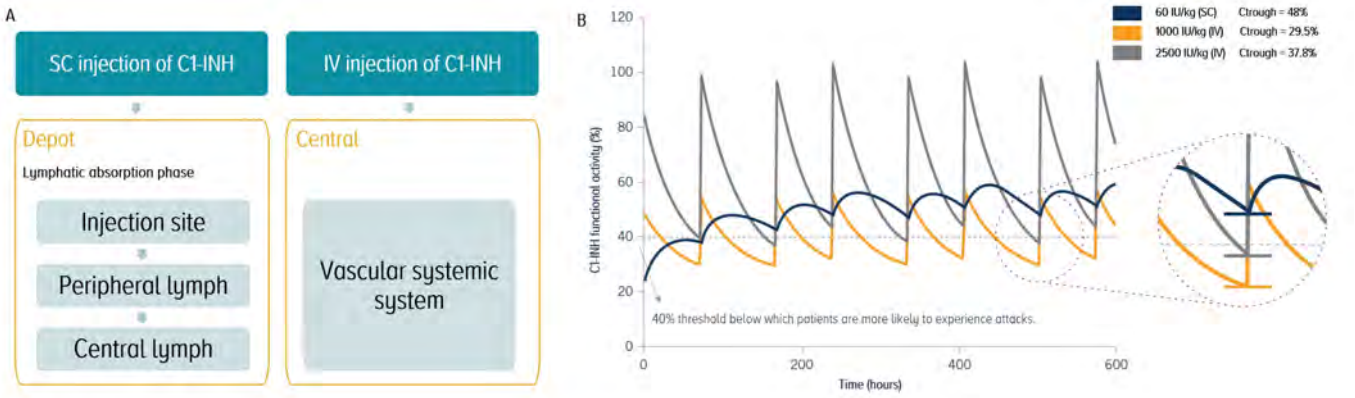
- **Haegarda SC administration offers 84% reduction in attacks.** The COMPACT phase III was a multicenter, randomized, double-blind, placebo-controlled, dose-ranging trial, that included 90 HAE patients maintained on treatment for 8 weeks. The patients included in the trial presented at least two attacks during any consecutive 4-week period or at least one attack during the first 2 weeks of the trial run-in period. An intention to treat (ITT, n=43 treated / n=44 placebo) data analysis showed that patients on the 60IU dose, self-administering the treatment twice a week, experienced a mean ~84% reduction in attacks (median 95%) from placebo, and the need for a rescue medication to

treat breakthrough attacks was reduced by 89% (median of 100%) from placebo (Longhurst 2017).

- **SC administration potentially leads to fewer breakthrough attacks.** Since the introduction of Cinryze in the market, it has been observed that repeated administration does not necessarily lead to a constant level of relevant activity, as patients continue to experience breakthrough attacks. When a product is administered IV, there is an almost instantaneously increase in the circulation level of C1-INH, and, as the protein is consumed, the concentration will eventually fall back to essentially the same level prior to the injection. Previous studies have reported that when C1-INH concentration and functional activity falls below a threshold, the risk of an attack increases (Henri Li 2018). On the other hand, when a C1-INH is administered subcutaneously, the protein is not readily available on the systemic circulation and its levels don't rise immediately to a peak, going, instead, through a lymphatic absorption phase that allows for a slower and steadier availability in the blood (see figure 9A). In a study of by Zuraw (2017), data from patients who received the dosages similar to the recommended ones for Haegarda and Cinryze revealed that SC administration would yield a C1-INH trough plasma concentration of ~48%, well above the 40% threshold to avoid breakthrough attacks, versus ~30% for IV administration (see figure 9B).

- **Cinryze SC phase III showed effectiveness in line with Haegarda**. In Q3'17, Shire announced top-line results from a phase III study with SC Cinryze for prophylaxis, showing that, versus placebo, an administration every 3-4 days yielded an attack rate reduction of 79% from day 0, and 85% from day 14, when the compound reaches a steady state (Shire annual report 2017).

**Figure 10 - A) SC and IV adminsitration of C1-INH. B) Simulated steady-state median C1-INH functional activity**




Source: Zuraw 2017

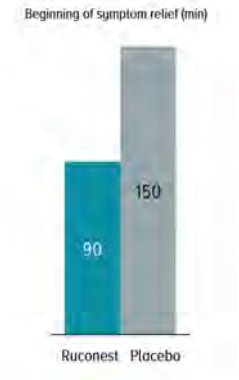
- **Thrombosis is the biggest safety concern for plasma-derived treatments.** Related to its source, all plasma-derived C1-INH products have, the same safety concerns of virus transmission, antibody induction, and thrombosis. Nevertheless, the risk of virus transmission is rather theoretical (Farkas 2017) and modern products have never been reported for transmitting infections. Nevertheless, some guidelines still recommend hepatitis B vaccination and annual hepatitis B/C screening and serum save (Longhurst 2018). Although concerns were raised on whether patients would have an antibody response against the introduction of foreigner proteins during treatment, neutralizing antibodies have not been reported. Furthermore, potentially mediated through increased levels of C1-INH and its interactions fibrinolytic proteases, venous

and arterial thrombosis are the biggest risks associated with these products, especially in patients using in-dwelling ports.

## Ruconest is the only approved recombinant C1-INH in acute HAE attacks

Ruconest (IV) is the only recombinant version of the C1-INH protein approved for the treatment of HAE acute attacks. The recombinant protein produced in the milk of rabbits is almost identical, has the same amino acid sequence and functional properties as the human endogenous protein commonly isolated from plasma. The only difference observed is an altered glycosylation pattern that leads to a half-life of ~2.5h, in contrast with ~22-56h for plasma-derived products. In our view Ruconest is just at par on efficacy with other acute treatments but with a less convenient IV administration.

**Figure 11 - Ruconest in HAE acute attacks: time to onset of relief and attack reduction per anatomical location**




Source: Ruconest FDA approval package

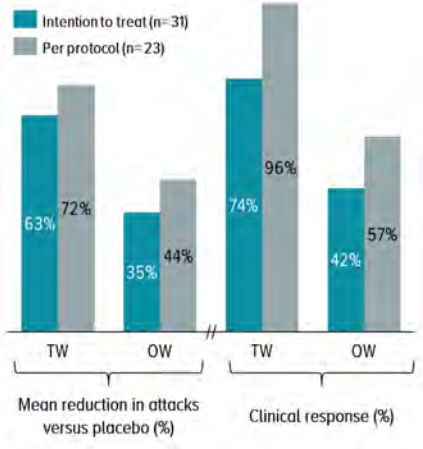
- **Acute attack relief initiates in ~90min with a low reoccurrence.** The FDA approval of Ruconest was based on placebo-controlled trials and on open-label extension studies. Ruconest was tested in a total of 205 patients with 650 acute attacks, at the 50 and 100 IU/kg dosage strengths. Clinical data demonstrated that patients treated with the 50 IU/kg dose experienced the beginning of symptom relief at ~90 min, versus ~150 min for placebo (Ruconest's US label) (see figure 10). Due to Ruconest's short plasma half-life, some concern was raised on the possibility of HAE symptoms recurring a few hours past treatment. In a post hoc analysis of two clinical trials for acute treatment, even at 72 hours after acute treatment, only 7.1% of patients reported symptom recurrence (Bernstein 2017).

- **Ruconest is only contraindicated for patients with rabbit allergy.** In terms of safety, recombinant products do not pose any virus transmission and thrombosis risks. Before approval, regulators voiced concerns about Ruconest eliciting antibodies against the recombinant protein and the small amount of rabbit-associated impurities, but post-treatment follow-up data did not identify any clinical immunological side effects and no antibody responses. Naturally, Ruconest is only contraindicated for patients with rabbit allergy.

## In prophylaxis, twice-a-week Ruconest reduces attacks by 63%

In January, Pharming filed a sBLA to expand Ruconest's label to HAE prophylaxis treatment, based on data from a phase II trial that recruited 32 patients with a mean attack rate of 6 attacks per month. Patients were randomly assigned to receive a treatment sequence consisting of three 4 weeks treatment periods, receiving Ruconest 50IU/kg twice weekly (TW), once weekly (OW) and placebo. Efficacy was measured in two ways: i) based on the mean reduction in attacks and, ii) based on the clinical response defined as >50% reduction in the number of attacks. Intention to treat (ITT, n=31) and per protocol (PP, n=23) analysis demonstrated that patients on the OW arm experienced a mean attack reduction of 35% from placebo (44% PP) and had a clinical response of 42% (57% PP), while patients on the TW arm experienced a mean attack reduction of 63% from placebo (72% PP) and had a clinical response of 74% (96% PP) (see figure 11).

**Figure 12 - Ruconest in prophylaxis: percentage reduction in attacks and clinical response**




Source: Riedl 2017

- **The concentration of C1-INH in blood does not seem to influence the effect of recombinant proteins.** The outcomes of the prophylaxis trial confirmed that a sustained response was obtained between doses administered a few days apart, despite Ruconest's plasma half-life of only ~2.5h. Even though there is no concrete scientific evidence, the investigator suggested that the effectiveness of C1-INH do not solely rely on plasma concentrations, pointing to the possibility of other factors also playing a role. One explanation is based on the fact that

recombinant C1-INH has a greater association with other protein (mannose-binding lectin), which translates into C1-INH binding to endothelial cells, being therefore undetectable in plasma, but still available to perform its inhibitory activity (Riedl 2017).

## Will Ruconest be approved for prophylaxis?

Given Ruconest's good safety profile and the phase II results, we believe Ruconest is likely to be approved for the prophylaxis treatment of HAE with the PDUFA data set for 21 September. Nevertheless, we highlight a few confounding factors which could be raised by the FDA but most likely more relevant for reimbursement purposes.

- **The dose regimen is based on observational data**. Ruconest PK and PD data do not support the dosing interval chosen for the trial, which was based on observational data rather than biochemical characteristics. So far, trials have not yet been able to explain the sustainable response observed even when the product is no longer detected in the circulation, contrasting the predictable behavior observed in plasma-derived C1-INH.

- **Small sample size and high drop-off rate.** A small sample of 32 patients was recruited, of which only 23 (PP) concluded the trial. (28% drop-off rate) Though drop-offs were deemed largely unrelated to treatment, the small sample does result in a less robust outcome. In contrast, in Haegarda's registrational trial with a similar dosing regimen, 90 patients were enrolled with 79 continuing until the trial completion (12% drop-off rate).

- **Sample size with high HAE attacks at baseline might not be representative.** Patients included in the trial presented a baseline attack rate of ~6 attacks per month, largely in contrast with the overall 2-4 attacks commonly seen in other trials. t. We note that the FDA does not require such a high number of attacks as an inclusion criterion and that HAE patients are not divided into more or less severe groups. The number of attacks at the baseline reflects the status of the population at a particular moment in time, being, by no means, an indication of past nor future number attacks. In addition, the number of attacks alone does not determine the choice for a prophylaxis regimen, and most private payers require that a patient experience a minimum of 1-2 attacks per month for prophylaxis prescription (Aetna and Cigna policies).

## Ruconest SC, ID and IM to be available in 2021

Pharming is working on the development of Ruconest lite and Ruconest liquid. Ruconest lite has a new lyophilized, concentrated formulation, of which a vial of 2100U can be dissolved in 3ml (instead of the current 14 ml) and decrease the reconstitution time from ~5 minutes to ~3 min. Ruconest liquid is a ready-to-use vial, conveniently containing the final 3ml dose, eliminating the reconstitution time a patient needs to prepare its treatment.

According to the company, the formulations will be explored further, and, due to its low volume, could be used subcutaneously. In addition, Pharming aims to explore the potential use as intramuscular (IM) injections and with "painless" intradermal microneedle delivery devices (dermal patch). IM administration route is normally used to promote rapid drug absorption, potentially being an attractive option for patients experiencing acute attacks and in need of an alternative over IV and SC options. Similarly, the ID devices could offer patients on prophylactic treatment an attractive option to alleviate the burden of constant SC and IV injections. The expected to run clinical trials with both formulations during 2019-2020, with a commercial version to be available in 2021.

## Lanadelumab is Shire's great prophylactic leap forward

In August 2018, Shire received FDA's approval for Takhzyro (lanadelumab), an antibody targeting plasma kallikrein, for the prophylaxis of HAE. Lanadelumab's great commercial advantage is based on a low volume SC injection to be administered once every two weeks, or once every to four weeks if the patient is well-controlled for more than 6 months. In contrast, to twice weekly with Cinryze, Haegarda, and Ruconest. The approval was based on data from four clinical trials, including a pivotal phase III that showed a monthly attack rate reduction vs placebo of 73-87% after 6 months of treatment.

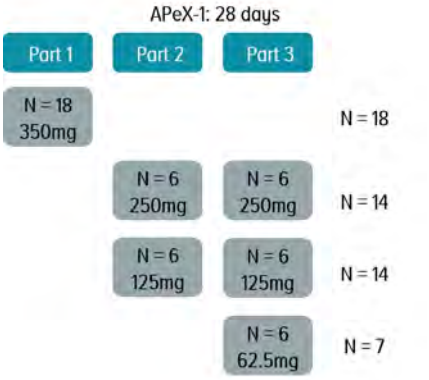
- **The phase III trial recruited a broad and representative sample.** The phase III HELP study (NCT02586805) recruited 125 HAE patients over 12 years of age, randomizing them into 3 treatment arms (150mg every 4w, 300mg every 4w, and 300mg every 2w) and one placebo arm (2:2:2:3), for a treatment period of 26 weeks. To be eligible for the trial patients had to present a baseline rate of at least one investigator-confirmed HAE attack per month. At baseline, the overall mean attacks/month was 3.7, with 52% having more than 3 attacks per month, which is representative of the average HAE patient (1-3 attacks per month) (Banerji 2017).

- **At the highest dose, lanadelumab was on par with Haegarda.** An ITT analysis showed that the monthly attack rate reduction vs placebo was 87% ($p<0.001$) in patients on 300mg every 2w arm, 73% ($p<0.001$) in the 300mg every 4w, and 76% ($p<0.001$) with 150mg every 4 weeks. In a post-hoc analysis by baseline attack frequency, significant efficacy was achieved regardless of baseline attack rate and dosing regimen (Riedl 2018). The number of attacks requiring acute treatment from day 0 to 182 was measured as 0.31, 0.42, and 0.21 monthly attack rate, from the smallest to the highest dose, against 1.64 in the placebo arm. In an exploratory endpoint, Shire also saw that during the steady-state stage of the trial (day 70-182) the attack reduction was 91%, with 80% of patients achieving an attack-free state. While this result will have to be confirmed in a follow-up study, it is indicative of long-term consistent protective effective that lanadelumab seems to have. Regarding safety, lanadelumab had a favorable profile with the most commonly reported adverse event being mild to moderate site injection pain (29% placebo vs 43% across lanadelumab arms), and 96% of patients chose to roll-over into the ongoing long-term extensions safety study (NCT02741596).

# Orals are the future of HAE treatments

With peak efficacy being achieved with Haegarda and lanadelumab, the HAE pipeline candidates are focused on increasing the quality of life for patients through oral administration. BioCryst's (BCRX US) BCX7353 is currently in phase III as once daily prophylactic oral capsule treatment for HAE with top-line results expected in Q2'19, which could result in a market launch in H1'20. With a liquid formulation of BCX7353, BioCryst recently reported initial supportive phase II results in acute. Furthermore, KalVista (KALV US) announced that it will be initiating a phase II acute trial with its own oral kallikrein inhibitor, KVD900 and raised $83m over the summer to fund KVD900 development beyond phase III and accelerate the development of two other oral HAE candidates. Earlier in the pipeline, Pharvaris (private) expected to start a phase I later in 2018 with an oral bradykinin B2 receptor agonist (essentially oral Firazyr), while Attune (private) has already initiated a phase I trial with its oral candidate in Q1'18. Whether one or all these compounds reach the market remains an open question, however, we believe the trend is clearly towards oral treatments.

**Figure 13 - APeX-1 phase II trial with BCX7353 in HAE prophylaxis**




Source: BioCryst's presentation, 2017

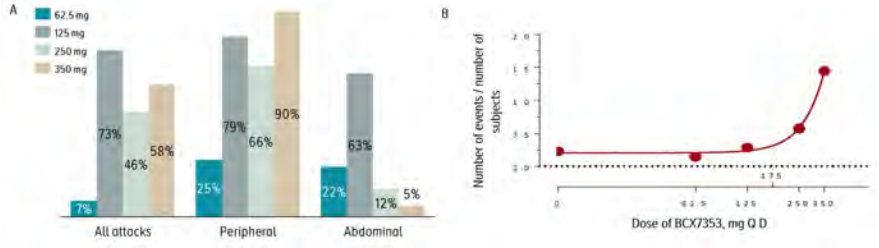
## BioCryst 's prophylaxis phase II trial left safety concerns hanging

APeX-1 (NCT02870972) was a phase II, double-blind, placebo-controlled, dose ranging study, evaluating the safety, tolerability, PK, PD, and efficacy of once-daily BCX7353 oral capsule for HAE prophylaxis. The study evaluated the 62.5, 125, 250 and 350 mg doses and enrolled 75 patients with at least two attacks per month, which were instructed to record their symptoms in a diary during the treatment period. The primary endpoint was the number of HAE attacks after 28 days (see figure 12). Overall, 72 patients completed the trial with a mean baseline of 0.95 attacks/week.

- **Efficacy was not dose-dependent.** Patients on the 125 mg treatment reported 73% attack reduction (PP and 74% ITT, p<0.001), while patients on the 250 mg and 350 mg doses reported 46% (PP, p=0.006 and 45% ITT, p=0.01) and 58% (PP, p<0.01 and 46% ITT, p=0.006) reduction compared to placebo, respectively. In addition, ~46% of patients in the 125 mg dose group were attack free after reaching steady-state (BioCryst; Pursun 2018). While efficacy with 125 mg is just a tad below most effective prophylaxis treatments, lack of dose-dependent response cast doubts over the drug's potential.

- **GI side effects at higher doses interfered with HAE symptom recording.** When the attacks were broken down into peripheral and abdominal, the rates among doses was similar for peripheral attacks while for abdominal attacks there was a clear imbalance between the 125 mg and the higher doses (see figure 13A). Further analysis revealed that the efficacy of the higher doses was probably masked by the GI side effects mistakenly recorded by patients as early symptoms of abdominal HAE attack, leading to a lower efficacy compared to the 125 mg dose. In fact, the rate of GI adverse events was higher in the 250 mg and 350 mg groups compared to placebo, 62.5 and 125mg groups (see figure 13C). Though this explanation is not conclusive, we believe it supports pursuing a phase III trial

**Figure 14 - A) HAE attack reduction from placebo B) Attack-free subjects C) GI events rate by dose**

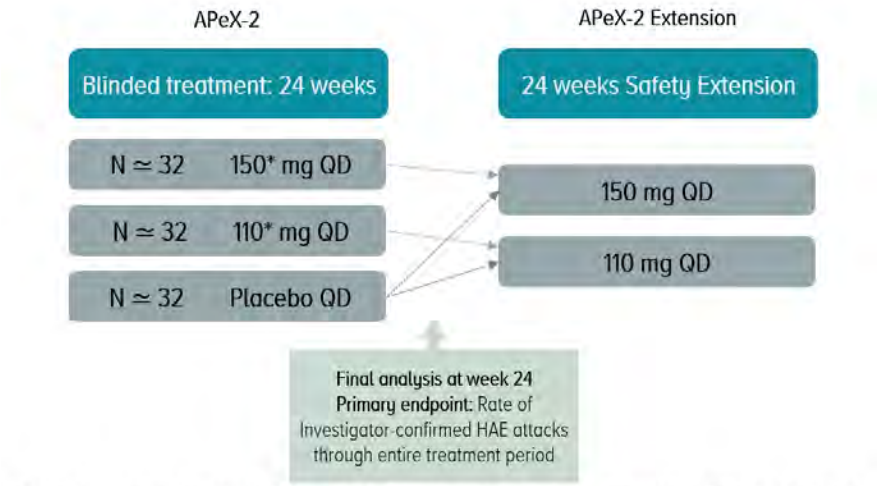



Source: BioCryst's presentation, 2017

## BioCryst's prophylaxis phase III top-line results in Q2'19

In Q1'18, BioCryst initiated a phase III, randomized, placebo-controlled trial (APeX-2, NCT03485911) testing 125 mg and 175 mg doses of BCX7353 oral capsule once-daily. The trial is expected to enroll approximately 100 patients with at least one attack per month, and the primary efficacy endpoint is the rate of attacks over 24 weeks of administration. After the initial period, patients will roll over into a 24 weeks extension portion, and to a long-term safety trial, APeX-S (NCT03472040). Based on the outcomes from the phase II study, the two doses selected were 125 mg and 175 mg, which due to a change in terminology to conform to current convention, are now described as 110 mg and 150 mg (see figure 14). Top-line results are expected in late Q2'19, which could see it approved late 2019 and launched in early 2020.

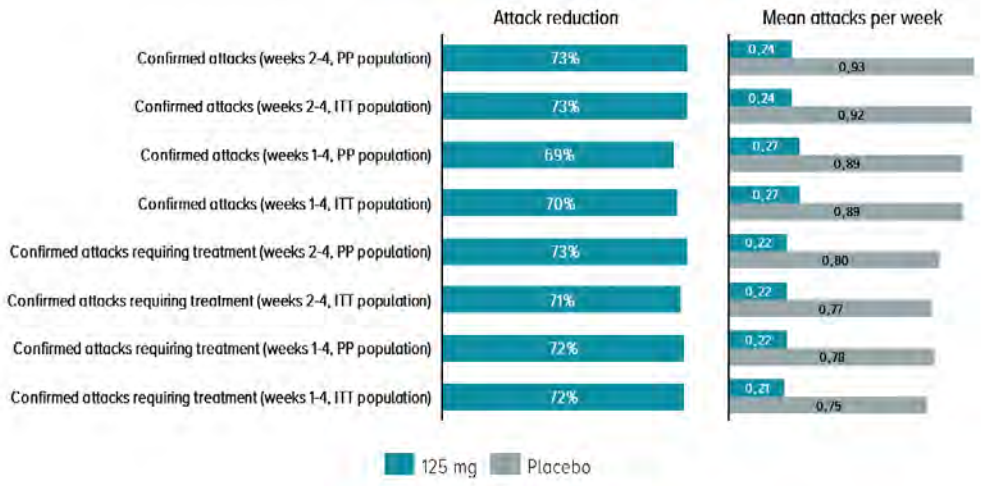
**Figure 15 - APeX-2: phase III trial with BCX7353 in HAE phophylaxis**




Source: BioCryst's presentation, 2018

- **125 mg dose was chosen based on phase II data.** The company is confident that the results observed in the 125 mg (110 mg) arm during phase II can be successfully reproduced in phase III. The ~73% attacks reduction was observed consistently: response was not only maintained from the interim analysis to the top-line results, but it was also maintained independently of the analysis performed (per-protocol, intent-to-treat, two- to four-week steady-state, and one- to four-week entire study) (see figure 15).

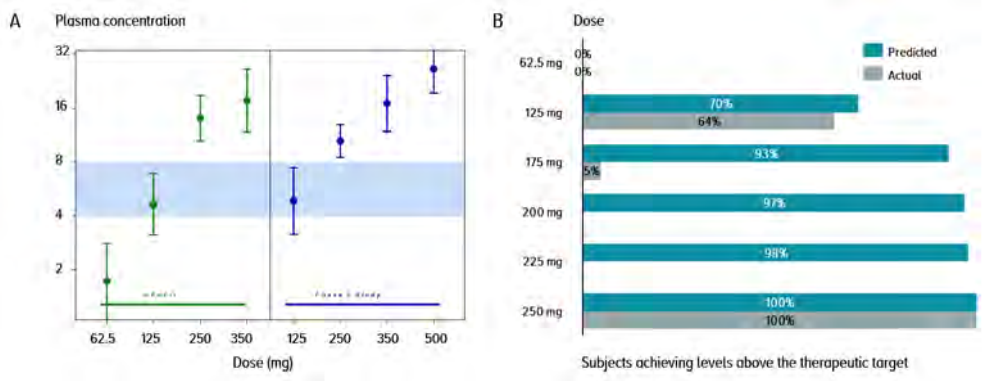
**Figure 16 - Consistent reductions in attack rate: % attack reduction vs placebo and mean attacks per week**




Source: BioCryst's presentation, 2017

- **175 mg dose was chosen based on PK simulations.** The second dose (175 mg /150 mg) was chosen based on phase II observations suggesting an intermediate dose between 125 and 250 mg (see figure 16A), and also based on PK simulations. Estimates showed that a relatively small increase above the 125mg dose would lead to a significant increase in the proportion of subjects achieving concentration levels above the therapeutic target. For instance, the same model suggested that a 125 mg dose would lead to ~70% of patients maintaining an appropriate drug concentration, and indeed, phase II data demonstrated that ~64% of patients maintained the concentration. Based on the same prediction, a 175 mg dose should maintain trough drug levels in ~90% of patients, supporting the dose choice (see figure 16B).

**Figure 17 - A) BCX7353 plasma concentrations at 24 hours post-dose B) PK simulations to predict the maintenance of trough drug levels > 4x EC50**




Source: BioCryst's presentation, 2017

- **We believe the phase III trial has a high chance of success.** Despite the initial setback with the observation of increased GI side-effects in the highest dose in phase II, we believe that BioCryst has been able to provide a reasonable and solid explanation, with a clear analysis of the phase II trial outcomes. Even though we do not discard the possibility of AEs having a significant influence in the pivotal trial outcomes, we believe that the choice of doses for the pivotal study will be able to strike the right efficacy/safety balance.