deficiencies were found more often in PE vs healthy pregnancies (Lokki 2014), and in the final activation of the pathway, elevated levels of C5a and C5b-9 have been observed in severe PE (Burwick 2013). In addition, there is some evidence that circulating levels of C1-INH are lower in healthy pregnant women than in non-pregnant women and preeclamptic patients, which could further denote decompensation of regulatory mechanisms and activation of the cascade, leading to pathophysiological consequences (Derzsy 2010).

Limited data support C1-INHs as safe during pregnancy

Plasma-derived C1-INHs have been reported as safe and well tolerated during pregnancy (Baker 2013; Fox 2017). Ruconest has a pregnancy category B label, which means that studies have only been performed in animal models, at higher doses of C1-INH, and could not exclude an effect on embryo-fetal development. Recently, a study evaluated the use of Ruconest in eight pregnant women with HAE and reported that all gave birth at full term to healthy neonates, concluding that the treatment was generally safe and well tolerated (Moldovan 2018).

Ruconest phase II trial to initiate in Q4'18

Pharming is expecting to initiate an open-label, proof-of-concept phase II study with Ruconest, estimating to recruit 20-30 PE symptomatic women. The trial will primarily look to establish safety and tolerability and will most likely also include as a secondary measure, the incidence of premature pregnancies, a registrational endpoint. Should results be supportive, we would expect Ruconest to required an additional phase II trial and two large phase III studies to support registration. Thus, the approval could come at best in 2024.

Most ongoing PE clinical trials are investigator-driven

Even though PE has an attractive potential market, few companies have expressed the intention to develop treatments for this indication. Anylan, Glenveigh, and A1M have previously announced preclinical results, but up to this moment, no further detail has been given. The clinical trials currently ongoing are generally focused on establishing data for drugs commonly used to manage symptoms, and on repositioning drugs from other indications (see table 7).

Table 7 - Main preeclampsia clinical trials

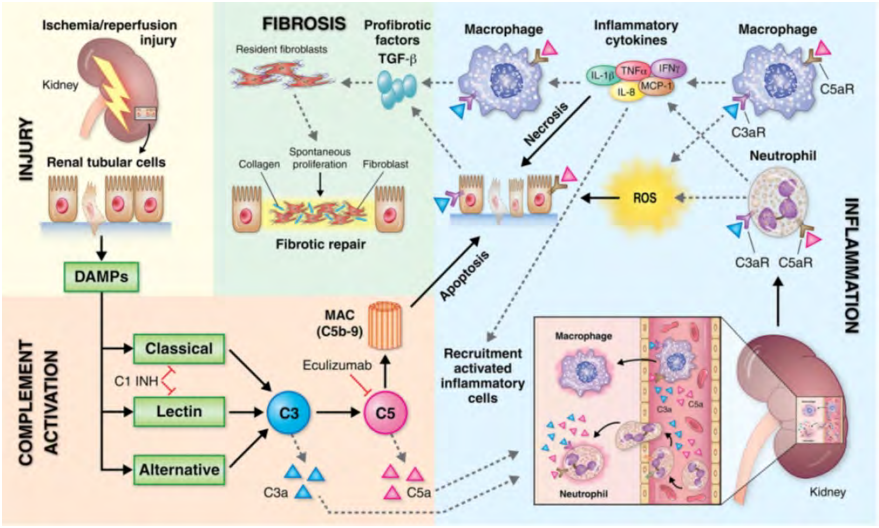
Phase	Company	Candidate / Trial	Description
III	University Hospital Strasbourg	Treatment of hypertension associated with severe PE, a trial of Urapidil versus Nicardipine (Uranic)	Treatment of hypertension associated with PE
II/III	Assiut University	ESOPE: Esomeprazole in treatment of early onset preeclampsia	Esomeprazole counters three key steps in pre-eclampsia pathogenesis: up-regulating heme oxygenase-1, decreasing the release of antiangiogenic factors, and quenching endothelial dysfunction.
II/III	Assiut University	Use of Sildenafil Citrate in Management of Mild Pre-eclampsia	Sildenafil citrate has been used for increasing utero-placental perfusion in cases with intrauterine growth restriction
II/III	Nantes University Hospital	CITRUPE: efficacy of citrulline supplementation on the delay of delivery for PE	Citrulline is a natural amino acid
II	University of North Carolina	Nicotinamide in early onset preeclampsia	Effect on maternal blood pressure
II	Velo Bio	Efficacy and safety of DigiFab in antepartum subjects with severe preeclampsia	Digoxin immune fab: anti-digoxin antibody Fab for endogenous digitalis-like factors (EDLFs), which are elevated in women with preeclampsia, to reduced blood pressure and preserve renal function
I	University of Texas Medical Branch	Pravastatin for prevention of preeclampsia	Statins: act on reversing the angiogenic imbalance by upregulating vascular endothelial growth factor (VEGF) and placental growth factor (PlGF), and reducing the antiangiogenic factors such as soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin (sEng). Statins also up regulate endothelial nitric oxide synthase

Source: clinicaltrials.gov

Exploring the complement role in tissue injury

Ischemia-reperfusion injury (IRI) is a complication arising from tissue damage caused by a lack of oxygen during an interruption of blood supply (ischemia), and, paradoxically, the damage caused by the return of blood flow (reperfusion). IRI can occur, for example, after a traumatic injury, in organs transplantation, as a result of stroke, and as a result of myocardial infarction. Complement activation and neutrophil stimulation are two major components in events leading to tissue injury. Figure 32 illustrates how the IRI activates the complement system and immune cells recruitment.

Figure 32 - Role of complement in renal ischemia-reperfusion injury, inflammation, and progression to kidney fibrosis



Source: Danobeitia et al., 2014

Initiated by the release of damage-associated molecular patterns (DAMPs) from the injured tissue, a membrane attack complex (MAC) is formed and results in direct injury, while the cleavage of C3 and C5 promotes inflammatory cell recruitment and release of pro-inflammatory signals and reactive oxygen species, intensifying the immune response. Pro-fibrogenic factors such as TGF-β and PDGF are also secreted, activating local fibroblasts inducing collagen deposition and tissue repair. C1-INH has been tested as a potential therapy for IRI injuries either in models or in specific diseases, as IRI of the myocardium, brain damage, and organ transplantation. Most trials were small and exploratory and did not reach a statistically significant conclusion. Driven by investigator-initiated trials, Ruconest use in IRI indications is being explored with ongoing studies in delayed graft function, hypovolemic shock, and contrast-induced nephropathy.

Table 8 - The Mehran risk score and associated risk of progression to CIN

Risk factor	Score
Hypotension	5
Intra-aortic balloon pump	5
Congestive cardiac failure	5
Age >75 years	4
Anemia	3
Diabetes mellitus	3
Contrast media volume	1 / 100cc3
Serum creatinine	4
Estimated glomerular filtration rate <60ml/min/1.73cm2	2

Source: Shabbir, 2015

Is contrast-induced nephropathy even an indication?

Nephropathy induced by contrast is a generally reversible form of acute kidney injury (AKI) that arises as a complication from procedures that require the administration of iodinated contrast media (CM). CIN (also called contrast-induced acute kidney injury, CI-AKI) is the consequence of renal ischemia, the toxic effects of CM, and subsequent inflammation in the reperfusion period. These complications are usually prevented by hydration strategies and are associated with consequences that include prolonged hospitalization, dialysis, and an increased risk of death. It was believed that CIN is responsible for a third of hospital-acquired AKI (Bushinsky 1983; Hafeez 2002), affecting 1-2% of the general population and up to 50% of high-risk subgroups (see table 8) following coronary angiography (CA) or percutaneous

coronary intervention (PCI) (Rear 2016). With more than 75m procedures with intravascular iodinated CM performed worldwide every year, of which 6-12m in patients considered at high risk (Nijssen 2017), the literature on the indication has recently proliferated coming at confounding conclusions.

CIN may not even be an indication for the general population

A few studies have raised the concern on whether CIN is a valid clinical risk and suggests that modern radiographic contrast does not increase the risk for nephropathy. Recently, a retrospective cohort analysis was performed in 17,934 visits of patients who underwent contrast-enhanced, unenhanced, or no CT between 2009 and 2014 showed that contrast administration was not associated with increased incidence of acute kidney injury, increased incidence of chronic kidney disease, dialysis, or renal transplant at 6 months (Hinson 2017). In addition, a meta-analysis of 28 studies involving 107,335 participants demonstrated that, compared with non-contrast CT, contrast-enhanced CT was not significantly associated with either acute kidney injury, need for renal replacement therapy, nor all-cause mortality (Aycock 2018).

In the high-risk population, CIN rate appears to be about 3%

In a study of prophylactic hydration in 330 patients undergoing iodinated CM administration at high risk of developing CIN, the investigators found a rate of CIN of 2.7% in the hydration arm vs. 2.6% without hydration (Nijssen 2017). The high-risk patients were defined according to the guidelines with an estimated glomerular filtration rate (eGFR) higher than 29 mL per min/1.73 m2 (30-59 in the trial). CIN was defined as an increase in serum creatinine (SCr) by more than 25% or 44 µmol/L within 2-6 days of contrast exposure, which is slightly longer than the usually accepted timeframe of 48-72 hours (KDIGO 2012). The authors note that although SCr rises within 48 hours, it peaks on average between 4-5 days post-contrasts.

The definition of CIN may be lacking sensitivity

Although most commonly used the 25% SCr increase definition of CIN has been criticized for lacking sensitivity confusing in the majority of cases CIN for just incidental cases of AKI. However, this definition has the advantage of being widely used as the endpoint in most CIN studies and it correlates well with adverse clinical endpoints (Rear 2016).

Is NGAL a better measure of CIN?

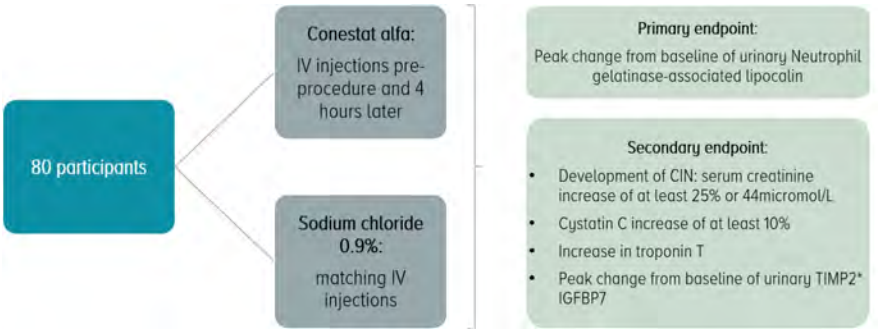
Neutrophil gelatinase-associated lipocalin (NGAL) is a protein belonging to the lipocalin superfamily initially found in activated neutrophils and has a role as an innate antibacterial factor. NGAL has been proven to have a high sensitivity in the early diagnosis of AKI, detecting AKI much faster than measuring an increase in SCr. However, in a study of patients with chronic kidney disease (CKD) exposed to CM, urinary NGAL (uNGAL) failed to predict CIN though previous studies showed some success (Ribitsch 2017).

Investigator-initiated Ruconest phase II trial in CIN reads out in Q3'18

The investigator-initiated phase II PROTECT study (NCT02869347) commenced in 2017 by the University Hospital in Basel, as a randomized, placebo-controlled, double-blind study, aiming to assess the effect of prophylactic administration of Ruconest in high-risk subjects undergoing elective coronary angiography. The same dose used in HAE treatment (50 U/kg) is given intravenously immediately before and 4 hours after the clinical intervention and patients are followed for cardiovascular and renal events over 12 weeks. The primary endpoint will measure the peak change from baseline of uNGAL within 48 hours after the contrast exposure. A key secondary endpoint is measuring the rate of CIN defined as serum creatinine (SCr) increase of at least 25% or 44micromol/L within 48 hours after contrast exposure.

As an additional endpoint, the investigator is also evaluating the increase in troponin T, a marker of cardiac damage. The trial is expected to read out in Q3'18.

Figure 33 - PROTECT study: Ruconest in the prevention of contrast-induced nephropathy in high-risk subjects



Source: clinicaltrials.gov

We believe the trial results will have limited commercial relevance for CIN

Given that the trial is investigator-sponsored we do not claim to have a view on the scientific relevance of the study, however, we believe that the trial results are not likely to provide Pharming with a proper direction regarding Ruconest in CIN as:

- Given an incidence of CIN as low as 2.6% in high-risk patients, we might not see a meaningful number of cases in the trial;
- Although inclusion criteria mandates at least one risk factor commonly associated with CIN it also sets an eGFR of <50 ml/min/1.73 m2, leaving the possibility of including patients who are not at high-risk of CIN. While this can be mitigated by a pre-specified subgroup, the trial size is might be insufficient for any meaningful conclusions;
- The primary endpoint measure of uNGAL lacks clear clinical validity and might not identify all CIN patients;
- The secondary endpoint to measure CIN, >25% increase in SCr within 48 hours, might miss cases that can develop up to 6 days after contrast exposure.

Troponin data could offer some options in cardiac protection

Coronary angiography is considered to be a safe tool for the evaluation of coronary artery disease and performed in approximately 12 million patients each year worldwide. Troponin is a specific protein released from heart cells when myocardial damage occurs. Depending on the reduction of troponin results in the CIN trial, Pharming could initiate further exploratory trials with Ruconest in cardiac protection. The scope and timing of such trial is not currently clear.

Ruconest in delayed graft function could have a limited survival benefit

Delayed graft function (DGF) is a form of IRI in the clinical transplantation setting, following kidney transplantation, and is defined as the need for dialysis during the first post-transplant week. DGF incidence depends on its definition, on the risk profiles of the donor and the recipient, and on the transplant center, being observed in around 15–30% of deceased donor transplantations. In 2014, 17,107 kidney transplants took place in the US. Of these, 11,570 came from deceased donors and 5,537 came from living donors.

Investigator-driven phase II trial to start in Q3'18

In previous experiments, C1-INH has been circulated into the organ before implant or added to the preserving solution that protects the organ during transport, which is thought to reduce complications due to the capacity of C1-INH to bind endothelial cells maintaining its functional capacity. A study conducted in 2013 at the University of Wisconsin in preclinical models showed that pre-treatment of harvested organs with Ruconest could reduce the incidence of DGF in transplant operations. According to Pharming, an investigator-initiated phase II study by the University of Wisconsin is due to start in Q3'18. According to clinicaltrials.gov a similar study (NCT01035593) started in 2010 and was withdrawn in 2011.

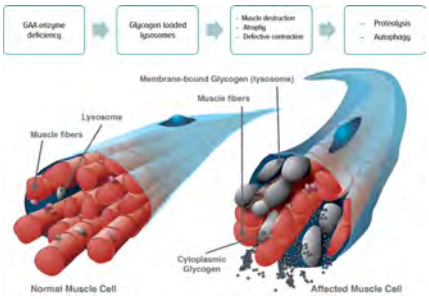
Berinert trial a good indication of Ruconest efficacy in DGF

An investigator initiated phase II trial with Berinert in preoperative and post kidney transplant to prevent DGF & IRI was initiated in 2014 and recently reported results. In a double-blinded, placebo-controlled trial (NCT02134314) in 70 patients, the investigators hypothesize that C1-INH treated patients would demonstrate an improved function of the kidney allograft compared to placebo. No statistical analysis was provided for the trial, but according to results posted on clinicaltrials.gov, in the Berinert arm, 15/34 patients developed DGF 7 days post-transplant vs 21/34 in the placebo group and the incidence of serious adverse events was also lower with Berinert, with 11 vs. 16 patients (up to 9 months after transplantation). However, patients survival at 90 days post transplantation was 100% for both arms. Although the trial was likely not powered for statistical significance, the results indicate a rather health economic benefit of C1-INH in DGF than a survival benefit.

Platform options in Pompe and Fabry

Pharming's transgenic rabbit platform allows for the production of other recombinant human proteins. In order to expand its capabilities, in 2014, the company acquired assets from the private French company Transgenic Rabbit Models SASU (TRM) for €0.5m. The transaction granted access to a transgenic rabbit founder technology and to five product leads (founder rabbits) for the production of -α-glucosidase for the treatment of Pompe's disease, α-galactosidase for the treatment of Fabry's disease, β-cerebrosidase for the treatment of Gaucher's disease, Factor VIII for the treatment of Haemophilia-A and Factor IX for the treatment of Haemophilia-B. The company focused the development on the preclinical candidates for Pompe and Fabry's diseases ERT, which are expected to enter phase I trials in H1'19 and 2020 respectively.

Figure 34 - Pathophysiology of late-onset Pompe disease



Source: Jasmi 2015

Pompe presents an interesting opportunity

Pompe disease, also known as acid maltase deficiency or glycogen storage disease type II, is a rare genetic recessive disorder that affects around 1 in 40,000 people and manifests typically as an impairment on the ability to function normally (Jasmi, 2015). The disorder is characterized by the accumulation of glycogen in the body's cells, especially in muscles, due to the insufficient activity of the enzyme acid alpha-glucosidase (GAA), responsible for breaking glycogen into glucose inside the lysosomes (see figure 34). Based on its recombinant technology in the rabbit platform, Pharming is developing a human recombinant GAA, which is currently undergoing upscaling of manufacturing for the clinical trials.

Genzyme stands alone in the market with Myozyme/Lumizyme

After a diagnosis, enzyme replacement therapy with GAA should be initiated in patients with symptoms or signs of the disease. Since 2006, Genzyme stands alone in the market with the commercialization of Myozyme for the treatment of infants and children, and since 2010 with Lumizyme for the treatment of patients with late-onset (non-infantile) disease, which became available for all ages after label extension in 2014. Both products are recombinant versions of the GAA enzyme produced in Chinese Hamster Ovary (CHO) cells, differing only by its manufacturing method. Patients receive Lumizyme/Myozyme via IV administration. After inoculation, the recombinant GAA enzymes will bind to mannose-6-phosphate receptors that are present on the muscle cell surface and, after entering the cell, will be transported to the lysosomes, where it degrades the glycogen. Despite the straightforward mechanism of action, both of Genzyme's products have been associated with severe immune responses drawbacks and can present a decline on efficacy over time.

Serious side effects are a major drawback for current treatments

Lumizyme and Myozyme carry a warning for anaphylaxis and hypersensitivity reactions: clinical trials in infantile and juvenile-onset patients registered that 51% of hypersensitivity reactions required intervention. In addition, special attention is strongly recommended when the treatment is administered in patients with respiratory illness or compromised cardiac/respiratory function, once these are at risk of symptoms exacerbation during infusions, possibly associated with the fluid overload that arises from IV administration. Immune-mediated cutaneous reactions have been reported within several weeks to 3 years after treatment initiation, with the majority of patients developing IgG antibodies, and some of those developing high and sustained titers that may lead to a reduced clinical efficacy (Lumizyme's prescription label). Even though these are the only available treatments to the moments, these factors have led Genzyme to achieve an estimated market penetration of 30-50%.

Genzyme acquired full rights for rabbit but pushed forward CHO instead

In 1998, Pharming and Genzyme initiated a partnership for the development of a recombinant therapy for Pompe's disease. Phase I/II trials with the transgenic rabbit recombinant GAA in a few infant patients suggested a positive safety/tolerability profile and a reduction in heart size and an improvement of heart and skeletal muscle functions (Van der Hout 2001, 2004). Following phase II/III trial initiation in 2001, Pharming's precarious financial situation led to Genzyme's acquisition of all assets related to the diagnosis and treatment of Pompe. In the agreement, Genzyme complied to fund the production of the transgenic rabbit enzyme only until the patients recruited for the phase II/III were switched to the CHO cells enzyme in development. In addition to the CHO recombinant products, Genzyme's chose to focus its Pompe development programs on the assets of the at the time recently acquired Novazyme, which was working on enhancing the targeting and uptake of Pompe's ERT for second-generation products.

A number of advanced gene therapies in the pipeline

Similarly to Shire and CSL in HAE in the early development years, Genzyme stands alone with an ERT for the treatment of patients with Pompe, and the market still offers an interesting entry possibility, reflecting on a busy and diverse development pipeline. Genzyme is running a phase III trial with a second generation ERT named avalglucosidase alfa (NeoGAA), a recombinant enzyme designed to improve delivery to lysosomes. Amicus is currently running a phase I/II trial with a chaperone therapy, on which the chaperone protein AT2221 is co-administered with a GAA enzyme (ATB200) in order to improve efficacy. In the long-term, Pompe is an attractive candidate for genome or RNA targeting therapies. The current early-stage development landscape includes, for instance, gene therapy candidates form Avrobio (preclinical), Audentes (IND-enabling studies) and Actus Tx (initiating phase I).

With the initiation of a phase I trial in H1'19, we anticipate that Pharming would be able to potentially introduce a new product in the market around 2023, facing competition not only from Genzyme but also from other potential candidates currently in development, in a similar situation to the one faced when the company launched Ruconest for acute HAE.

Table 9 - Clinical candidates for Pompe disease

Phase	Company	Candidate / Trial	Description
III	Genzyme	COMET: Efficacy and safety of ERT neoGAA and alglucosidase alfa administered every other week in late-onset Pompe disease not previously treated	NeoGAA: a second-generation alglucosidase alfa ERT, designed for enhanced receptor targeting and enzyme uptake, therefore improving clinical efficacy
I/II	Actus Therapeutics	AAV2/8-LSPhGAA in ate-onset Pompe Disease	Gene therapy: AAV2/8-LSPhGAA is intended to enable expression of a functional copy of the GAA gene in subject's hepatocytes
I/II	Amicus Therapeutics	Safety, tolerability, and PK of intravenous ATB200 alone and co-administered with AT2221	Chaperone/ERT combinations: in the CHART program, a chaperone is designed to bind to a specific therapeutic enzyme, stabilizing the enzyme in its properly folded and active form
I/II	Valerion Therapeutics	VAL-1221 delivered intravenously in ambulatory and ventilator-free patients with late-onset Pompe Disease	VAL-1221 : a recombinant fusion of the delivery antibody 3E10 with GAA
I	Audentes	Re-administration of intramuscular AAV9 in patients with late-onset Pompe Disease	Gene therapy: increases of GAA activity in cardiac and skeletal muscle
Preclin.	Shire and NanoMedSyn	Recombinant acid alpha-glucosidase conjugated with AMFA	Agreement settled in March 2018 for the development of a ERT combined with compounds targeting mannose 6-phosphate receptors, in order to facilitate their cellular entrance
Preclin.	Pharming	PGN-004: recombinant human alpha glucosidase	PGN-004 elicits therapeutic intervention by restoring acid alpha-glucosidase enzyme function
Preclin.	Spark Tx and Genethon	Adeno-associated viral (AAV) gene therapy targeting the liver	
Preclin.	Greenovation	ERT with Moss-GAA	Being produced in moss, this ERT products exhibit > 95 % uptake of mannose-terminated N-glycans
Preclin.	Oxyrane	OXY2810 is a recombinant human GAA for use as an enzyme replacement therapy for Pompe disease.	Produced by an engineered yeast expression platform, OXY2810 presents the natural targeting structure required for efficient localization to lysosomes

Source: clinicaltrials.gov