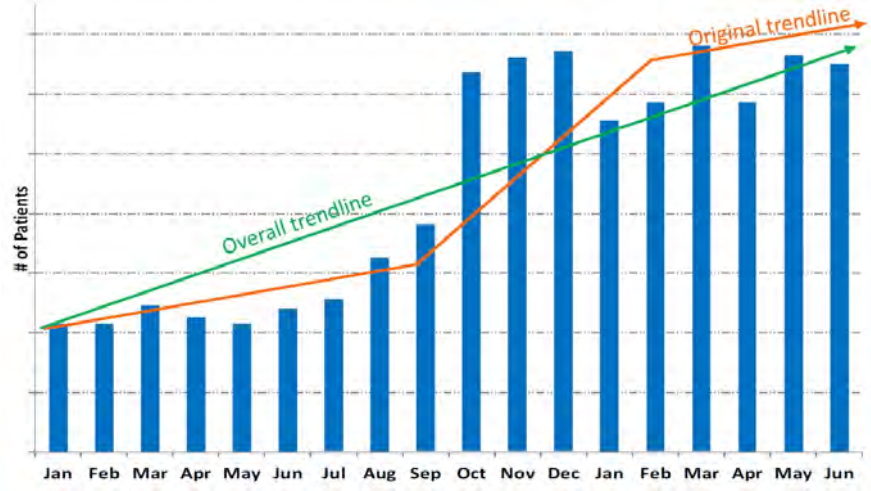
CSL focusing on price and incremental improvement

For its part, CSL is focused on plasma-derived therapies with Berinert and Haegarda being more like byproducts of their core immunoglobulin business, accounting for roughly 6% of their total sales. While Haegarda is essentially concentrated Berinert, it was the first prophylactic SC C1-INH on the market and was launched at an 18% discount to Cinryze in July 2017. Furthermore, in May 2018, CSL exclusively licensed a recombinant C1-INH from Cevec (private), which is a direct competitor to Ruconest, having shown better half-life in early pre-clinical studies. While the technology is a departure from CSL core business, it signals that CSL is ready to defend its HAE market share and as Haegarda was ready to be launched after Cinryze's exclusivity expired, it seems that CSL will also have a potentially better recombinant C1-INH ready to be launched in 2026, when its market exclusivity expires.

We estimate $223m in US HAE Ruconest peak sales

Launched in 2014, Ruconest was a late entrant into the US HAE market. At face value, it did not present any particular advantage compared to other drugs on the market thus, so it was not surprising that the ramp-up was slow in the first couple of years. After the drug swapped hands three times due to M&A, Pharming stepped in to regain the rights in Q3'16 which lead to a 50% increase in sales that year. This was driven primarily by Shire having supply issues with Cinryze in H2'16, as production was handled externally by Sanquin. The supply issues continued to persist in 2017 which allowed both Pharming and CSL to gain further market share. As of Q1'18, Shire moved Cinryze production in-house leading to a normalization of the situation and seemingly halting Ruconest sales growth in H1'18 (see figure 26).

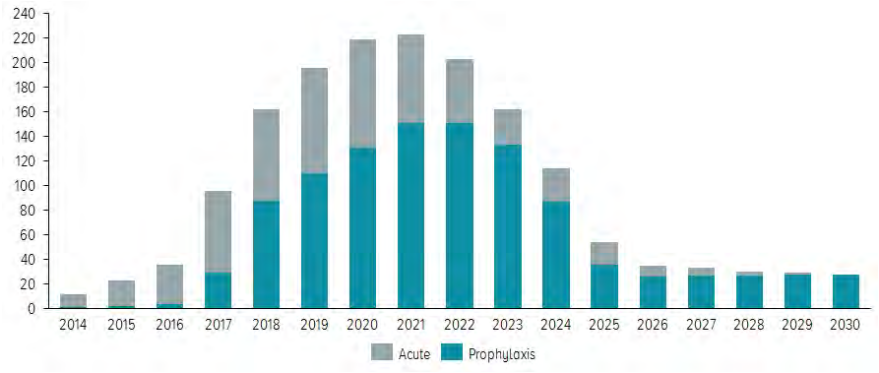
Figure 26 - Monthly Ruconest volumes 2017-H1'18



Source: Pharming H1'18 results presentation (unedited)

Nevertheless, we expect the prophylaxis label extension and the focused sales force to allow Pharming to gain incremental market share in the near term. Therefore we project Ruconest to reach $223m in peak sales in 2021 (see figure 27)

Figure 27 - Ruconest US sales forecast (USDm)



Source: Pharming, Kempen estimates

We project $88m acute peak sales in 2020

We expect Ruconest to incrementally gain space in the acute setting primarily through targeting new HAE patients, increasing market share to 10% by 2020. Since our base case forecast assumes launch of BCX7353 in 2020 as prophylaxis, we expect BioCryst to also launch the liquid formulation for acute treatment by 2022 (and KVD900 in 2022). Thus we project a gradual loss of Ruconest market share starting in 2022 and an acceleration after the FDA market exclusivity expiration in July 2026. Our pricing estimate of $220k is based on the average patient experiencing an attack every other week, approximately in line with 26.9 seen by Banerji (2015) in a 2013 survey of 186 patients. While we could expect pricing pressure in the mid-term across HAE treatments, we maintain a stable price until market exclusivity expire, when we expect a biosimilar to be launched at a significant discount (see table 5).

We project $151m prophylaxis peak sales in 2021

Due to Cinryze shortages in 2017, we estimate that about 30% of Ruconest patients are currently on a (pseudo) prophylaxis dosing regime with an average of one dose per week. This results in an estimated price of $475k per year, in line with Cinryze but 20% higher than (the more efficacious) Haegarda. We expect that the upcoming label expansion in prophylaxis to almost triple the market share to 8% in 2019. As with our acute forecast, we expect that the launch of oral treatments and market exclusivity expiration will result in a decline in market share as of 2022 (see table 5). While specific sales thresholds have not been disclosed, given our sales forecast, we would expect the $65m milestone payments to Valeant to be triggered over 2018, 2019 and 2020.

Table 5 - Ruconest US HAE sales forecast (USDm)

	2017A	2018E	2019E	2020E	2021E	2022E	2023E	2024E	2025E	2026E	2027E	2028E	2029E	2030E
HAE prevalence forecast														
HAE prevalence	10,383	10,457	10,531	10,606	10,681	10,757	10,833	10,909	10,984	11,059	11,134	11,207	11,280	11,351
Diagnosed %	78%	80%	85%	88%	90%	90%	90%	90%	90%	90%	90%	90%	90%	90%
Treated/ not on adrogens%	75%	79%	81%	83%	85%	90%	90%	90%	90%	90%	90%	90%	90%	90%
HAE treated patients	**6,111**	**6,609**	**7,251**	**7,656**	**8,171**	**8,713**	**8,775**	**8,836**	**8,897**	**8,958**	**9,018**	**9,078**	**9,137**	**9,194**
Patients on acute treatments %	*67%*	*64%*	*60%*	*55%*	*40%*	*30%*	*20%*	*18%*	*15%*	*13%*	*11%*	*10%*	*9%*	*8%*
Patients on prophylaxis treatments %	*33%*	*36%*	*40%*	*45%*	*60%*	*70%*	*80%*	*83%*	*85%*	*87%*	*89%*	*90%*	*91%*	*92%*
Acute sales forecast														
Doses/patient	24	24	24	24	24	24	24	24	24	24	24	24	24	24
Revenue/patient (USD)	219,187	219,187	219,187	219,187	219,187	219,187	219,187	219,187	219,187	153,431	153,431	153,431	153,431	153,431
Patients on acute Ruconest	304	338	392	400	327	235	132	124	80	58	40	18	8	2
market share %	*7%*	*8%*	*9%*	*10%*	*10%*	*9%*	*8%*	*8%*	*6%*	*5%*	*4%*	*2%*	*1%*	*0%*
Ruconest acute sales (USDm)	**67**	**74**	**86**	**88**	**72**	**52**	**29**	**27**	**18**	**9**	**6**	**3**	**1**	**0**
growth %	*111%*	*11%*	*16%*	*2%*	*-18%*	*-28%*	*-44%*	*-6%*	*-35%*	*-49%*	*-32%*	*-54%*	*-55%*	*-78%*
prophylaxis sales forecast														
Doses/patient	52	52	52	52	52	52	52	52	52	52	52	52	52	52
Revenue/patient (USD)	474,906	474,906	474,906	474,906	474,906	474,906	474,906	474,906	474,906	332,434	332,434	332,434	332,434	332,434
Patients on prophylaxis Ruconest	60	184	232	276	319	318	281	182	76	78	80	82	83	85
market share %	*3%*	*8%*	*8%*	*8%*	*7%*	*5%*	*4%*	*3%*	*1%*	*1%*	*1%*	*1%*	*1%*	*1%*
Ruconest prophylaxis sales (USDm)	**29**	**88**	**110**	**131**	**151**	**151**	**133**	**87**	**36**	**26**	**27**	**27**	**28**	**28**
growth %	*713%*	*207%*	*26%*	*19%*	*16%*	*0%*	*-12%*	*-35%*	*-59%*	*-28%*	*3%*	*2%*	*2%*	*2%*
Total Ruconest HAE sales	**95**	**162**	**196**	**219**	**223**	**203**	**162**	**114**	**53**	**35**	**33**	**30**	**29**	**28**
growth %	*171%*	*70%*	*21%*	*12%*	*2%*	*-9%*	*-20%*	*-30%*	*-53%*	*-35%*	*-6%*	*-9%*	*-3%*	*-2%*
difference to bb consensus %		*6%*	*-7%*	*-33%*	*-50%*									

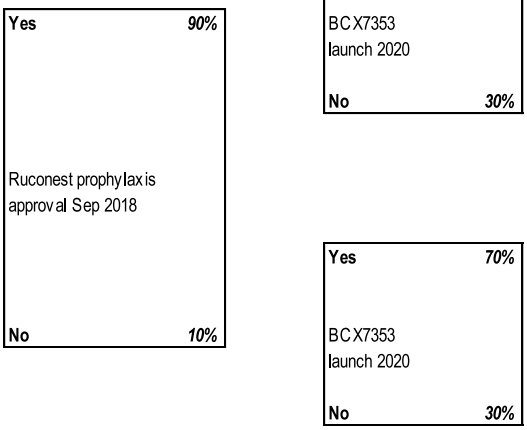
Source: Lumry 2018, Shire, CSL, Pharming, BioCyrst, Banerji 2015, Kempen estimates

Delay in oral therapies launch could increase peak sales to >$350m

Our base case valuation assumes i) Ruconest prophylaxis sBLA approval (90% probability), ii) BCX7353 launch in 2020 (70% probability), following positive phase III results in H1'19 and iii) other oral treatments entering the market in 2022-2023 (see figure 28).

- In the most extreme case, should all oral treatments currently in development fail, there is 66% upside to our valuation, though we deem the probability of this scenario just 3%, given the various approaches and well understood HAE pathogenesis. In this scenario, peak sales could reach $352m.
- Should Ruconest gain prophylaxis approval, BCX7353 fails the phase III delaying the launch of orals to 2022, we see a 44% upside to our valuation, with Ruconest peak sales reaching $340m.
- We see further up to 39% downside to our valuation if Ruconest's prophylaxis sBLA is rejected. We believe there is limited range if oral treatments do not enter the market, as we think Haegarda and lanadelumab will simply continue gaining market share. Ruconest peak sales would be around $157-257m.

Figure 28 - Ruconest scenario analysis



			Peak sales (USDm)			
		Probability	Acute	Prophylactic	Total	Implied PT
Yes 90% / Other orals launch 2022-2023		57%	88	151	239	0.6
No 10%		6%	88	158	245	0.7
Yes 90% / Other orals launch 2022-2023		24%	90	250	340	0.9
No 10%		3%	99	254	352	1.1
Yes 90% / Other orals launch 2022-2023		6%	88	69	157	0.4
No 10%		1%	88	69	157	0.4
Yes 90% / Other orals launch 2022-2023		3%	90	145	234	0.6
No 10%		0%	99	158	257	0.7

Source: Kempen estimates

We estimate €15m in EU HAE Ruconest peak sales

While there is no real difference in prevalence in Europe and the US, European market size is limited by the high (long-term) use of androgens and over 10x lower pricing. Thus we estimated peak sales of €15m in Europe (primarily from the direct sales force) by 2024 and declining after market exclusivity expiration in 2026.

Ruconest indications expansion is commercially attractive but highly risky

While we think there is merit in pursuing proof-of-concept studies in preeclampsia, contrast-induced nephropathy and delayed graft function (see appendix), we believe there is insufficient clarity on the clinical path to approval and commercial strategy to consider these in our base case valuation. That said, commercially we find preeclampsia the most promising estimating over 100k severe preeclampsia cases in the US per year (2.5% incidence, Ananth 2013). However, we expect an extensive and expensive clinical program, involving at least two phase II studies and two phase III studies, with launch no earlier than 2025. While there is some anecdotal evidence of safety in pregnant women, there is no proper data to back it up and given the sensitive nature we believe enrollment will be difficult. In terms of valuation, should Pharming lay out a clear clinical plan, we see a potential ~20% upside.

Too late to get back in the Pompe and Fabry game

While Pompe is an interesting indication for the development of recombinant proteins, we believe Pharming is relatively late given the clinical stage of a number of promising gene therapies. Nevertheless, should a Pharming candidate enter phase I in H1'19, we see ~10% upside to our valuation. The development of a Fabry candidate seems less certain given the company is penciling in a phase I initiation in 2020 and given less urgent medical need we would not include the program in our valuation.

Newsflow

Q3'18:

- Ruconest prophylaxis sBLA PDUFA date 21 September
- Readout phase II Ruconest in contrast-induced nephropathy
- Initiate phase II Ruconest delayed graft function study

Q4'18:

- 9M'18 results on 25 October
- Initiate phase II Ruconest SC, IM and ID studies
- Initiate phase II Ruconest preeclampsia study

H1'19:

- Initiate phase I Pompe study

Risks to our SELL case

Supply issues of plasma-derived C1-INH

While we believe that Shire and CSL should not face any issues in supplying the market with their plasma-derived C1-INH, should this occur in the coming 12 months, Ruconest may be able to gain market share faster than we forecast.

Launch delay of lanadelumab

Shire is currently envisaging to launch lanadelumab in late 2018 or early 2019, any additional delay could result in Ruconest gaining additional market share.

Positive CIN and preeclampsia study results

Should readouts in the phase II studies in CIN and preeclampsia show a clear medically significant benefit with Ruconest in these indications, path to market could be significantly shorter thus increasing Ruconest's total peak sales.

A partnership of Pompe and Fabry programs

Although Pharming intends to fund the development of the Pompe and Fabry programs, we do not exclude a potential partner stepping in. This could result in an acceleration of clinical timelines and faster access to the market. One such partner could be Sanofi, which previously worked with Pharming on a Pompe candidate and is currently involved in the manufacturing of Ruconest

Appendix

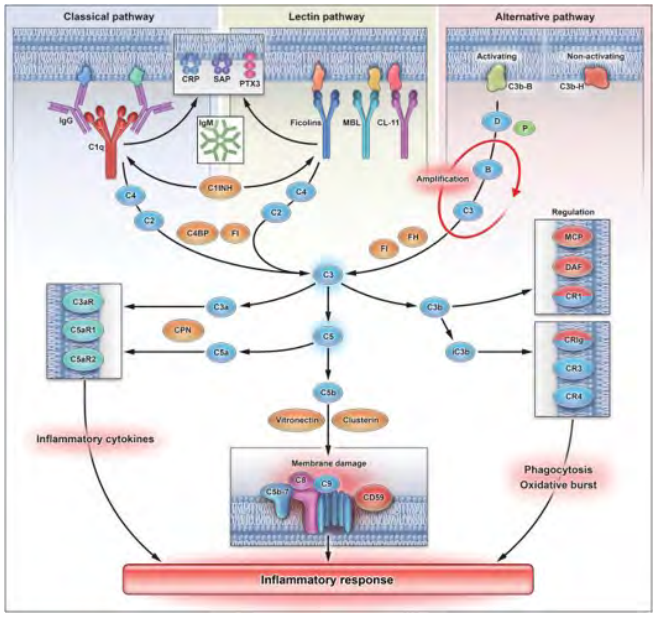
Expanding Ruconest's franchise

C1-INHs participate in a broad range of activities, inactivating several different proteases in the complement, contact, coagulation, and fibrinolytic systems. Despite its broad reach, HAE is the only abnormality that results from the lack of C1-INH itself. However, there are several pathological conditions involving other pathways in which this protein plays a key inhibitory role, especially regarding the complement system. These potential applications are not exclusive to the recombinant C1-INH, but as production capacity is a constraint for plasma-derived products, the role of C1-INH beyond the straightforward HAE indication has not been widely explored.

The complement system triggers immune response and inflammation

Originally identified by their ability to amplify and complement the immune response, the complement system (CS) consists of serum and membrane components mainly produced in the liver. When stimuli are received, the complement cascade is activated via three different pathways that converge into a single point, eventually leading to the formation of a membrane attack complex pore that promotes cell lysis.

Figure 29 - The complement system



Source: Havland et al., 2015

- The first activation pathway, named the classical pathway, is triggered by antigen/antibody complexes and involves the activation of the C1 complex (C1q, C1r and C1s) that cleaves C4 and C2 into C4b and C2a, which will then bind and cleave C3.
- The second, the lectin pathway, is stimulated when mannose-binding lectins (MBLs) identify patterns on the surface of microorganisms, leading to the activation of MASP-1, MASP-2, and MASP-3, which will also cleave C4 and C2.
- The last, called the alternative pathway is constitutively active at low levels and starts with C3 activation (see figure 29).

The potential to cleave C3 is the point at which the three pathways converge to activate the cascade downwards. The complete activation will result in stimulation

of the phagocytes to clear foreign and damaged material, inflammation to attract additional phagocytes, and activation of the cell-killing membrane attack complex.

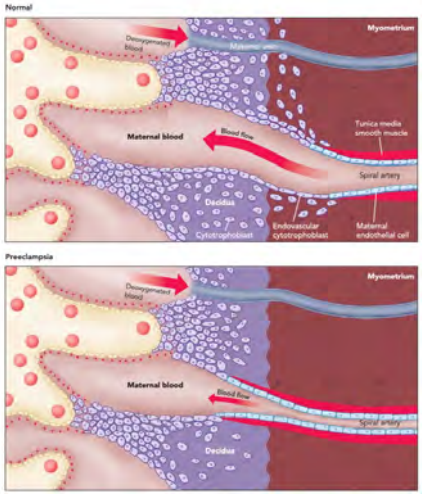
C1-INH has an important role in regulating the complement system

The undesired effects of complement activation are controlled by several complement regulators, acting at different steps of the cascade to prevent unwanted damage. One key regulator is C1-INH, which binds and blocks the activity of C1r, C1s, and MASPs in the classical and lectin activation pathways by a suicide mechanism, which means that the molecule is destroyed after use. Based on the wide range of biological activities, preclinical studies have identified that C1-INH might play a role on several pathological conditions, including ischemia-reperfusion injuries, septic shock, capillary leak syndrome, organ transplantation, and pancreatitis (Cicardi 2005). Based on investigator interest, Ruconest is being evaluated in three new indications on which complement regulation seems to play an important role.

Preeclampsia phase II with Ruconest to start in Q4'18

Driven by investigator interest, Pharming is planning to initiate an exploratory phase II trial with Ruconest in preeclampsia (PE) in Q4'18. PE is a multisystem condition that manifests during pregnancy, being part of a group of pregnancy hypertensive disorders that affects around 4-5% of expectant mothers worldwide (Stevens 2017). During early, normal pregnancy, spiral arteries in the uterus are transformed into large vessels of low resistance, in order to capably sustain the growing fetus. In preeclampsia, this spiral artery transformation is incomplete and shallow, forming small caliber, resistant vessels (see figure 30). Historically, PE recognition was based on the onset of the most common symptoms in the second half of pregnancy; high blood pressure and proteinuria. More recently, the definition has broadened to include systemic manifestations such as liver dysfunction, renal insufficiency, thrombocytopenia, pulmonary edema, or cerebral and visual disturbances.

Figure 30 - Abnormal placentation in PE

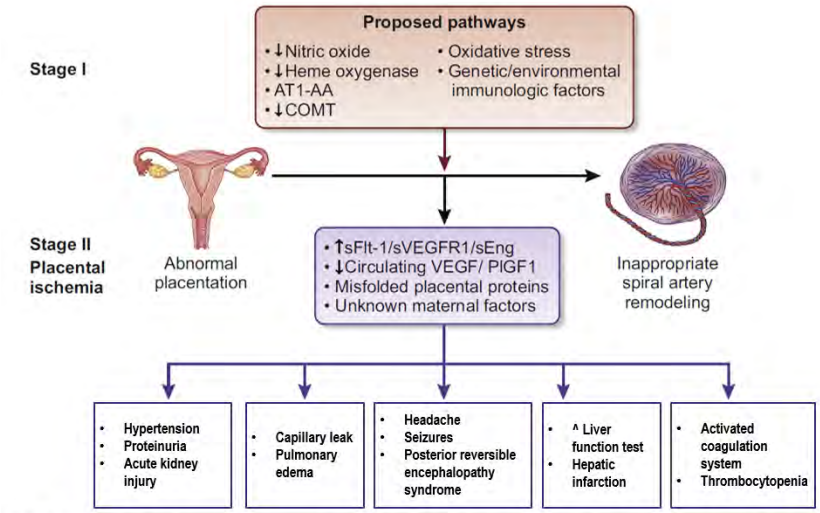


Source: Wang et al., 2009

Preeclampsia is a multisystem disorder with a complex pathogenesis

PE pathogenesis is not fully understood, however, it is generally believed to be initiated by placental ischemia followed by a placental release of antiangiogenic factors into the circulation. The underlying events inducing the placental disease remain unknown, and various pathways are proposed to have important roles, including deficient heme oxygenase expression, impaired corin expression, hypoxia, genetic factors, autoantibodies against the angiotensin receptor, oxidative stress, inflammation, altered natural killer cell signaling, and deficient catechol-O-methyl transferase (see figure 31). More recent evidence also suggests that a systemic inflammatory response to pregnancy is involved in the pathogenesis of the disease, with the complement system playing a crucial role in immune processes.

Figure 31 - Pathogenesis of preeclampsia: two-stage model



AT1-AA: autoantibodies to angiotensin receptor, COMT: catechol-O-methyltransferase, PlGF1: placental growth factor, sEng: soluble endoglin, sFlt-1: soluble fms-like tyrosine kinase, sVEGFR1: soluble vascular endothelial growth factor receptor, VEGF: vascular endothelial growth factor.

Source: Phipps et al., 2016

PE prevention and treatment uses common medications

The primary therapeutic goal with PE patients is to reduce blood pressure sufficiently to prevent the progression of systemic issues and to prolong the pregnancy. There are no treatments developed specifically for the prevention or treatment of PE: women considered under a higher risk are often put through prevention medications, more commonly low dose aspirin, and the treatments of symptomatic patients are directed towards preventing disease exacerbation with, for instance, anti-hypertensive drugs. (see table 6).

Table 6 - Interventions that are recommended for prevention or treatment of pre-eclampsia and eclampsia

Recommendation	Quality of the evidence
In areas where dietary calcium intake is low, calcium supplementation during pregnancy is recommended for the prevention of pre-eclampsia in all women, but especially those at high risk of developing pre-eclampsia.	Moderate
Low-dose acetylsalicylic acid (aspirin, 75 mg) is recommended for the prevention of pre-eclampsia in women at high risk of developing the condition.	Moderate
Women with severe hypertension during pregnancy should receive treatment with antihypertensive drugs.	Very Low
Magnesium sulfate is recommended for the prevention of eclampsia in women with severe pre-eclampsia in preference to other anticonvulsants.	High
Magnesium sulfate is recommended for the treatment of women with eclampsia in preference to other anticonvulsants.	Moderate
The full intravenous or intramuscular magnesium sulfate regimens are recommended for the prevention and treatment of eclampsia.	Moderate
Induction of labor is recommended for women with severe preeclampsia at a gestational age when the fetus is not viable or unlikely to achieve viability within one or two weeks.	Very Low
In women with severe pre-eclampsia at term, early delivery is recommended.	Low
In women treated with antihypertensive drugs antenatally, continued antihypertensive treatment postpartum is recommended.	Very Low
Treatment with antihypertensive drugs is recommended for severe postpartum hypertension.	Very Low

Source: WHO, 2011

Without a clear role, CS components are found to be unbalanced in PE

The role of the CS in pregnancy has not been completely elucidated yet, but there is increasing evidence indicating that a dysregulation plays a role in the development of PE. For instance, pregnancy is a known trigger for syndromes commonly related to complement dysregulation (such as lupus erythematosus), women with PE are found to have elevated levels of circulating and placental complement components, and mutations in complement regulatory proteins are thought to predispose to PE (Lokki 2014).

Although the sample sizes have been a limiting factor, studies have pointed out that women with PE often present imbalances in complement components. C4