Capital Markets Briefing

New York City
and by webcast
21 June 2018

Pharming

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Agenda

1. Introduction
2. HAE Therapeutics Overview – Professor Marc Riedl, UCSD
3. HAE US market overview
4. Building the RUCONEST® franchise in HAE
5. rhC1INH: Indications beyond HAE
6. rhC1INH development for Pre-eclampsia – Professor Gustaaf Dekker, University of Adelaide
7. Contrast-induced nephropathy and cardiac protection, delayed graft function, hemorrhagic shock
8. Protein Replacement Therapy in Pompe and Fabry's diseases
9. Pharming's Commercial Potential
10. Summary

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Presenting Team

- Pharming's Board of Management:
  - Sijmen de Vries, *Chief Executive Officer*
  - Bruno Giannetti, *Chief Operating Officer*
  - Robin Wright, *Chief Financial Officer*
- Pharming US Management
  - Stephen Toor, *General Manager, Pharming Americas Region*
  - Anurag Relan, *Head of Clinical Research and Medical Affairs*
- Key Opinion Leaders
  - Professor Marc Riedl, *UCSD and US HAEA Angioedema Center*
  - Professor Gustaaf Dekker, *University of Adelaide*

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Company Overview

- Mission: To develop Pharming into an integrated global leader in commercializing recombinant human therapeutic proteins for innovative therapies addressing important unmet patient needs
- Euronext: PHARM - market capitalization: ~€945 million ($1.1 billion) at €1.57 per share
- Headquarters in NL, R&D in France, EU and US commercial operations with c.150 employees
- 1st product approved and marketed : RUCONEST®
  - Recombinant human C1-esterase inhibitor (rhC1INH :- enzyme replacement therapy)
  - For acute angioedema attacks in patients with hereditary angioedema (HAE)
  - Filed for prophylaxis of HAE, with action date of 21 September 2018
- Transgenic Mammal Platform technology enables Pharming to produce complex recombinant human molecules
- New Enzyme Replacement Therapies (ERT) for other genetic conditions to enter clinic from 1H2019
- Profitability and positive cashflows achieved from own commercialisation in USA and W. Europe (re-acquired US rights from Valeant in Dec 2016)

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What is unique about Pharming's technology platform

"Transgenic Mammal" Platform

- Human proteins expressed in the milk (only) of transgenic animals as bioreactors
- Full mammalian biochemistry to produce near-perfect recombinant versions of complex human proteins, with low immunogenicity (such as rhC1INH)
- So far, all versions have been closer to natural human protein than other methods allow

As a result:

- RUCONEST® has proved efficacious, safe and well-tolerated to date.
  - Other companies' CHO-cell version C1 developments have been abandoned for HAE therapy
- The glycosylation pattern of Pharming's α-glucosidase presently under development for Pompe disease is very different from the CHO-cell-derived current products and much closer to human natural α-glucosidase
  - All current Pompe ERT products have FDA boxed warnings in the US for immunogenicity

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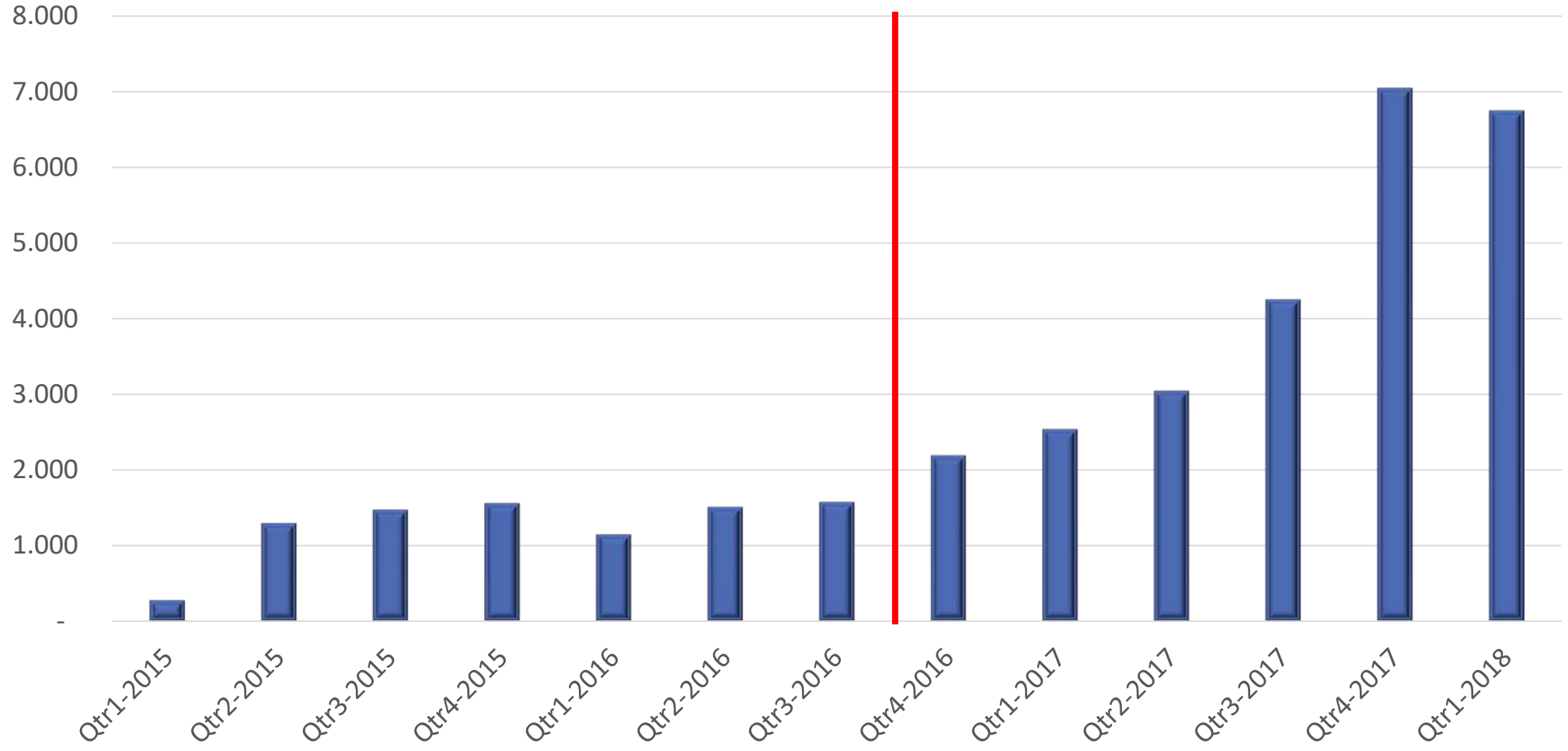
US quarterly sales development in volumes



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Pharming: Scientific and regulatory milestones/ events

1988	Foundation: 11 Nov (GENEPHARMING) - making human proteins in the milk of transgenic animals
1990	Dec 16th Birth of the World's first transgenic bull ("Herman")
1994	Proof of Concept: Human protein from cow milk (rh-lactoferrin)
1996	Proof of Concept: Human protein from rabbit milk (α-glucosidase for Pompe's disease)
1998	Transgenic rabbits express rh C1INH (RUCONEST®)
2001	Phase II α-Glucosidase, Start clinical development rhC1INH
2008	Transgenic cows express rhC1INH (lower yield, closer protein
2010	RUCONEST® approved by EMA for acute treatment of HAE attacks
2014	RUCONEST® approved by FDA for acute treatment of HAE attacks
2015	New Leads for α-glucosidase (Pompe) and α-galactosidase (Fabry)
2016	Positive Phase II results for RUCONEST® in prophylaxis of HAE
2018	FDA accepts sBLA for prophylaxis of HAE for review; action date 21 Sep 2018

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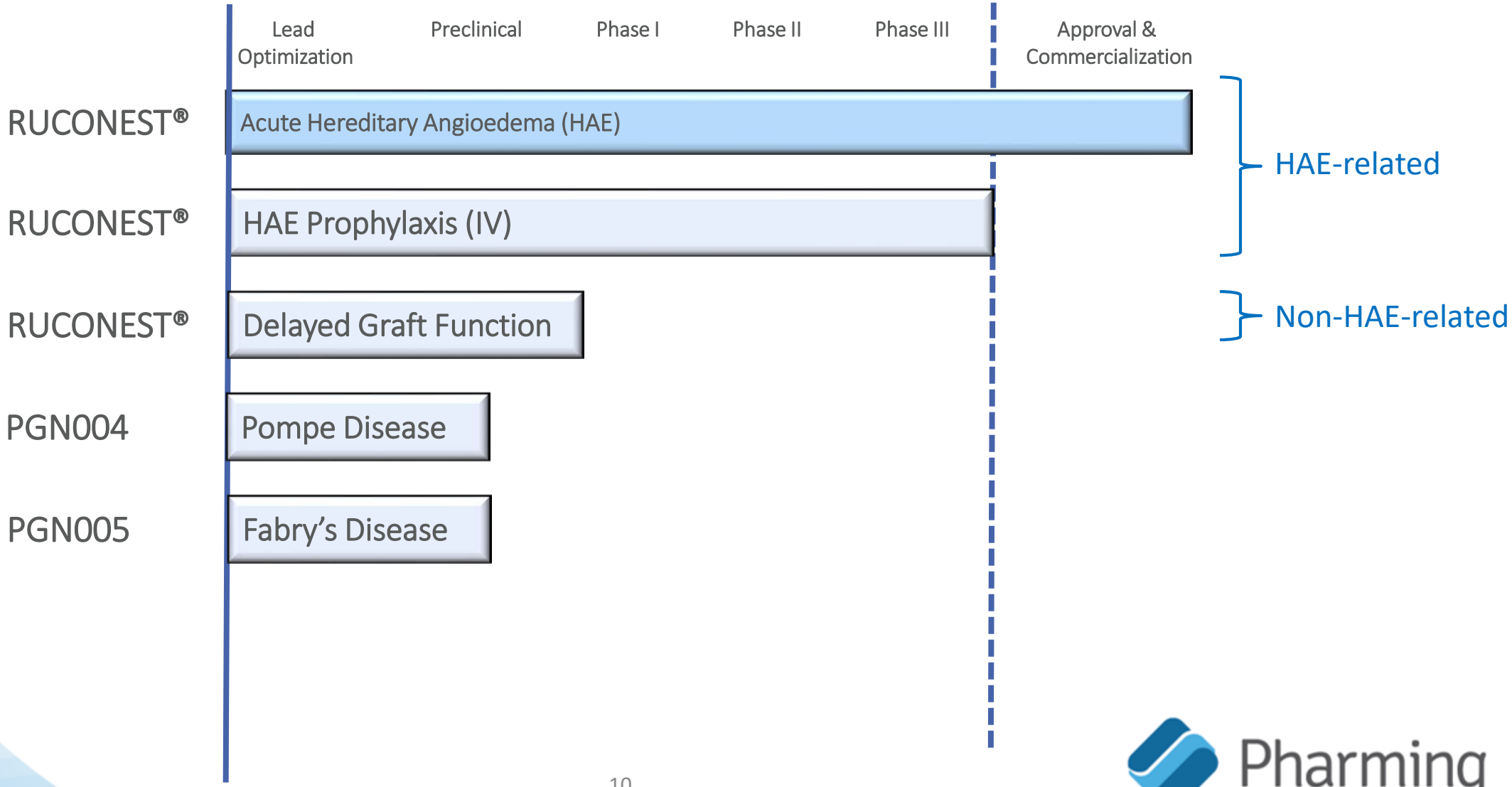
Pharming Pipeline yesterday



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Three horizons of growth

Today – An HAE company with a very good IV-only product and profitable commercialisation

Making RUCONEST® a better HAE product

- FDA approval for Prophylaxis
- Low volume IV
- Subcutaneous
- Intramuscular
- Painless intradermal

Add more HAE sales

Meeting other unmet medical needs with the same product

- Pre-eclampsia
- Others such as Contrast-induced Nephropathy, Cardiac Protection, Delayed Graft Function and Hemorrhagic Shock

Add more RUCONEST® sales

Meeting other unmet medical needs with other products

- α-glucosidase (Pompe)
- α-galactosidase (Fabry)
- Others

Add more products to sell

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Therapeutic Development in Hereditary Angioedema

- Professor Marc Riedl

Director, Hereditary Angioedema Center of Excellence
University of California San Diego

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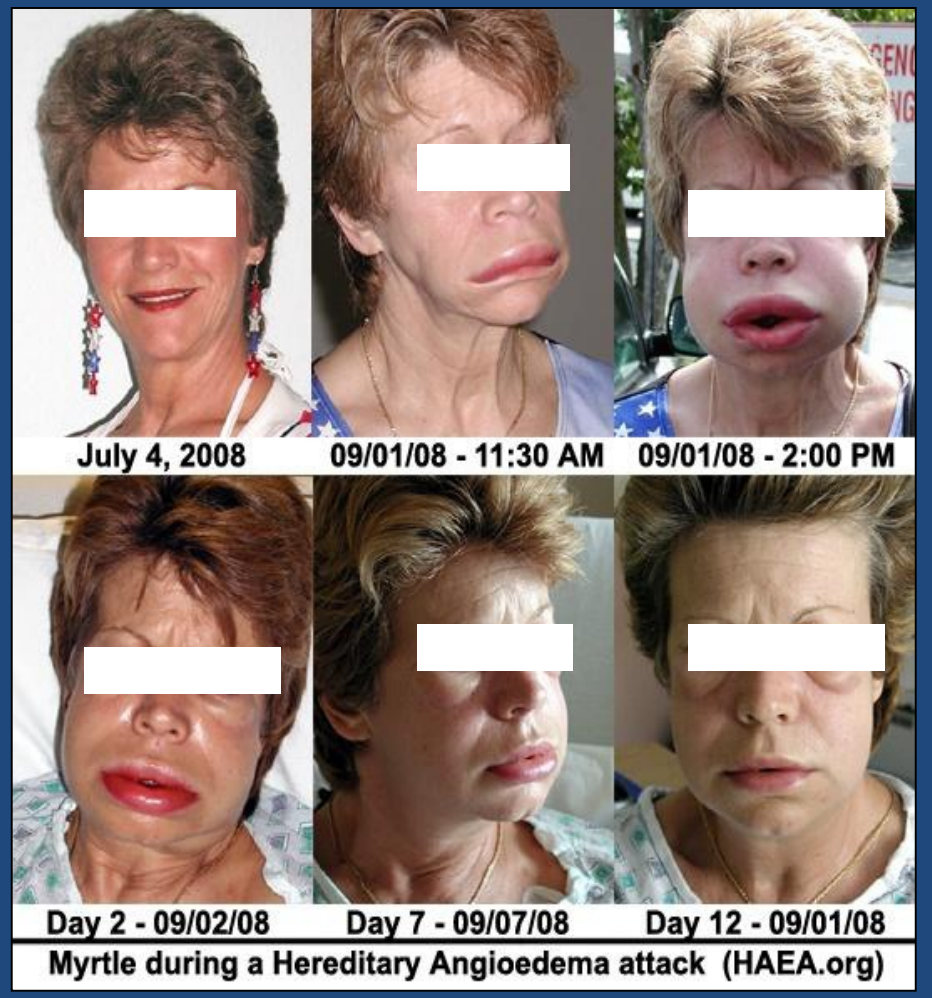
Hereditary Angioedema: Background and Treatment Landscape

Marc Riedl, MD MS
Professor of Medicine
University of California, San Diego

Hereditary Angioedema (HAE)

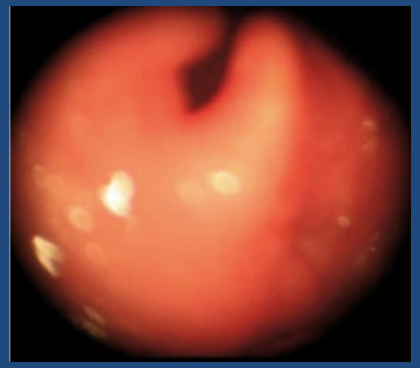
- Potentially fatal genetic disorder associated with deficiency or dysfunction of C1 inhibitor (C1-INH)
- Characterized by swelling involving the deep dermis; generally localized; mildly pruritic and/or burning or painful; lasts hours to several days

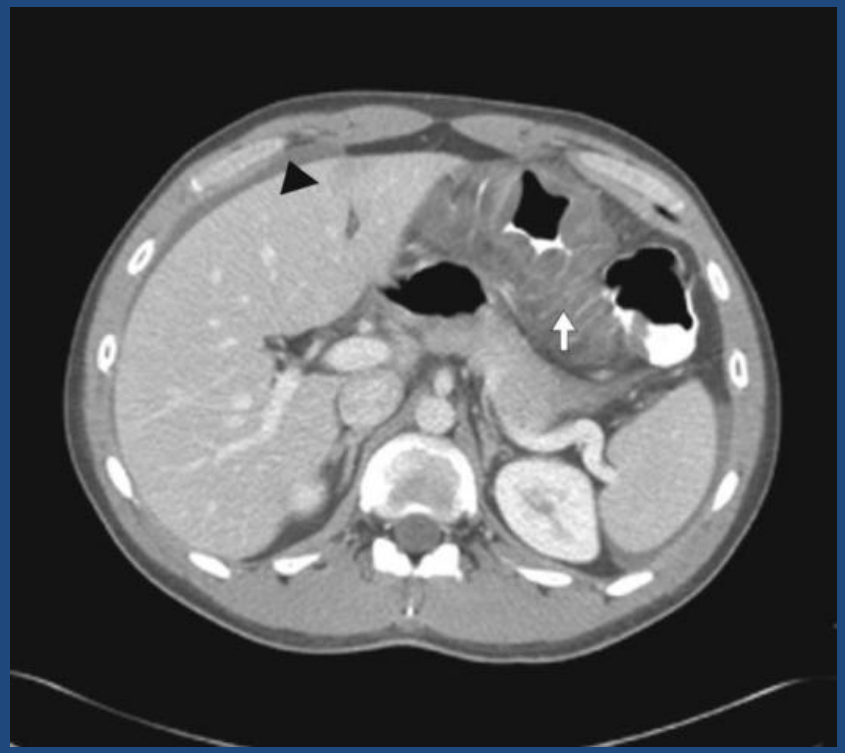


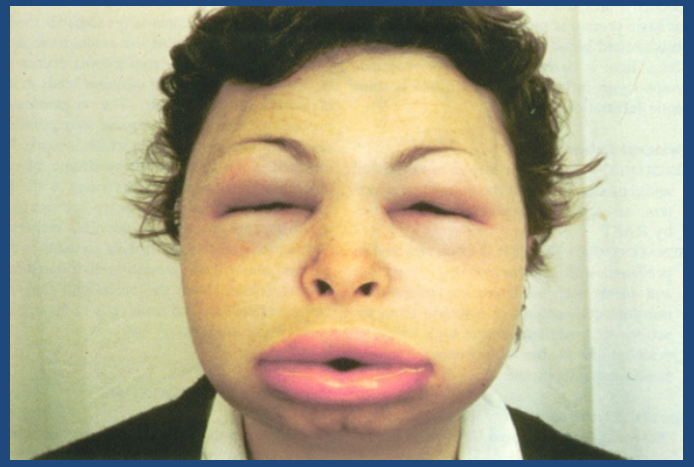
Clinical Features of HAE

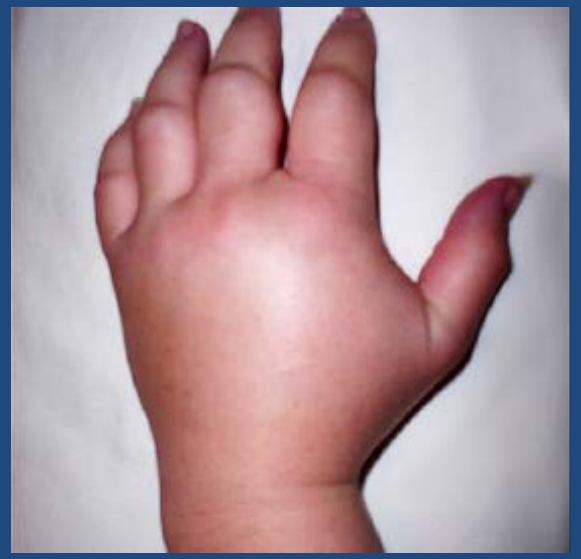
- Angioedema often severe
  - Face, oropharynx, extremities, GI system, genitourinary tract
- Attacks prolonged
  - Increasing intensity over 24 hours, resolve in 2-4 days
  - Unresponsive to therapy with antihistamines, corticosteroids, or epinephrine
- Attacks occur unpredictably and are of varying frequency
- Frequently worsened by estrogen-containing oral contraceptives, hormone replacement therapy
- Often precipitated by trauma or stress

Clinical Symptoms of HAE







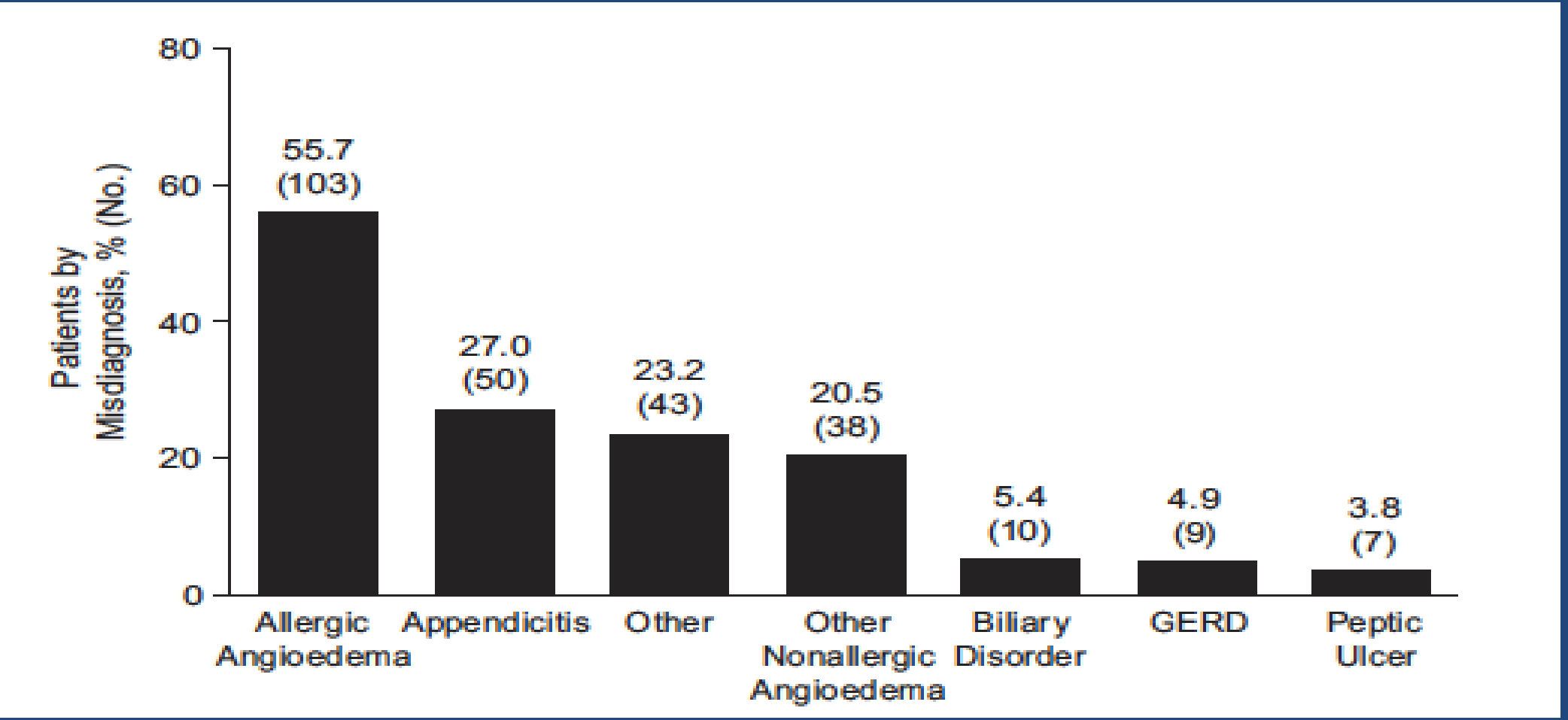


Epidemiology of HAE

- Prevalence difficult to ascertain due to under recognition and diagnosis
  - Autosomal dominant inheritance
  - Estimates 1 in 30,000 to 1 in 80,000
  - No known ethnic or gender differences
- Average angioedema attack frequency: one episode per 2-week period
- Disease severity is highly variable
  - Between patients and within families
  - No simple relationship between disease severity and C1 esterase inhibitor (C1-INH) level

Frank MM, et al. *Annals Int Med*. 1976;84:580-593.
Agostoni A, et al. *J Allergy Clin Immunol.* 2004;114:S51-S131.

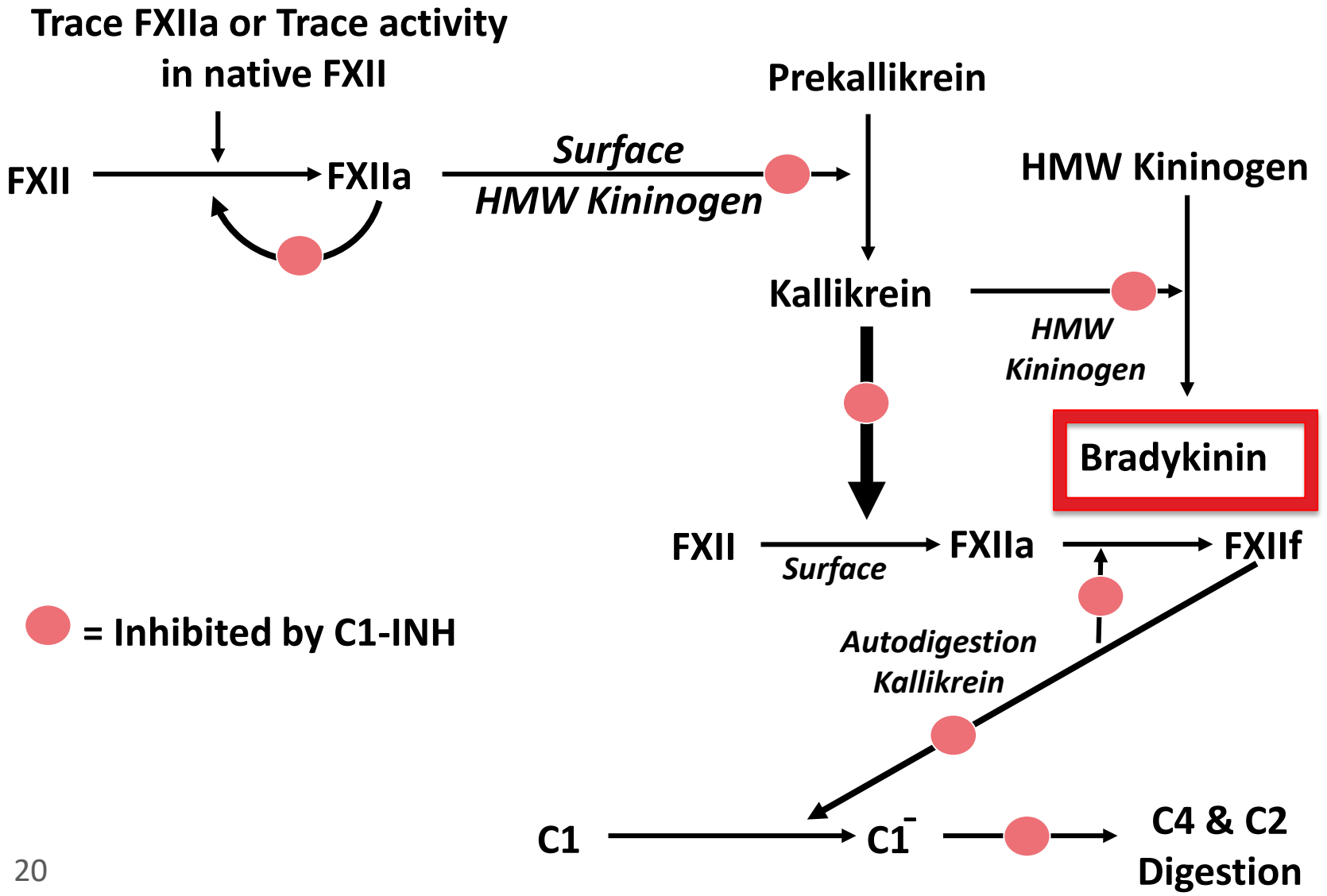
HAE Misdiagnosis



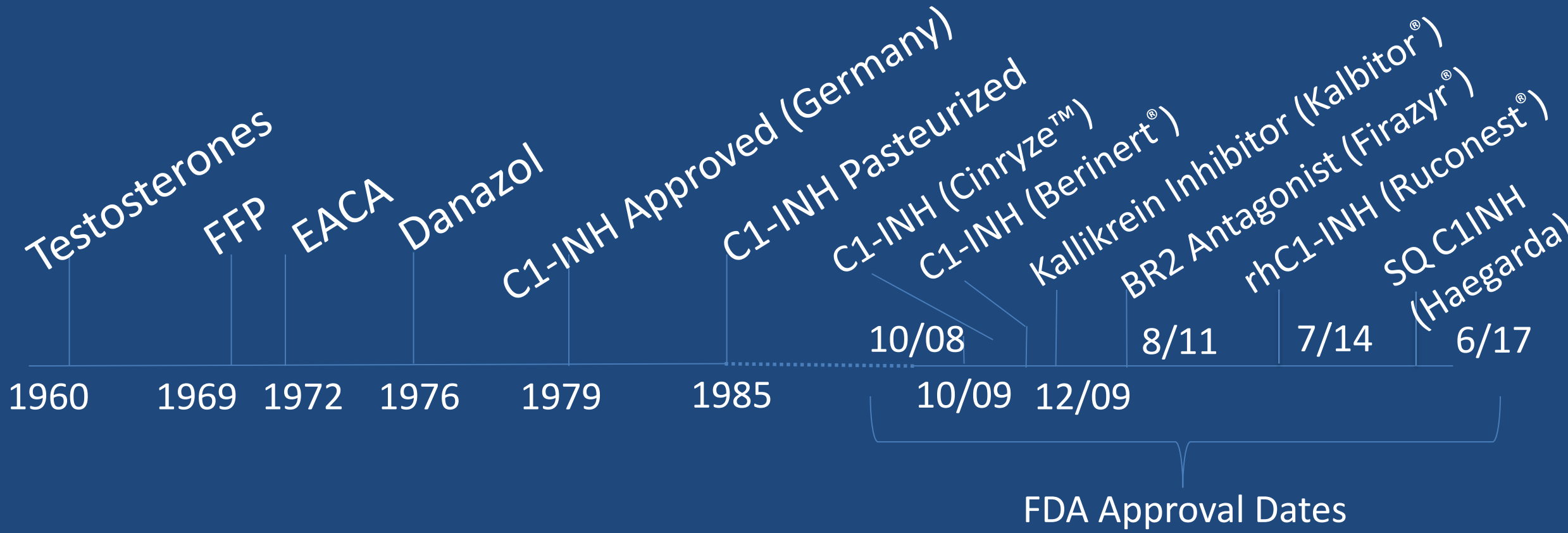
- 185/418 patients (44%) had 1 or more misdiagnosis prior to HAE dx
- Prior misdiagnosis: Median diagnostic delay of 13.3 years compared to 1.7 years if no misdiagnosis

Zanichelli et al. Ann AllergyAsthma Immunol, 2016

Function of C1-INH



HAE Therapy Timeline



Hereditary Angioedema due to C1INH Deficiency

POSITION ARTICLE AND GUIDELINES Open Access

The international WAO/EAACI guideline for the management of hereditary angioedema – the 2017 revision and update

Marcus Maurer[1*†], Markus Magerl[1†], Ignacio Ansotegui[2], Emel Aygören-Pürsün[3], Stephen Betschel[4], Konrad Bork[5], Tom Bowen[6], Henrik Balle Boysen[7], Henriette Farkas[8], Anete S. Grumach[9], Michihiro Hide[10], Constance Katelaris[11], Richard Lockey[12], Hilary Longhurst[13], William R. Lumry[14], Inmaculada Martinez-Saguer[15], Dumitru Moldovan[16], Alexander Nast[17], Ruby Pawankar[18], Paul Potter[19], Marc Riedl[20], Bruce Ritchie[21], Lanny Rosenwasser[22], Mario Sánchez-Borges[23], Yuxiang Zhi[24], Bruce Zuraw[25] and Timothy Craig[26]

World Allergy Organization Journal (2018) 11:5

WAO Guideline: Acute Treatment Recommendations

- All HAE attacks are considered for on-demand treatment and any attack affecting or potentially affecting the upper airway is treated (100% agreement)
- HAE attacks are treated as early as possible (100%)
- HAE attacks are treated with either C1-INH, ecallantide, or icatibant (90%)
- All patients have sufficient medication for on-demand treatment of two attacks and carry on-demand medication at all times (100%)
- All patients who are provided with on-demand treatment licensed for self-administration should be taught to self-administer (100%)

Maurer M, et al. Allergy. 2018

FDA-Approved Acute HAE Therapies

Drug	Potential Safety Concerns	Disadvantages	Advantages	Status
Plasma-derived C1-INH	• Infectious risk • Potential infusion reactions	• Intravenous • Dependent on plasma supply	• Extensive clinical experience • Relatively long half-life	• **Berinert®:** Approved in USA and many countries worldwide for HAE acute treatment[1] • **Cinryze®:** Approved in USA for HAE long-term prophylactic therapy; in Europe for acute and prophylactic treatment[2,3]
Recombinant C1-INH	• Potential hypersensitivity	• Intravenous	• No human virus risk • Scalable supply	• **Ruconest®:** Approved in Europe and USA for HAE acute treatment
Ecallantide	• Allergic reactions • Antibody formation	• Requires administration by a healthcare provider	• No infectious risk • Subcutaneous administration	• **Kalbitor®:** Approved in the USA for acute HAE therapy[5]; currently not approved in Europe
Icatibant	• Local injection reactions		• No infectious risk • Stable at room temperature • Subcutaneous administration	• **Firazyr®:** Approved in USA and numerous other countries for acute HAE therapy[6]

1. Berinert SPC; 2. CINRYZE USPI; 3. CINRYZE SPC; 4. Ruconest SPC; 5. Kalbitor SPC; 6. Firazyr SPC.

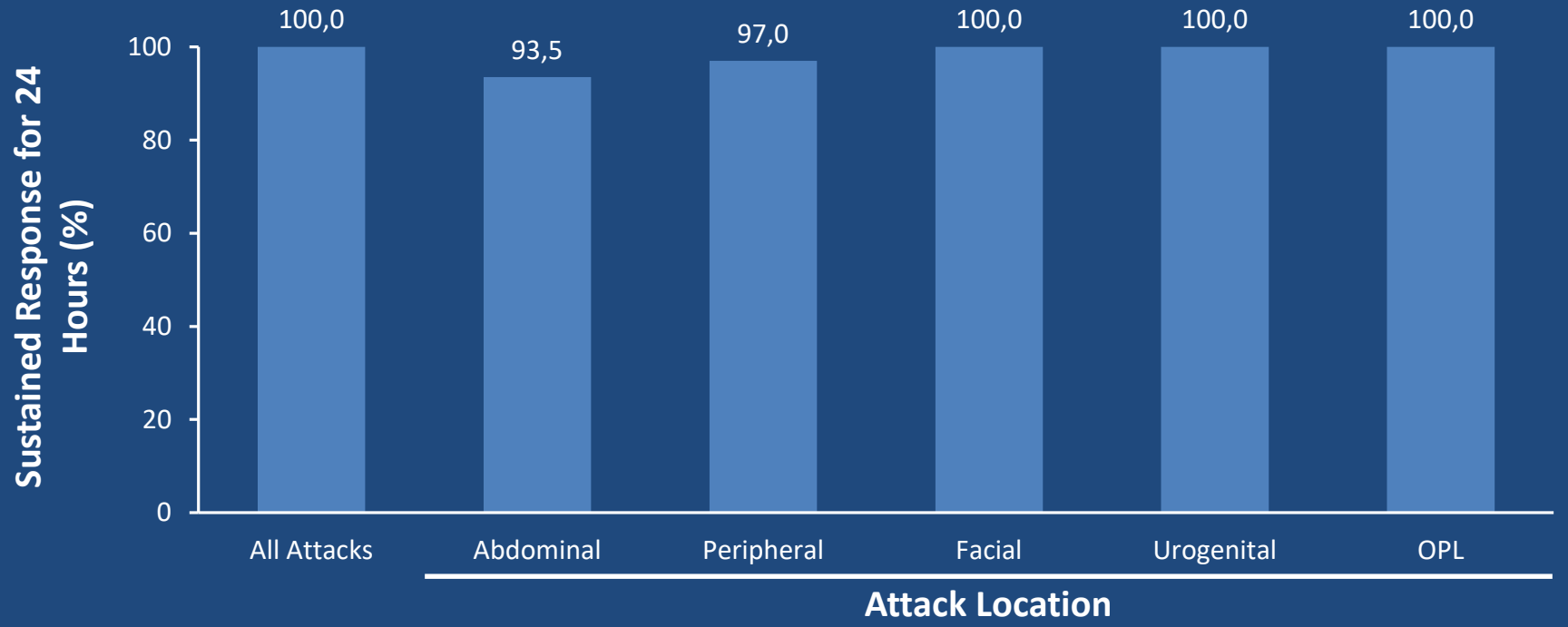
Home Administration of Acute Medications for HAE

- Offers possibility of earlier treatment, earlier resolution of attack and overall better disease control
- Demonstrated ability of self/partner to infuse allows:
  - Increased QoL, flexibility & convenience
  - Decreased time to treatment, severity/duration of attacks
- Training required but majority of patients achieve self-administration

Longhurst H, et al. *Allergy Asthma Clin Immunol*. 2010;6(1):22.
Levi M, et al. *J Allergy Clin Immunol*. 2007;117:904-908.
Dagen C, et al. *Allergy Asthma Clin Immunol.* 2010;6(1):11.
Bygum A, et al. *Eur J Dermatol*. 2009;19(2):147-151.
Kreuz W, et al. *Transfusion*. 2009;49(9):1987-1995.

rhC1INH: Sustained Response for 24 Hours

- Most patients had sustained response* with one rhC1-INH dose
  - Only 1 of 263 attacks required a second dose of rhC1-INH within 24 hours



*Sustained response defined as a response (≥20 mm decrease of VAS scores at 2 consecutive time points during 4 hours post-treatment) that was not associated with an increase of ≥20 mm within 24 hours postdose.

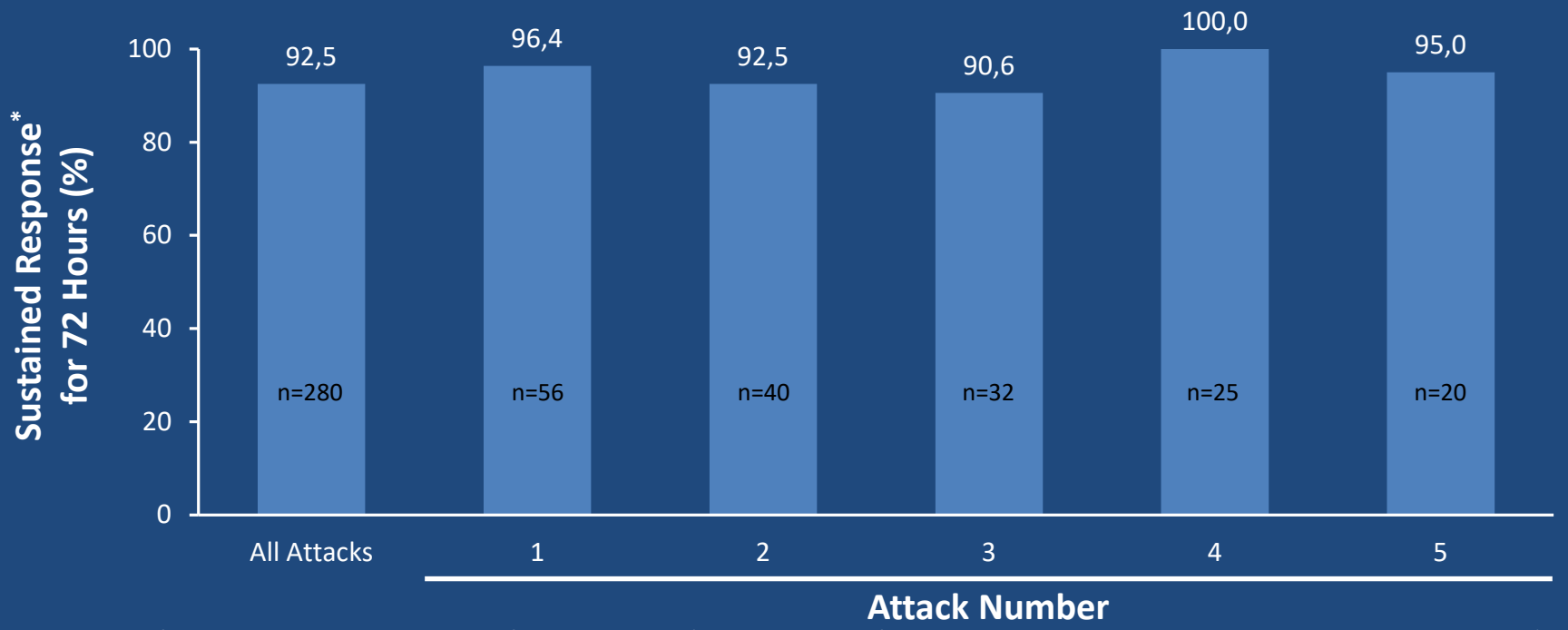
OPL = oropharyngeal-laryngeal; rhC1-INH = recombinant human C1 esterase inhibitor; VAS = visual analog scale.

Bernstein JA, et al. *Ann Allergy Asthma Immunol*. 2017;118(4):452-455.

Figure data from: Bernstein JA, et al. Ann Allergy Asthma Immunol. 2017;118(4):452-455.

rhC1INH: Sustained Response for 72 Hours

- Majority of patients had sustained response* for at least 72 hours, regardless of attack number



*Attacks with 72-hour postdose follow-up data. Sustained response defined as a response (≥20 mm decrease of VAS scores at 2 consecutive time points during 4 hours post-treatment) that was not associated with an increase of ≥20 mm or onset of new attack symptoms (ie, new attack[s] at different location[s]) within 72 hours postdose.

Bernstein JA, et al. *Ann Allergy Asthma Immunol*. 2017;118(4):452-455.

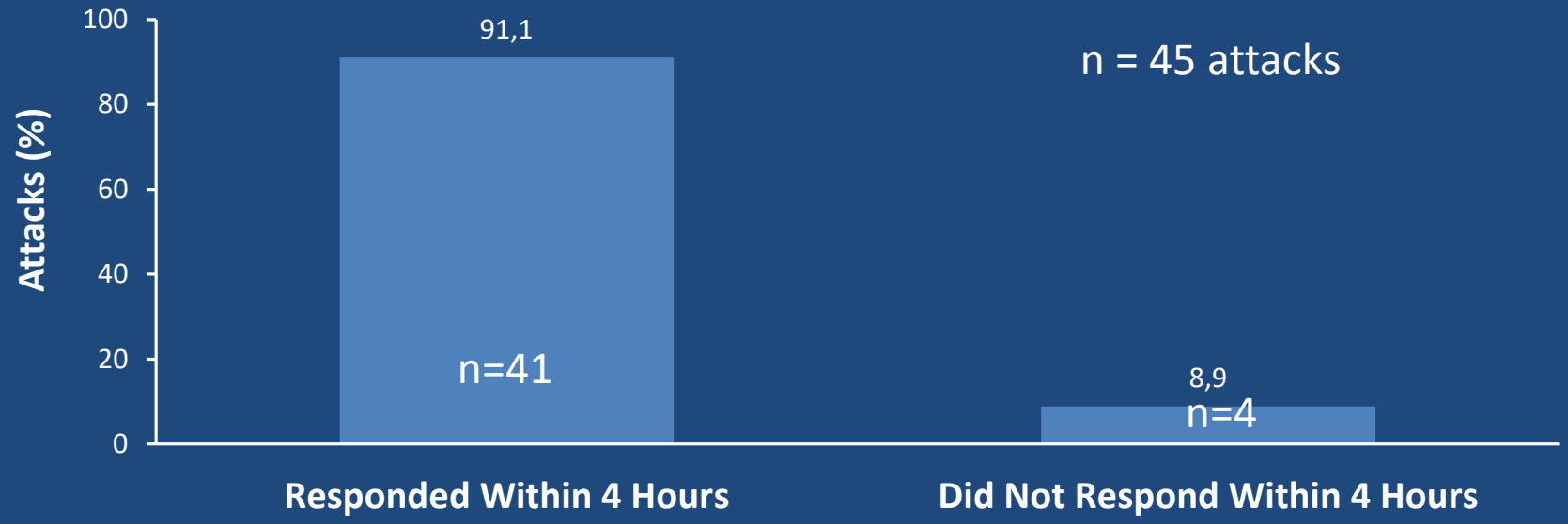
Figure adapted with permission from: Bernstein JA, et al. Ann Allergy Asthma Immunol. 2017;118(4):452-455; additional data from: Bernstein JA, et al. Ann Allergy Asthma Immunol. 2017;118(4):452-455.

Efficacy of rhC1-INH for HAE Attacks Affecting the Upper Airway

Upper Airway HAE Attack (patients)	Number of Attacks	Median Time to Beginning of Relief, min (95% CI)	Median Time to Minimal Symptoms, min (95% CI)
Any attack (n=34)	45	67.0 (60 to 120)	272.5 (240 to 738)
First attack (n=32)	32*	91.5 (62 to 120)	243.0 (240 to 728)
Subsequent attacks (n=5)	10*	63.5 (37 to 481)	900.0 (240 to —)

*Attacks occurring during the OLE phase only, as the number of attacks from the RCT (n = 3) was not sufficient to allow this calculation.
— = not calculable; CI = confidence interval; HAE = hereditary angioedema; OLE = open label extension; RCT = randomized controlled trial; rhC1-INH = recombinant human C1 esterase inhibitor.
Riedl MA, et al. *Allergy Asthma Proc.* 2017;38(6):462-466.
Table reprinted with permission from: Riedl MA, et al. Allergy Asthma Proc. 2017;38(6):462-466.

Upper Airway Symptom Relief* Within 4 Hours



- Time to beginning of symptom relief in the 4 HAE attacks with upper airway involvement not responding within 4 hours was:
  - Approximately 8 hours (465 to 481 min; n=3) to 12 hours (719 min; n=1)
- No upper airway HAE attack required other additional medication or surgical intervention

*VAS score decreased from baseline by ≥20 mm for 2 consecutive time points (persistence).
HAE = hereditary angioedema; VAS = visual analog scale.
Riedl MA, et al. *Allergy Asthma Proc.* 2017;38(6):462-466.
Figure data from: Riedl MA, et al. Allergy Asthma Proc. 2017;38(6):462-466.

WAO Guidelines: Prophylactic Treatment Recommendations

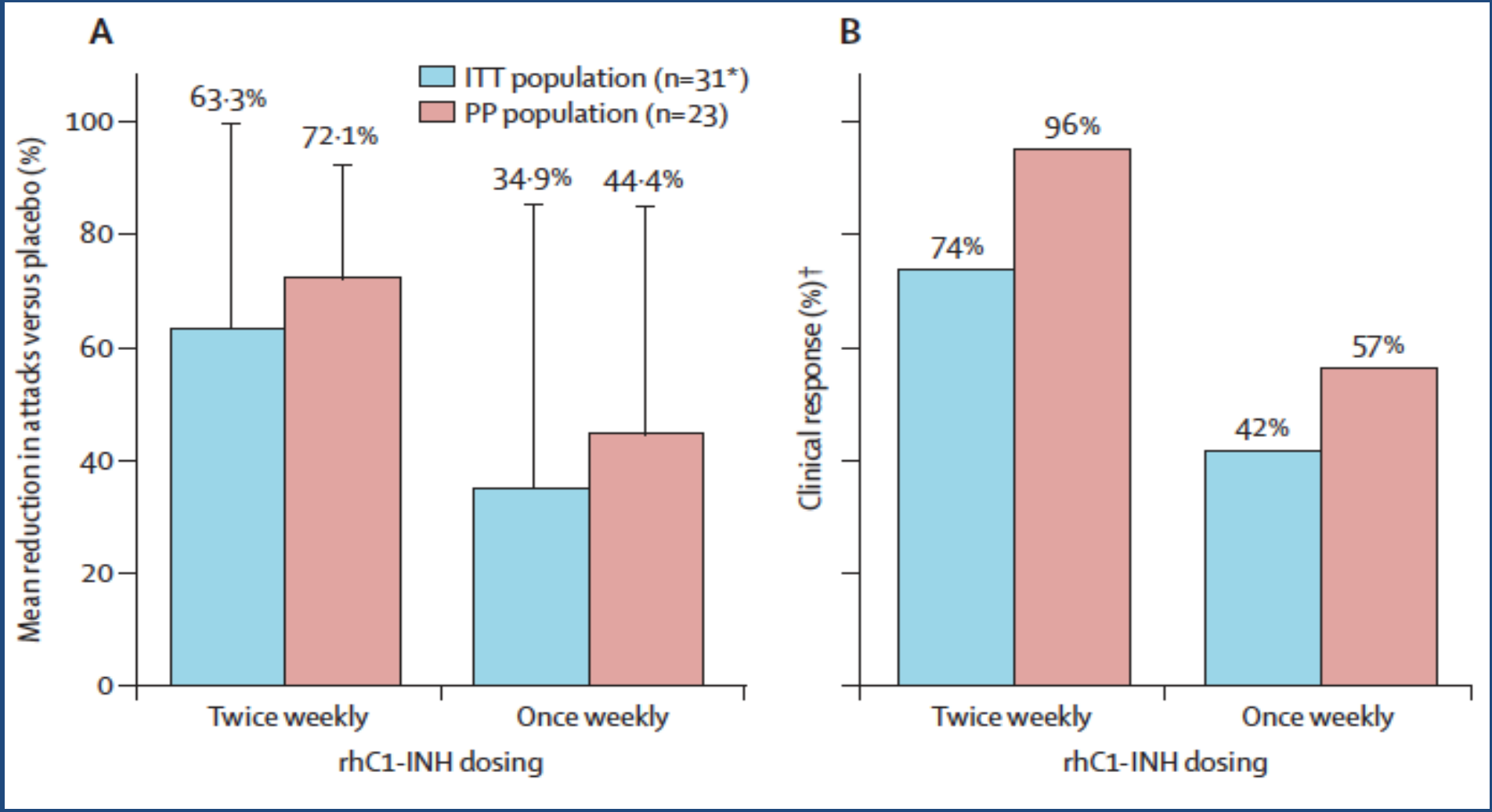
- Patients are evaluated for long-term prophylaxis at every visit. Disease burden and patient preference should be taken into consideration (100% agreement)
- Use of C1-Inhibitor for first line long term prophylaxis (50-75% agreement)
- Suggest to use androgens as second-line long-term prophylaxis (50-75%)
- Suggest adaptation of long-term prophylaxis in terms of dosage and/or treatment interval as needed to minimize burden of disease (100%)

Maurer M, et al. Allergy. 2018

FDA-Approved Prophylactic HAE Therapies

Drug	Potential Safety Concerns	Disadvantages	Advantages	Status
Plasma-derived C1-INH (Intravenous)	• Infectious risk • Potential infusion reactions • Thrombosis	• Needs IV access • Dependent on plasma supply	• Extensive clinical experience • Relatively long half-life	• **Cinryze®:** Approved in USA for HAE long-term prophylactic therapy; in Europe for acute and prophylactic treatment[1,2]
Plasma-derived C1-INH (Subcutaneous)	• Infectious risk • Potential infusion reactions • Thrombosis	• Local infusion site reactions • Dependent on plasma supply	• Improved steady-state C1INH levels • No IV access required	• **Haegarda®:** Approved in USA for long-term prophylactic treatment
Attenuated Androgens	• Hepatic toxicity, elevated LDL, weight gain, hypertension •Virilization, amenorrhea •Psychological effects	• Adverse effects • Contraindicated in pregnancy, lactation, children, oncologic conditions	• Oral medication	• **Danazol®:** Approved in the USA for prophylactic HAE therapy

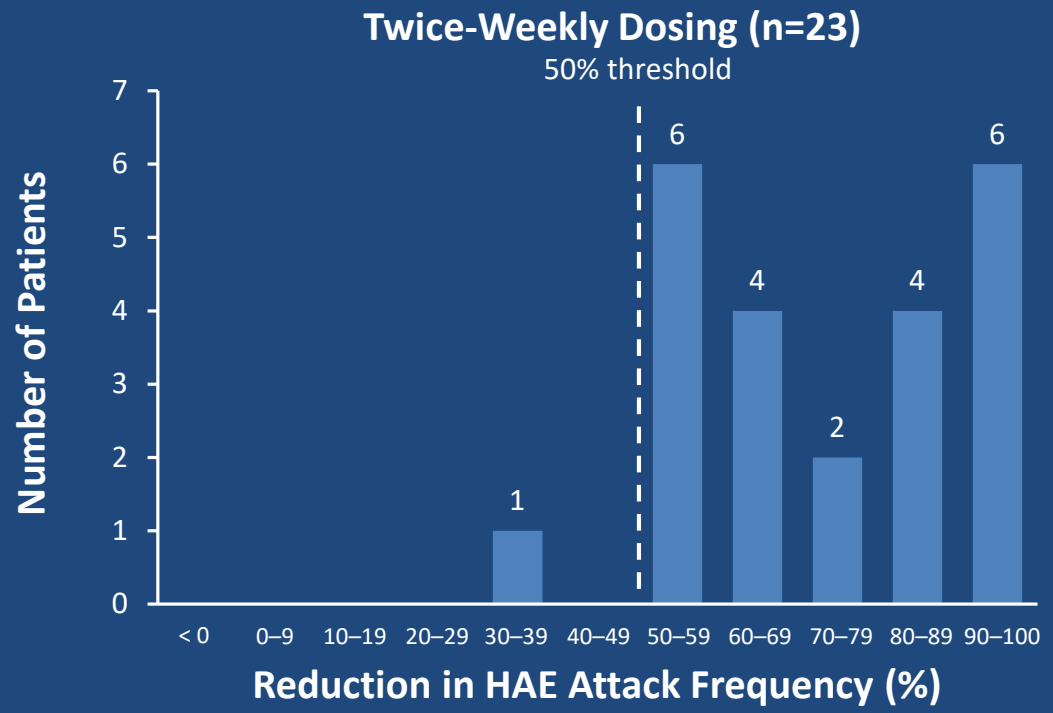
Recombinant C1-INH for HAE Prophylaxis

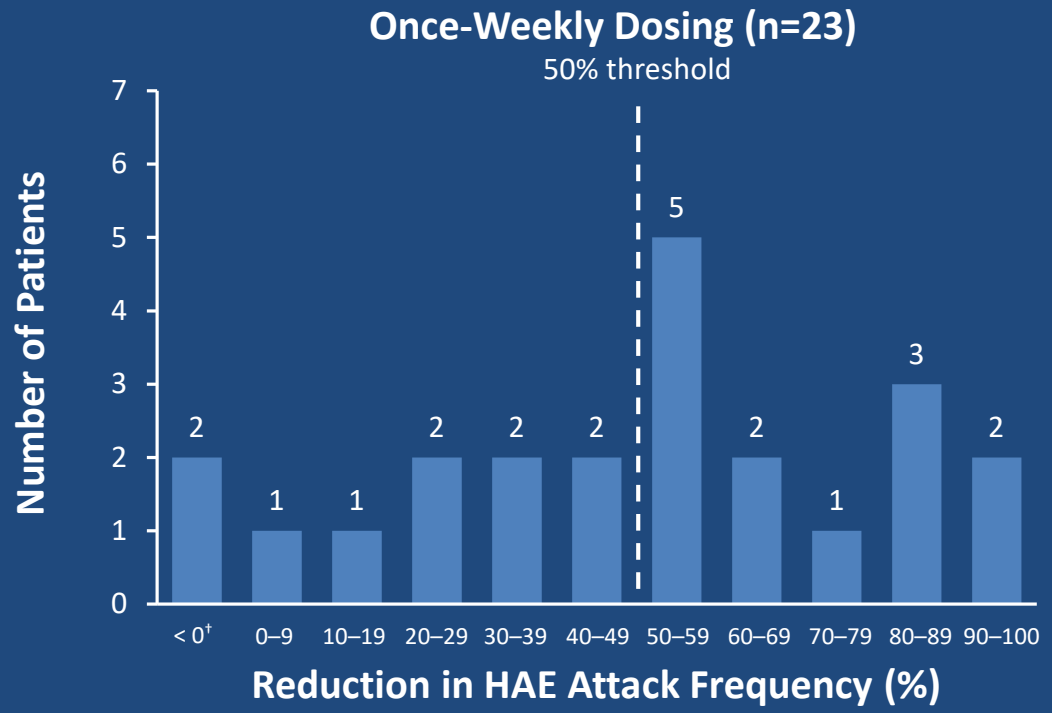


Riedl M. *Lancet*. 2017 Sep 30;390(10102):1595-1602.

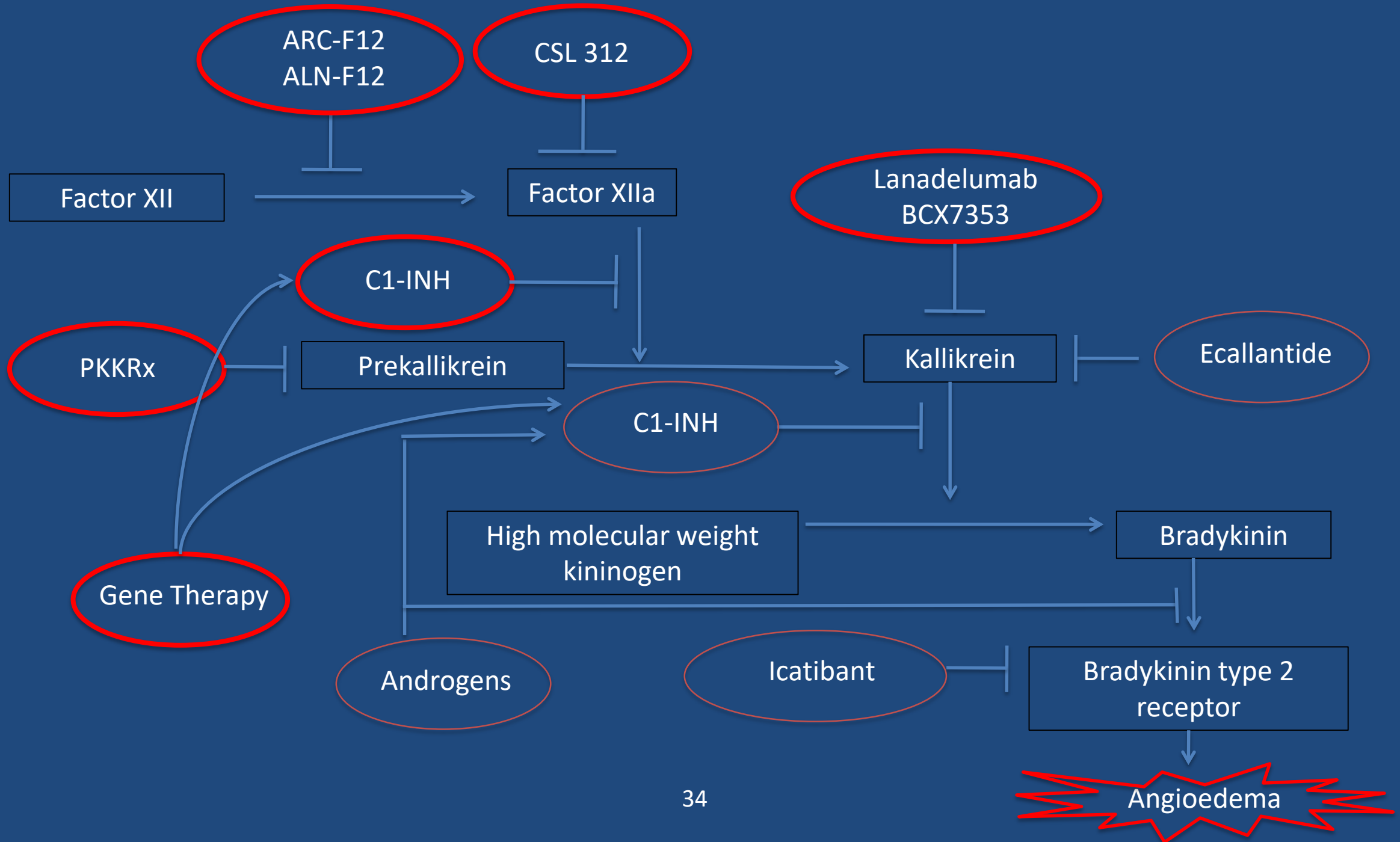
Clinical Response Frequency (PP Population)

- Achievement of clinical response* more consistent with twice-weekly dosing of rhC1-INH





*Defined as a ≥50% reduction in the number of HAE attacks that occurred during rhC1-INH treatment versus attacks that occurred during placebo treatment.
†Two patients had an increase in HAE attack frequency while receiving once-weekly rhC1-INH prophylaxis (one patient had an increase of 40%, and one patient had an increase of 62.5%).
HAE = hereditary angioedema; PP = per protocol; rhC1-INH = recombinant human C1 esterase inhibitor.
Riedl MA, et al. *Lancet.* 2017;390(10102):1595-1602.
Figures reprinted with permission from: Riedl MA, et al. Lancet. 2017;390(10102):1595-1602.

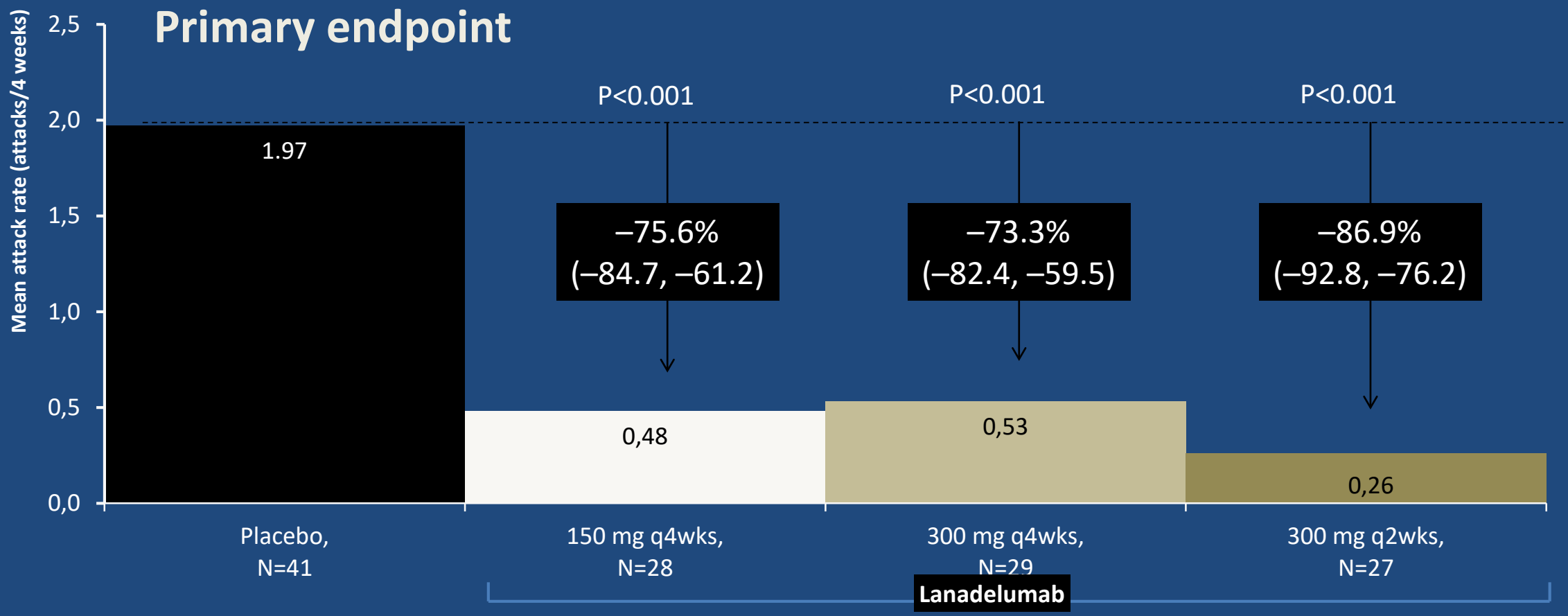

ARC-F12
ALN-F12
CSL 312
Factor XII
Factor XIIa
Lanadelumab
BCX7353
C1-INH
PKKRx
Prekallikrein
Kallikrein
Ecallantide
C1-INH
High molecular weight kininogen
Bradykinin
Gene Therapy
Androgens
Icatibant
Bradykinin type 2 receptor
Angioedema

In Development: Prophylactic HAE Therapy

- PHASE 3
  - Monoclonal Antibody: Plasma kallikrein
- PHASE 2
  - Oral kallikrein Inhibitor
- Earlier Phase Development
  - Additional oral kallikrein inhibitors
  - RNAi-based treatment
    - Prekallikrein
    - Factor XII
  - Monoclonal Antibody: Factor XII
  - Gene Therapy

- More effective?
- Safer?
- More convenient?
- Cost?

Lanadelumab Phase 3 Study Results: Reduction in Mean HAE Attack Rates



Attack rates are presented as attacks/4 weeks (95% CI). Results are from a Poisson regression model; treatment group and normalized baseline attack rate were fixed effects and the logarithm of time (days) each patient was observed during the treatment period was an offset variable.

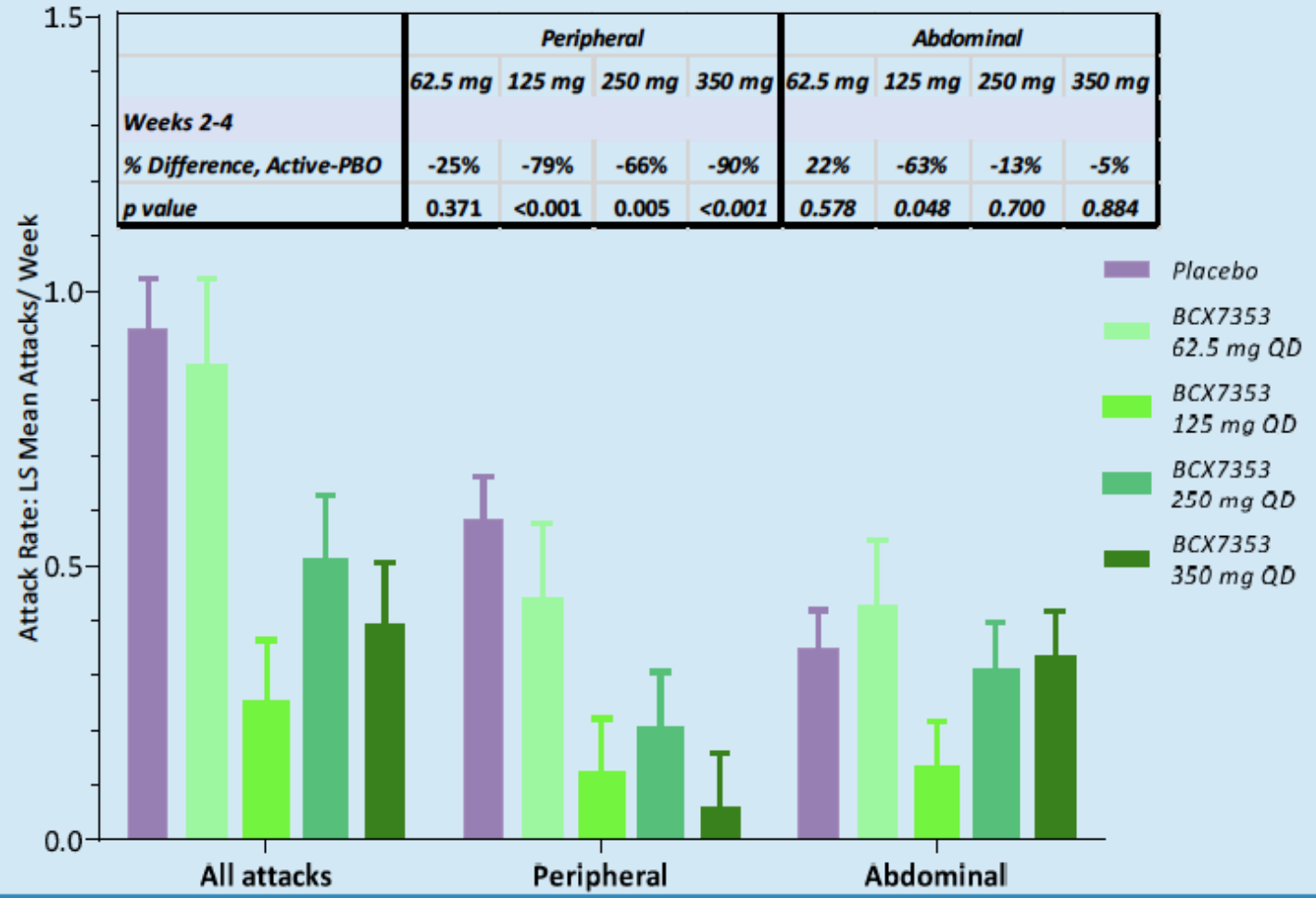
q4wks = every 4 weeks; q2wks = every 2 weeks.

Banerji A. Presented ACAAI October 2017. Boston, MA.

BCX-7353: Oral Kallikrein Inhibitor Phase 2 Results

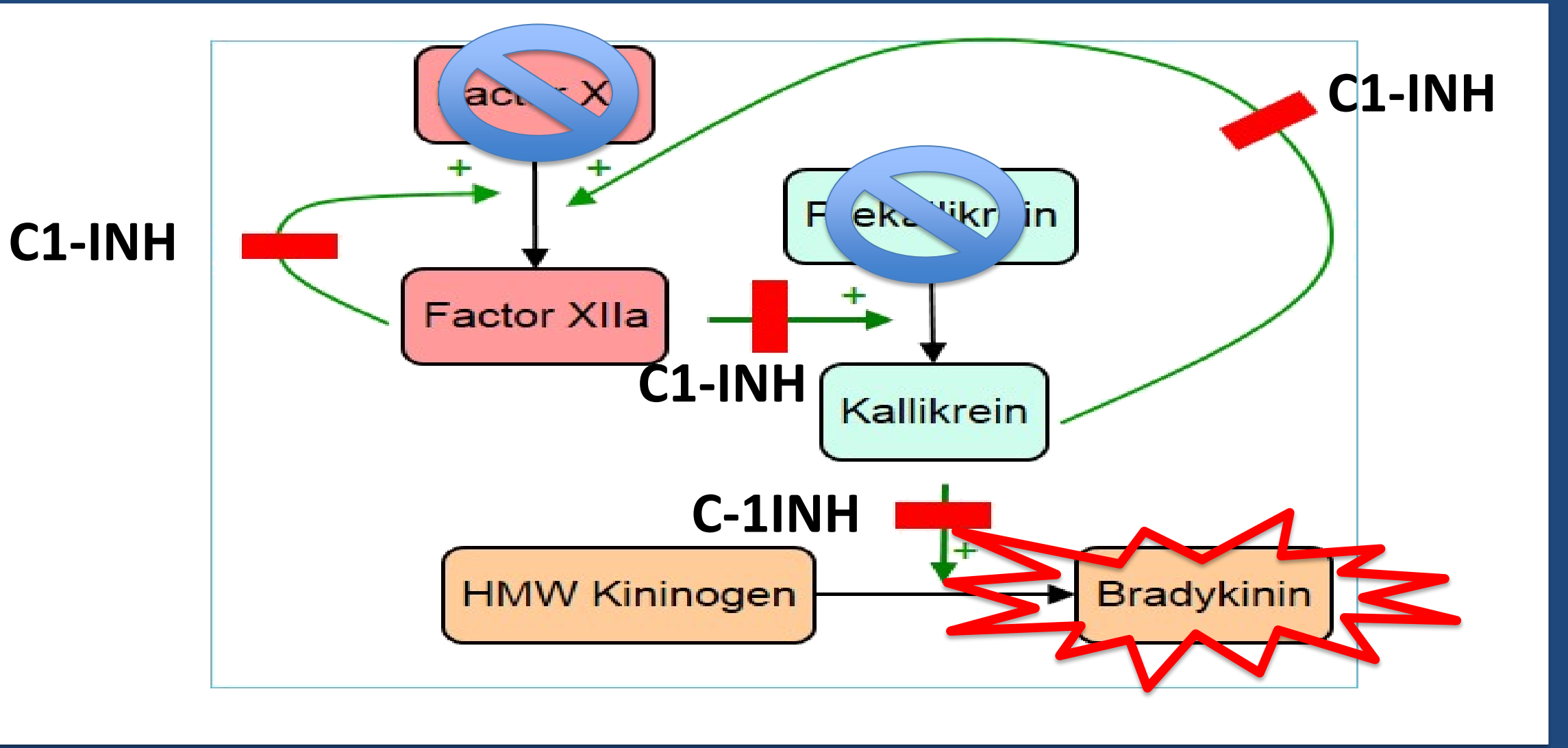
Attack rate by anatomical location - PP

	Peripheral				Abdominal			
	62.5 mg	125 mg	250 mg	350 mg	62.5 mg	125 mg	250 mg	350 mg
Weeks 2-4								
% Difference, Active-PBO	-25%	-79%	-66%	-90%	22%	-63%	-13%	-5%
p value	0.371	<0.001	0.005	<0.001	0.578	0.048	0.700	0.884



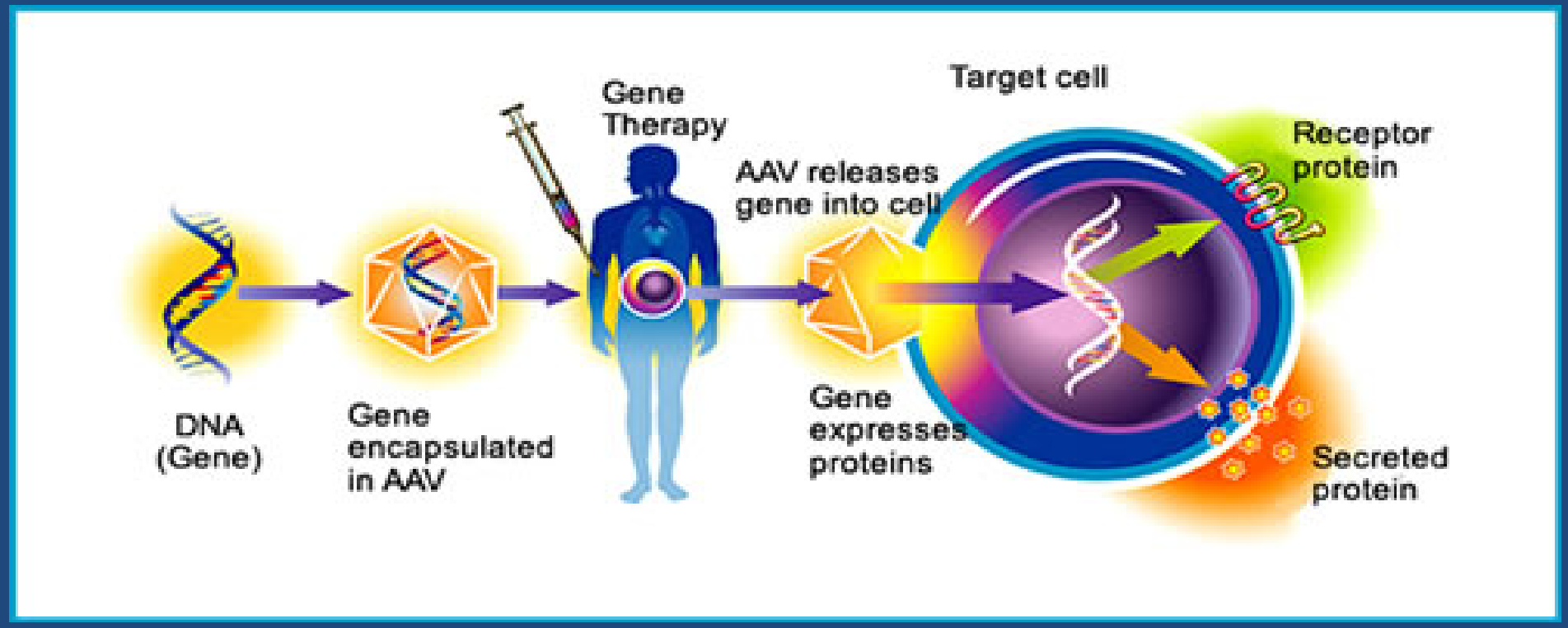
Aygören Pürsün E. Presented ACAAI October 2017. Boston, MA

RNA-Targeted Treatment for Hereditary Angioedema



Gene Therapy for HAE

- Animal studies show successful C1INH expression
- Gene therapy – AAV based gene transfer (ANN-002)



Summary: Advances in HAE

- Reduction in misdiagnosis and diagnostic delays
- Treatment guideline emphasis on access to modern effective FDA-approved medications: acute and prophylactic
- Improved safety, efficacy, tolerability of prophylactic agents
- Increased emphasis on quality of life

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Pharming

The USA HAE Market from Pharming's Perspective

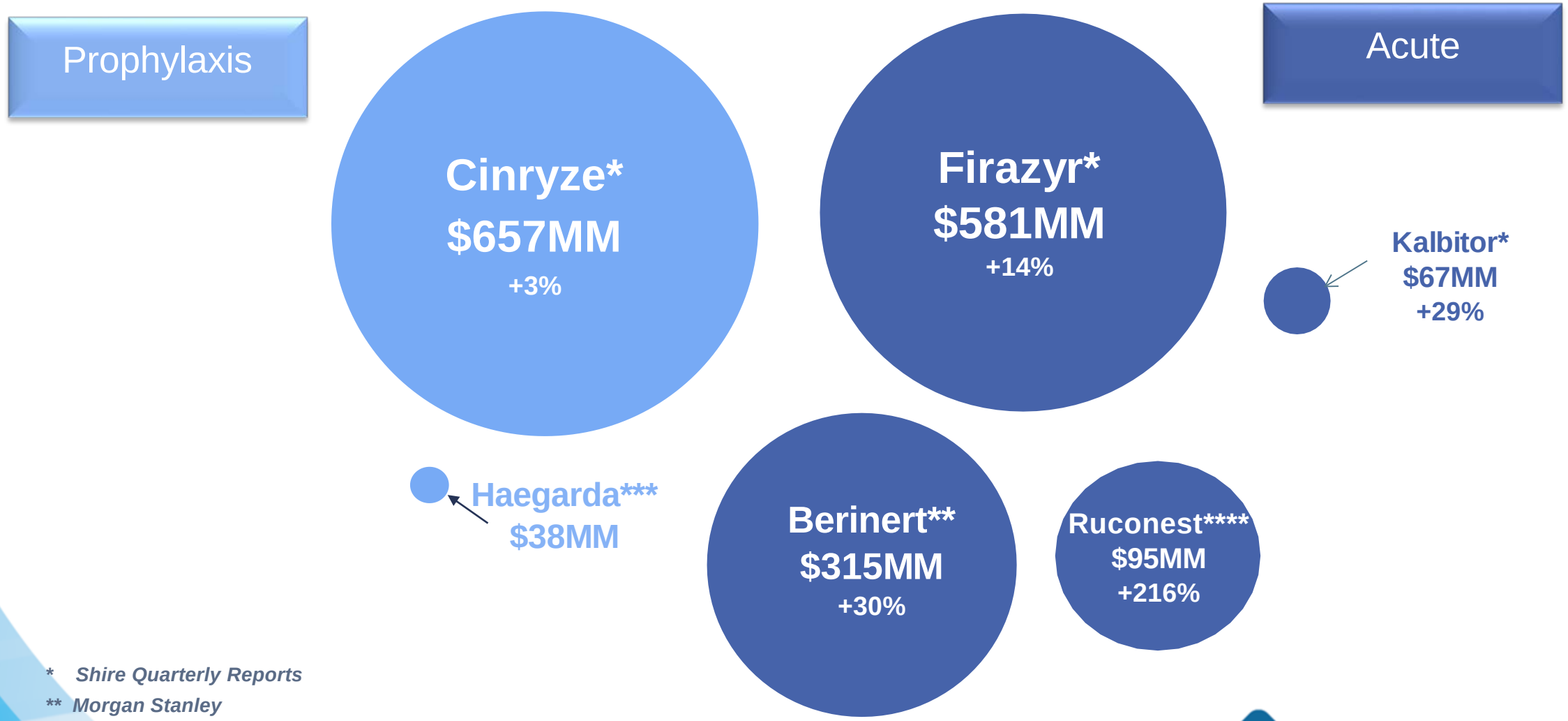
Stephen Toor

General Manager, Pharming Americas Region

Pharming

US Market for HAE drugs: ~$1.7 billion sales in 2017

(Year-on-year growth 17%)



* *Shire Quarterly Reports*

** *Morgan Stanley*

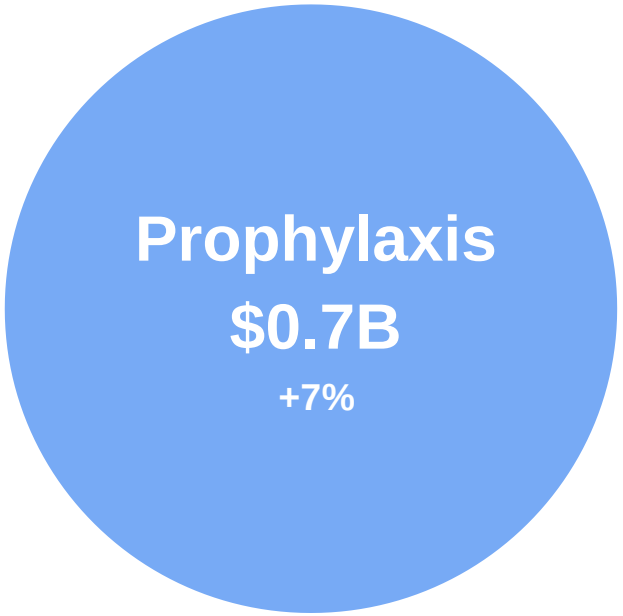
*** *Evaluate Pharma*

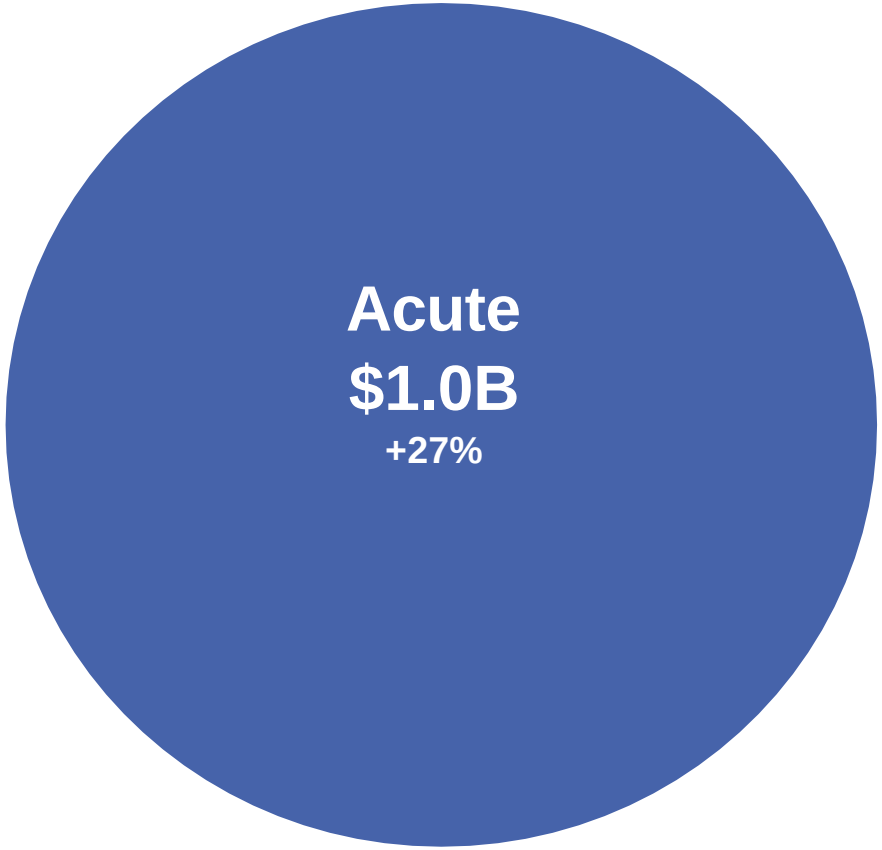
**** *Pharming Reported Net Sales*

Pharming

Current US market breakdown, Prophylaxis vs Acute treatment

FDA Approval Dates	
Cinryze	October, 2008
Berinert	October, 2009
Kalbitor	December, 2009
Firazyr	August, 2011
Ruconest	November, 2014
Haegarda	June, 2017

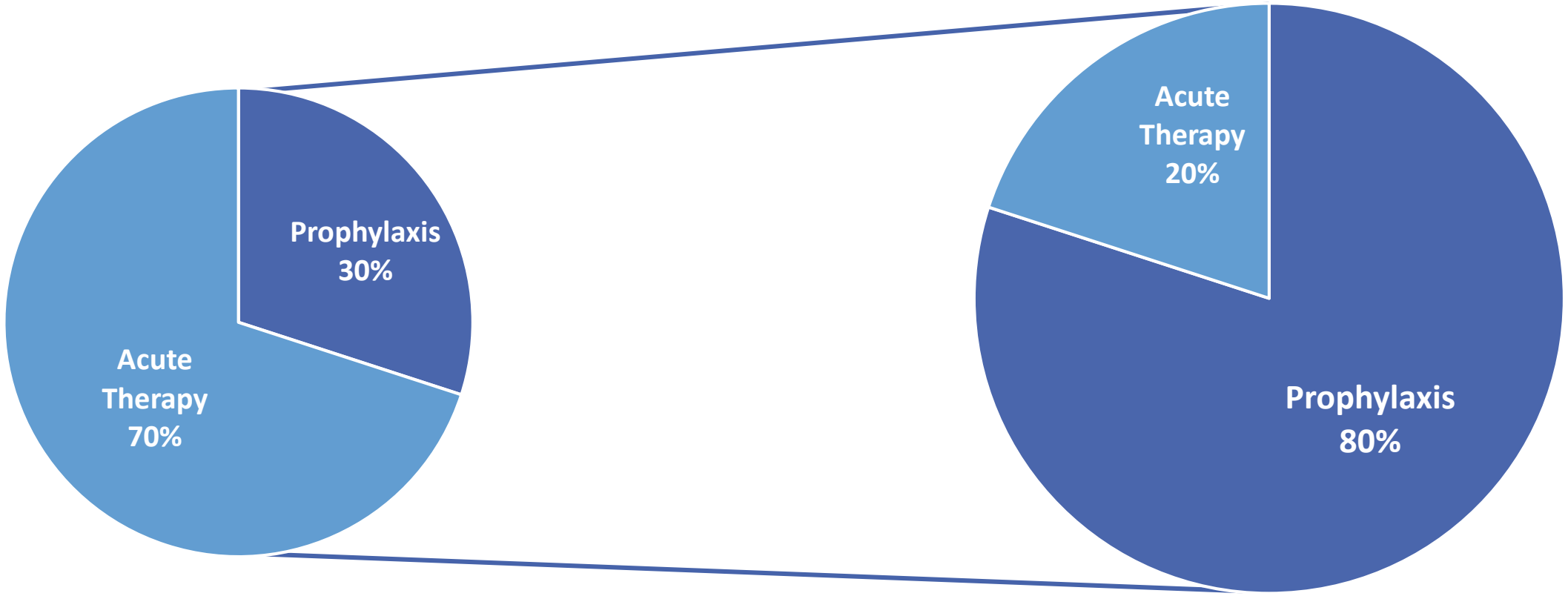




** Market sizes based on Corporate Quarterly Reports, Morgan Stanley and Evaluate Pharma*

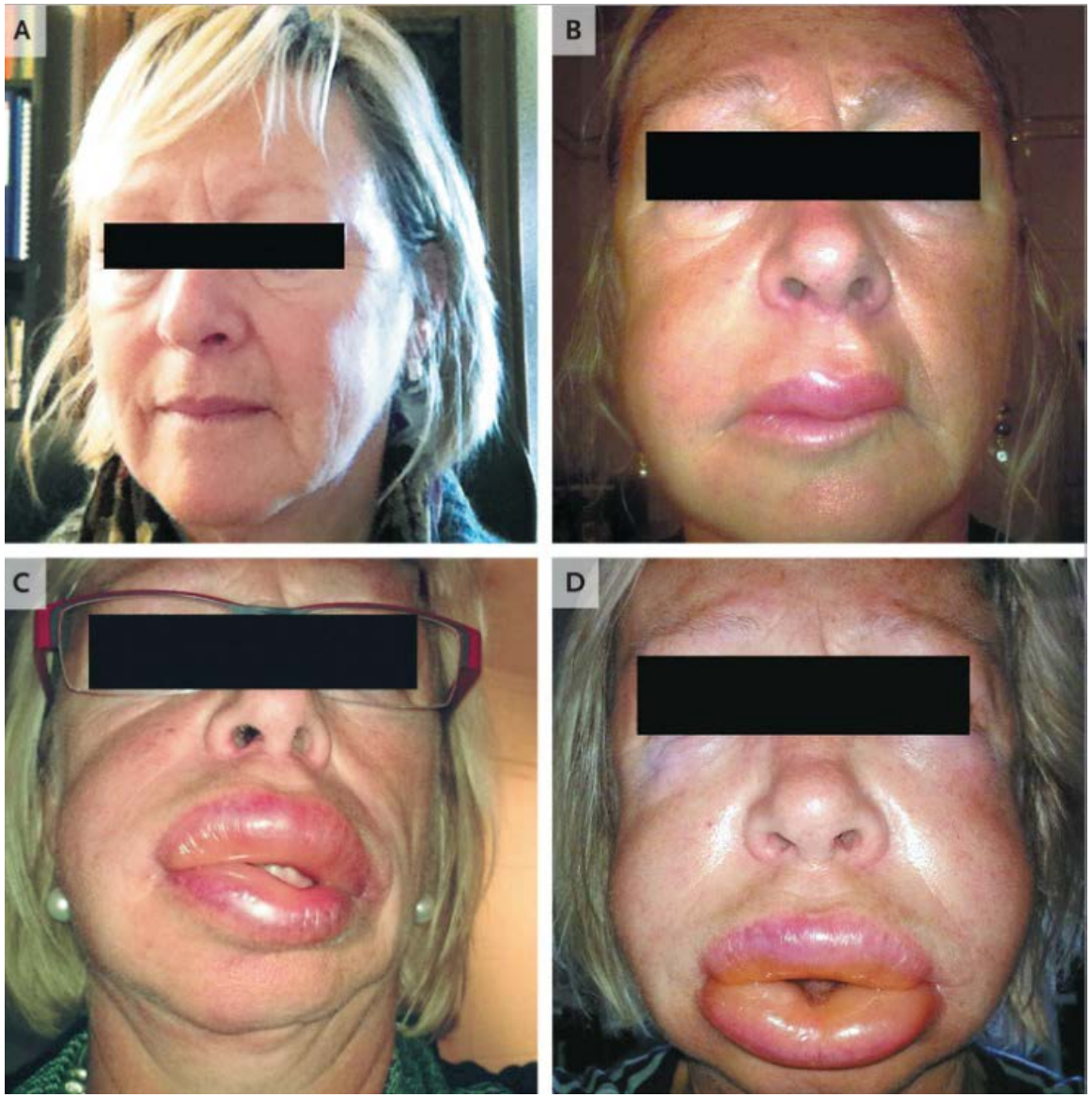
Pharming

Majority of US patients expected to be on prophylaxis within 5 years



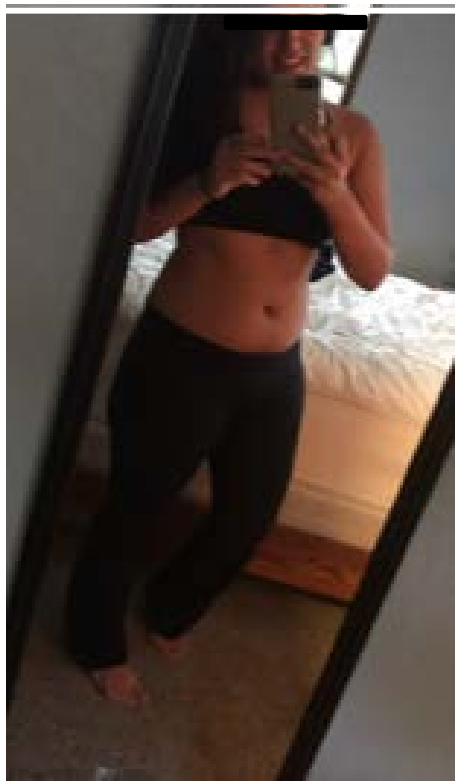
Pharming

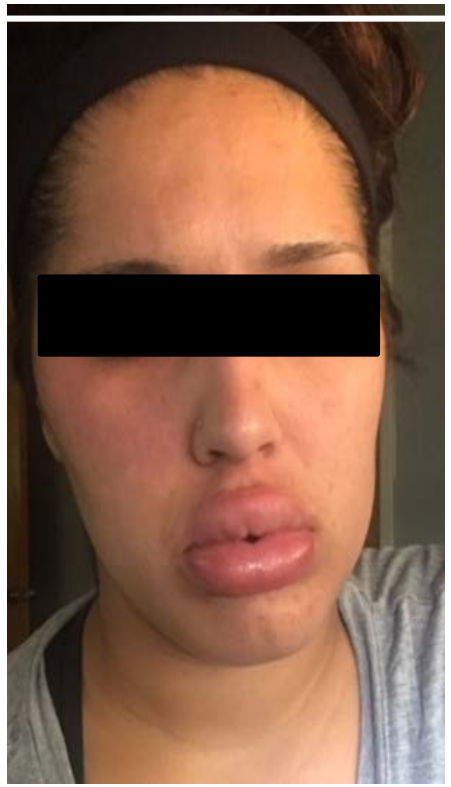
Adult patient before and during a facial attack



Pharming

Ruconest patient before & after treatment





Pharming

RUC-US-2017-0136

What patients want when living with HAE

Patients want to be attack free

"I was just so sick I became depressed. I was just like, 'What is the point of living like this?'. … I wondered, 'Is this really worth the battle? Is the type of lifestyle I want to live?"

Patients want to live normal lives

"My coworkers never know how I'm fighting to be normal… to still be able to be successful at my job… they don't know what I go through."

"We have to be real careful when we leave the house because … you never know when an attack's going to happen. … We don't travel."

Patients want a therapy that is convenient and pain-free

"My veins are shot, so I inject my medicine in my stomach. It is so painful and my stomach has bruises everywhere. I wish I had a medicine that didn't hurt and was quick and easy to use."

Pharming

RUC-US-2017-0136

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Pharming

Building the Ruconest Franchise in HAE

Dr Anurag Relan
Head of Clinical Research and Medical Affairs, Pharming Group

Pharming

Hereditary Angioedema (HAE)

Pharming

What is RUCONEST®?

- RUCONEST® = Recombinant human C1 esterase inhibitor (rhC1INH)
- C1 Esterase Inhibitor is a major part of the braking system for inflammation in the body
- RUCONEST® has an identical amino acid sequence to that of endogenous C1-INH in humans
- Same binding affinity to target-proteases and the highest purity of all available C1-INHs
- No risk of blood-borne pathogens
- EMA approval 2010, FDA approval 2014
- More than 70,000 post-marketing doses administered – safe and well-tolerated
- Strong know-how protection and data exclusivity until July 2026
- Easily scalable supply to match future demand; unlike plasma-derived C1-INH versions

Pharming

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RUCONEST is the only C1-INH that is not dependent on human plasma donations to treat HAE[1]

Product	Dose	Source	Per dose	Required for 1 patient for a year	
			Human donations	Human donations/yr (2 doses/week)	Total amount of plasma/yr
Berinert®[2]	20 IU/kg	Plasma	5	Varied	Varied
Cinryze®[3]	1000-2500 IU	Plasma[a]	3-8	300-750	0.2-0.6 tons
Haegarda®[4]	60 IU/kg	Plasma	15	1500	1.2 tons
RUCONEST[1]	50 IU/kg	Recombinant	0	0	0

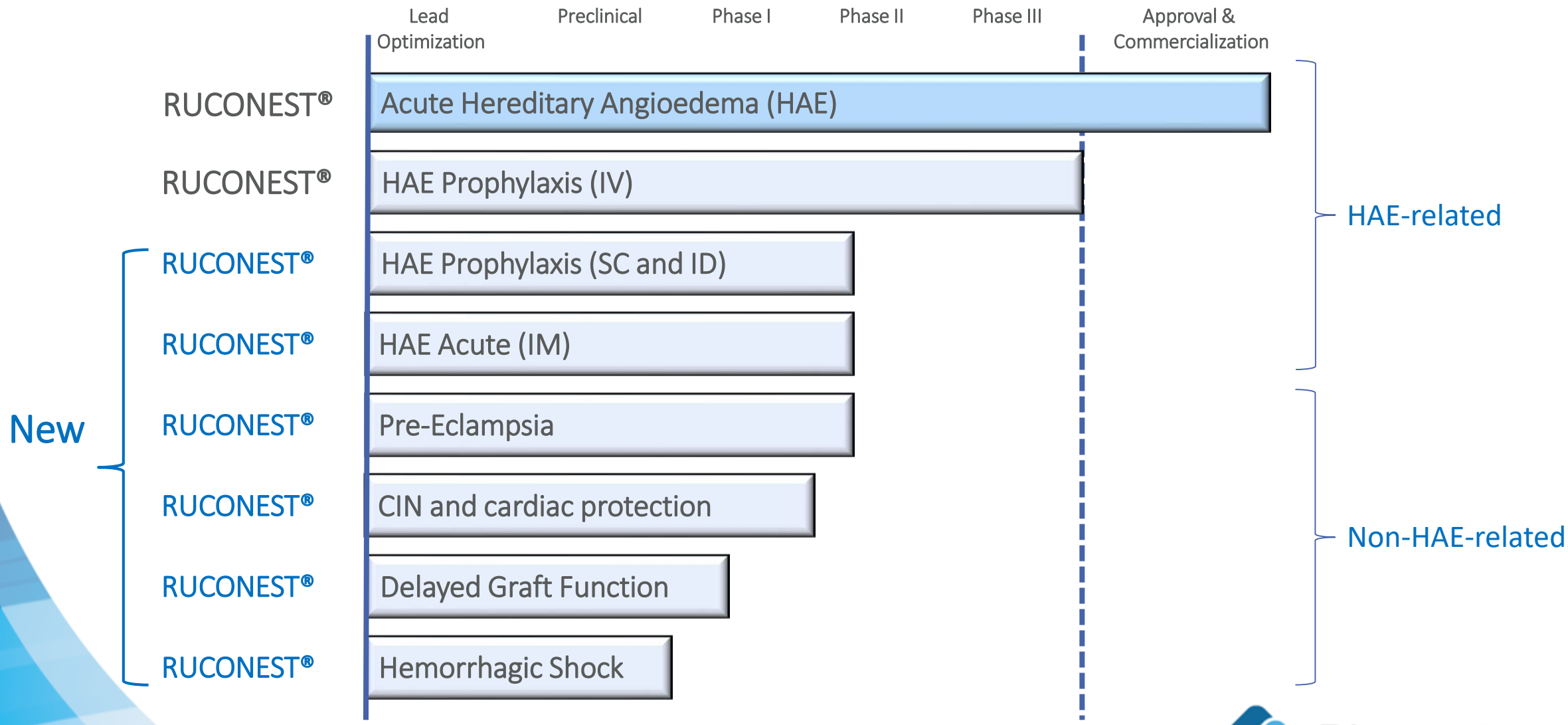
[a] Plasma yield ranges from 20%-50% (assumed 50%).[5,6]

Information presented only to show how various products are sourced; it is not intended to suggest comparative safety or efficacy.

1. RUCONEST [package insert]. **2**. Berinert [package insert]. Kankakee, IL: CSL Behring LLC; 2016. **3**.Cinryze [package insert]. Lexington, MA: Shire ViroPharma Incorporated; 2016. **4.** Haegarda [package insert]. Kankakee, IL: CSL Behring LLC; 2017. **5.** Feussner A, et al. *Transfusion.* 2014;54(10):2566-2573. **6.** Over J, et al. *Production of Plasma Proteins for Therapeutic Use*; 2013.

Pharming

Expansion of RUCONEST® to a multiple market franchise



Pharming

Treatment of HAE Attacks with RUCONEST® :

Most Patients Have Symptom Relief With Just 1 Dose:

UP TO 97% OF PATIENTS

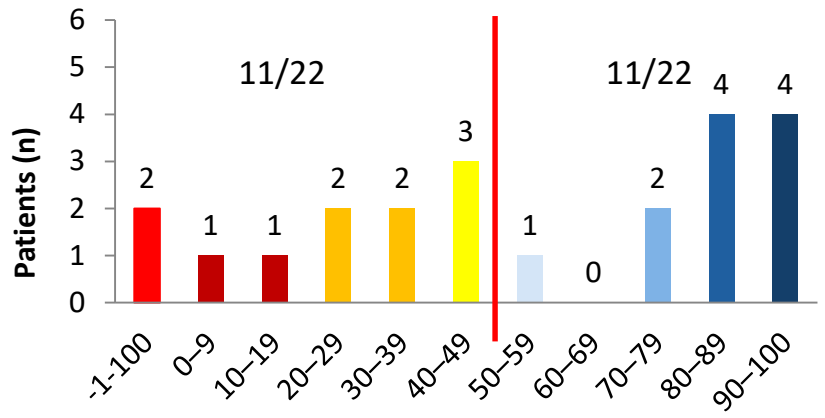
achieved symptom relief with **JUST ONE 50 IU/kg dose** of RUCONEST (n=44)

- **89%** of patients needed just one 50 IU/kg dose of RUCONEST per attack in a clinical study
- **97%** of attacks needed just one 50 IU/kg dose in an extension of the clinical study
- Ongoing investigator-initiated study of therapy failure rates head-to-head between RUCONEST® and icatibant (*Firazyr*®), due to report later in 2018

Source: RUCONEST® [package insert].

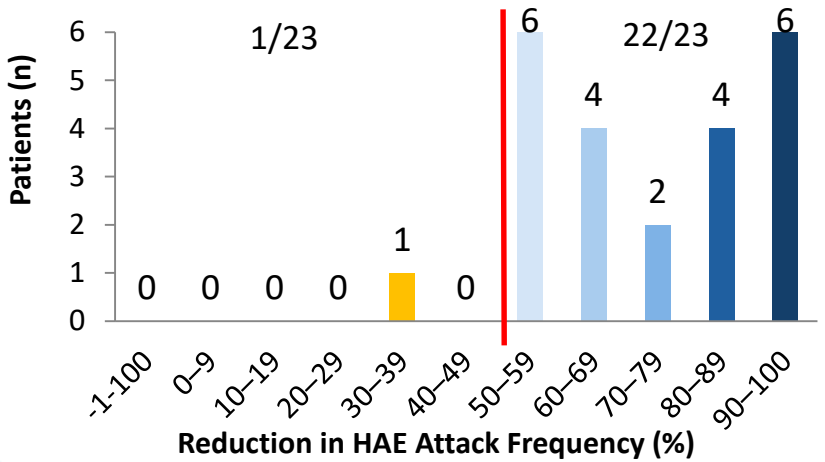
Pharming

Comparing published results on HAE Prophylaxis



Cinryze® (1000 U Twice weekly)

- Varying reduction of HAE attack frequency
- 12.7 attacks (placebo) vs 6.1 (Cinryze - pooled data across 12 weeks)
- 50% clinical response
- 52% reduction in attacks



RUCONEST® (50 U/kg Twice weekly)

- Heavily affected patients (average 7.2 attacks/month)
- Consistent reduction in attack frequency (n=23)
- 95.7% clinical response (all but one)* (PP)
- 74% reduction in attacks (PP)

*Patients who had ≥50% reduction in the number of HAE attacks (normalized for the number of days the patient participated in the treatment period) from the placebo treatment period to the rhC1INH treatment period.

Source: Published data, US Food & Drug Administration

Pharming

RUCONEST® in HAE: More convenient, Better control

- Generally effective, safe and well-tolerated
- Ongoing approval process in pediatrics and prophylaxis
- Developments planned with new formulations, including:
  - Subcutaneous for prophylaxis of HAE attacks
  - Intramuscular for the treatment/prophylaxis of HAE attacks and
  - Intradermal device/patch for prophylaxis and/or HAE attacks
- Following FDA approval for prophylaxis: Would be only product approved for both acute HAE and prophylaxis of HAE

Pharming

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RUCONEST®: Developing better and painless formulations for SC/ IM/ ID

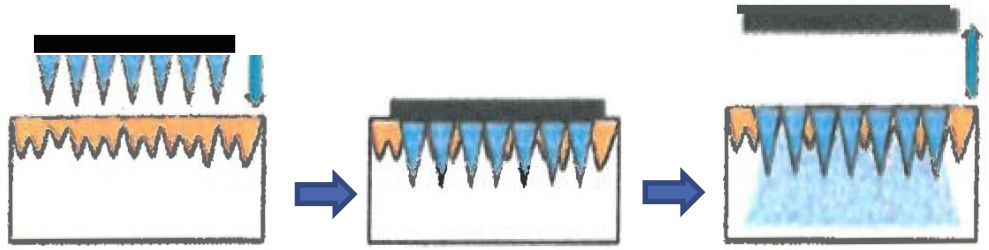
- RUCONEST® line extension: vial containing 1000 U of rhC1INH (pediatric use)
- "RUCONEST®lite": vial containing 2100 Units lyophilized rhC1INH to be dissolved in 3 ml water
  - Reconstitution time: 3 minutes (5-6 minutes for normal RUCONEST®) (convenience)
  - Entering the final phase of clinical preparation for filing IND
- "RUCONEST® Liquid": ready to use 3 ml vial containing > 500 U/ml, in final development (convenience)
- "RUCONEST®lite" or "RUCONEST® Liquid" could be used for the IV or, subject to regulatory approval, future IM treatment of HAE attacks or SC or ID prophylaxis of HAE attacks
- Required clinical studies expected to start later this year

Pharming

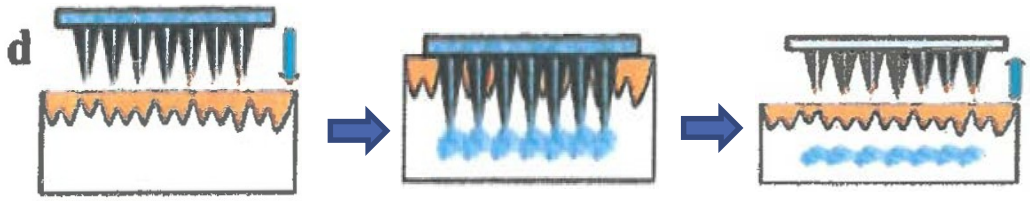
New intradermal formulations with RUCONEST®

- The “RUCONEST®liquid” formulation can be used as starting material for the generation of intradermal application systems
- New proprietary ‘painless’ intradermal delivery applications are being developed:

- Dissolving point device:



- Reservoir device:



- These painless versions will differentiate RUCONEST® from competitors, all of whom have painful injections
- New IP filed on microinjector device combination earlier this year

Pharming

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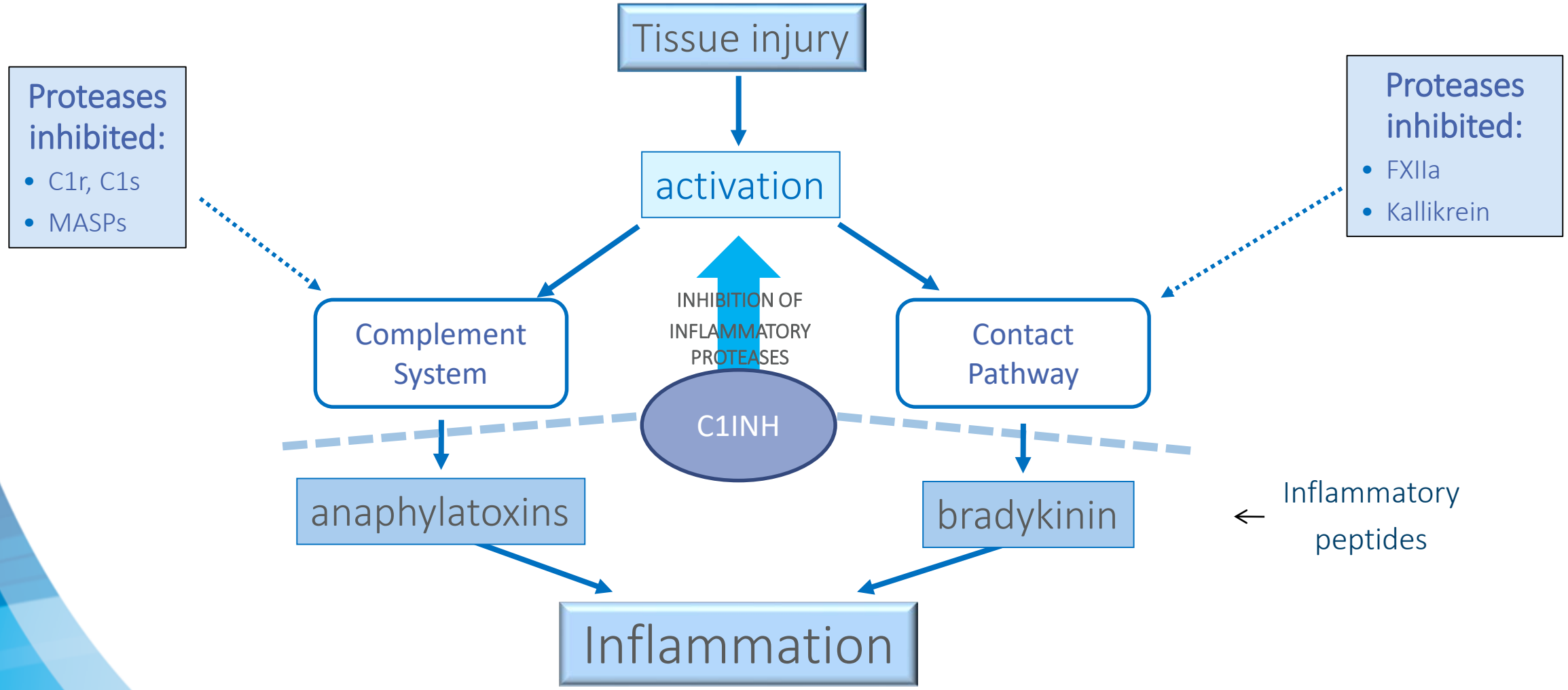
Pharming

rhC1INH: Indications beyond HAE (RUCONEST® or variant)

Professor Bruno Giannetti
Chief Operating Officer, Pharming Group

Pharming

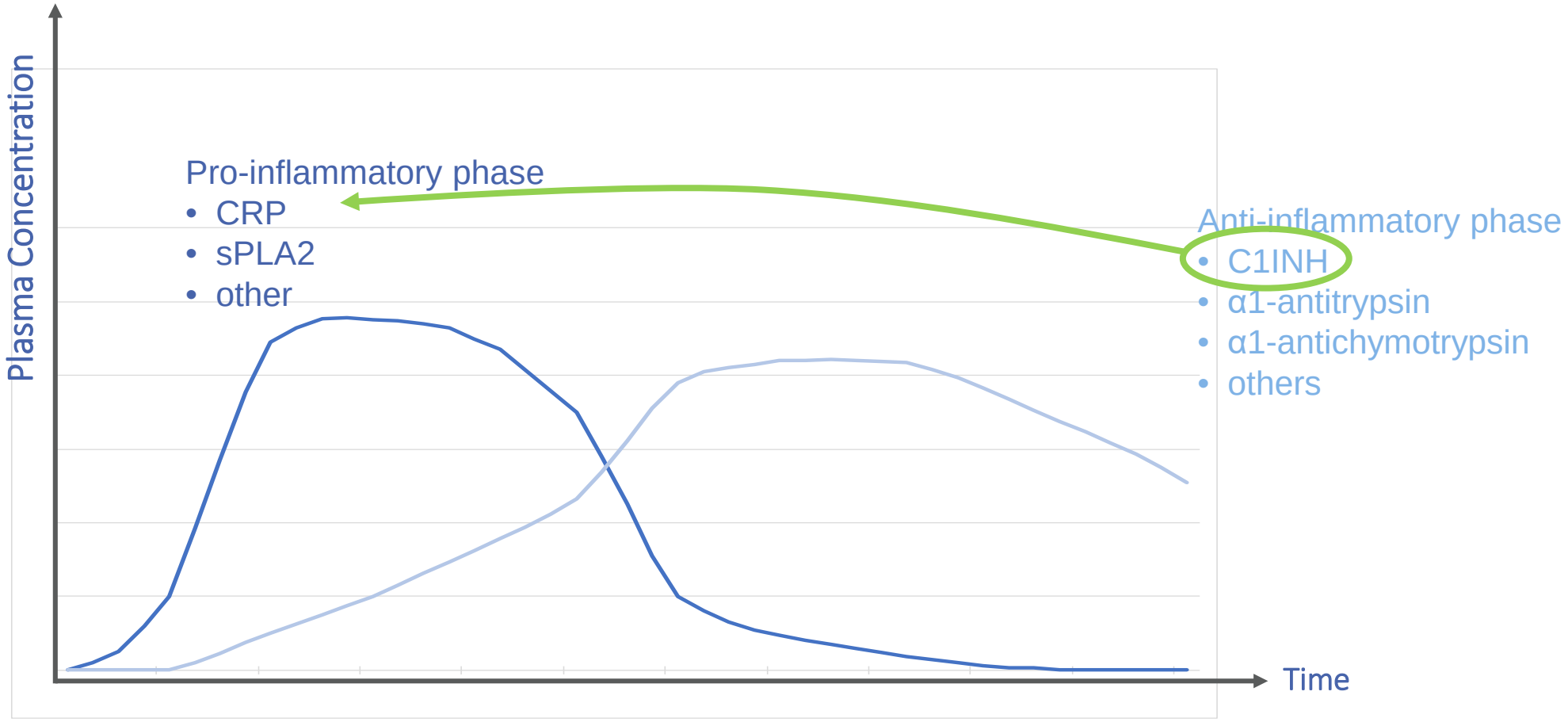
C1INH : Multiple Anti-inflammatory Effects



Pharming

Other potential indications for rhC1INH

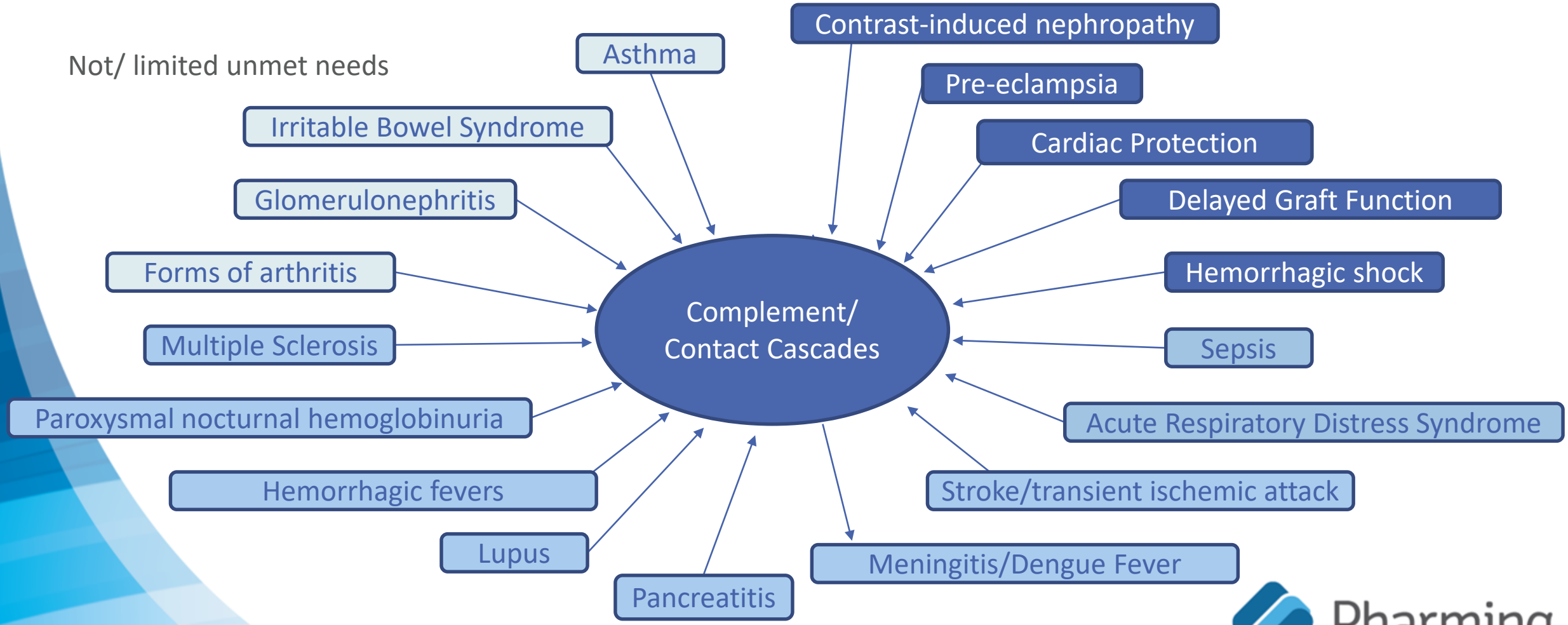
C1INH appears to slow inflammatory response and limit tissue damage



Pharming

Other potential options for development of rhC1INH

- The complement and contact systems are known to play a role in many diseases with an immune component, such as:



Pharming

New Activities with rhC1INH

Initial Therapeutic Indications selected:

- New Potential Indications using existing formulation
  - Tissue Damage after Toxic Event :- **Pre-eclampsia** (new Pharming)
  - Tissue Damage after Hypoxic Event :- **Delayed Graft Function** (new investigator-initiated study (IIS))
  - Organ damage after contrast media application:- **Contrast-induced Nephropathy** (ongoing IIS)
  - Vascular/cardiac damage due to investigation/operation:- **Cardiac protection** (depends on data from above study)
  - Shock response after trauma:- **Hemorrhagic Shock** – ongoing preclinical research projects with US Army and US Air Force

Brand New IP:

  - New Pharming patents filed in 2018 covering the new indications
  - Patents cover all forms of C1INH

Pharming

Agenda

Pharming

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Pharming

Recombinant human C1 esterase inhibitor in the treatment of Pre-eclampsia

- Professor Gustaaf Dekker

School of Obstetrics & Gynaecology
University of Adelaide, Australia

Pharming

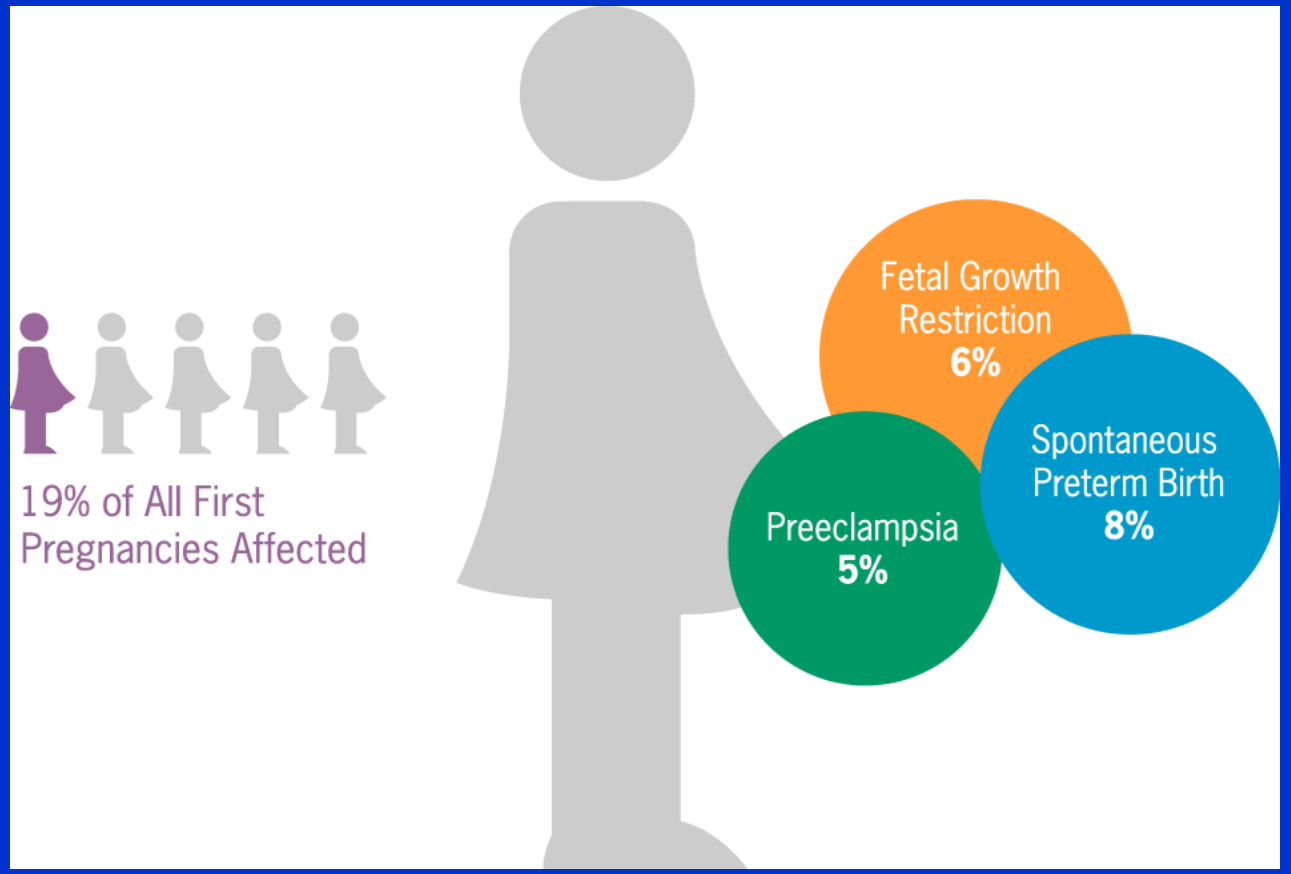
Preeclampsia
an Inflammatory Syndrome

New York June 2018

Gus Dekker,
University of Adelaide

introduction

Three Major Diseases of Late Pregnancy



INCIDENCES

hypertension of pregnancy	7-13%
preeclampsia	3-5%
eclampsia	< 1%*

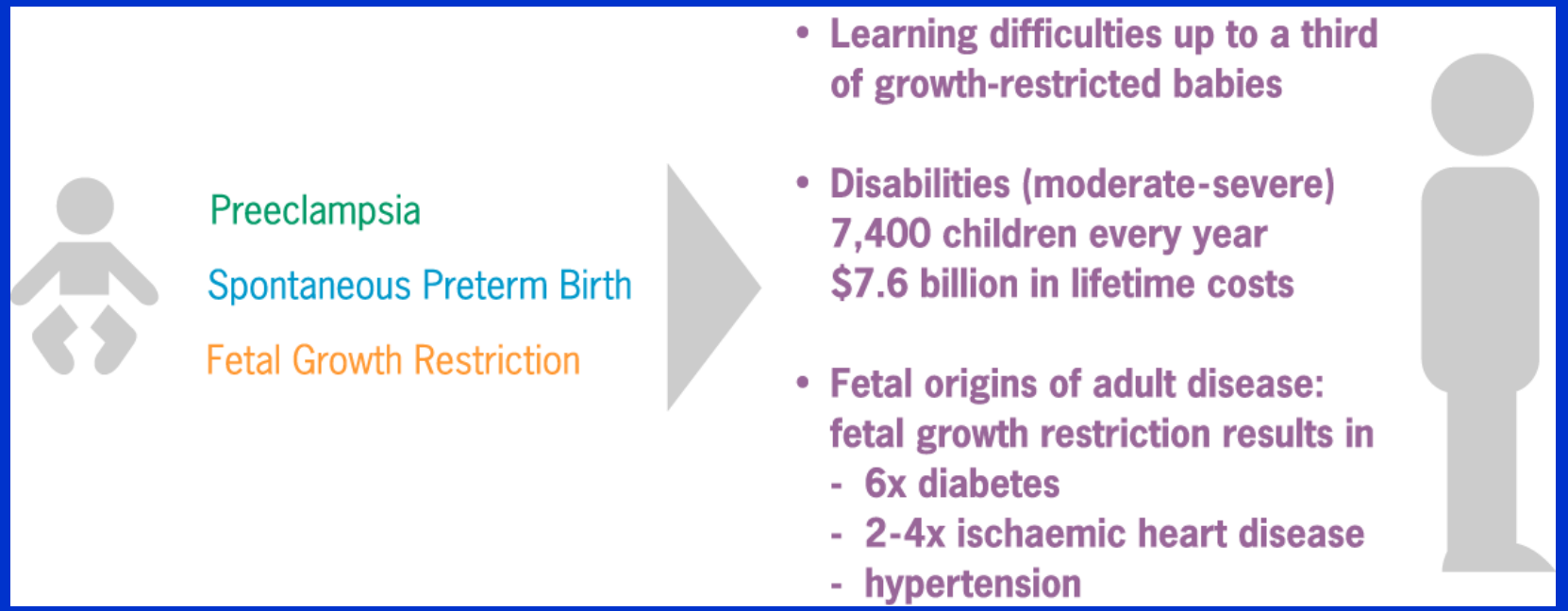
Note: several SA public hospitals have preeclampsia incidences around 10%

*** 50.000** ***maternal deaths worldwide yearly***

Why are these diseases important?

Lifelong Health Impact

costs impact USA as example



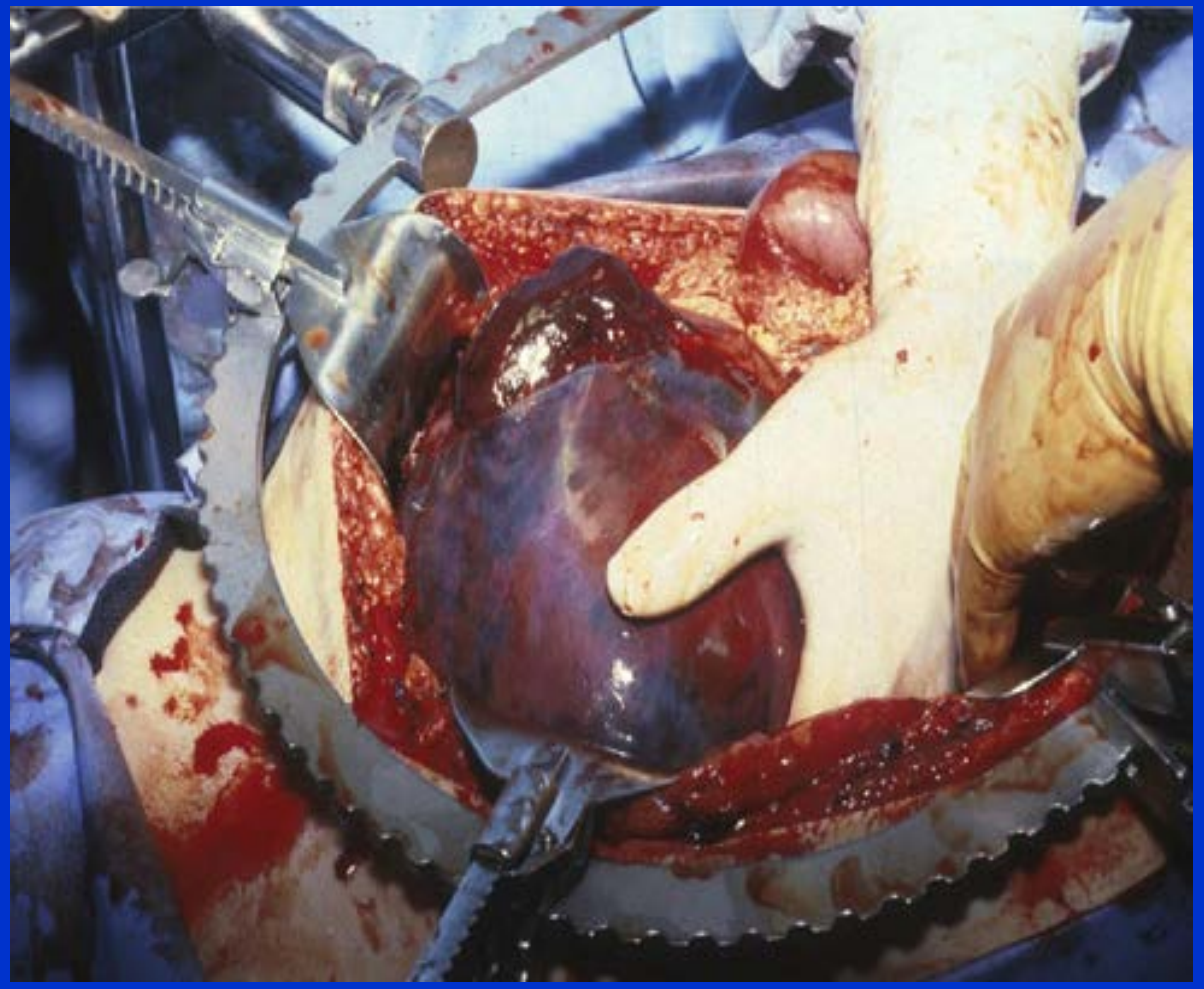
Panel 1: Maternal and fetal complications in severe pre-eclampsia

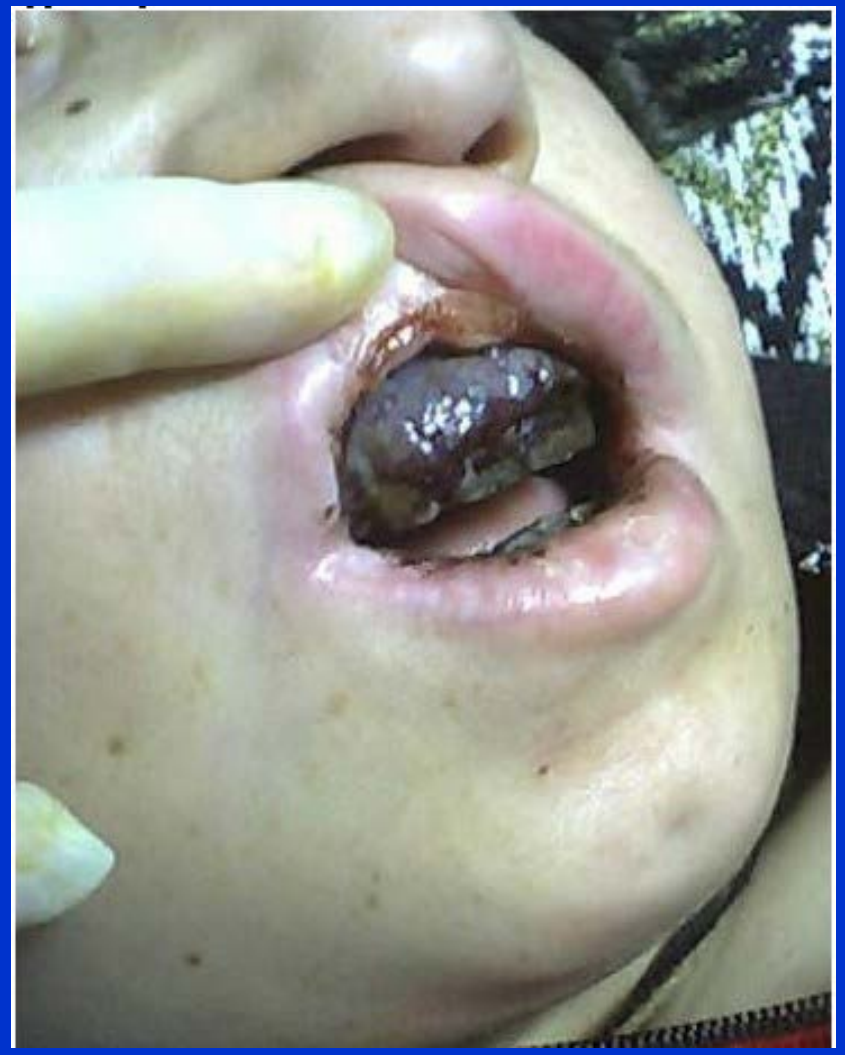
Maternal complications

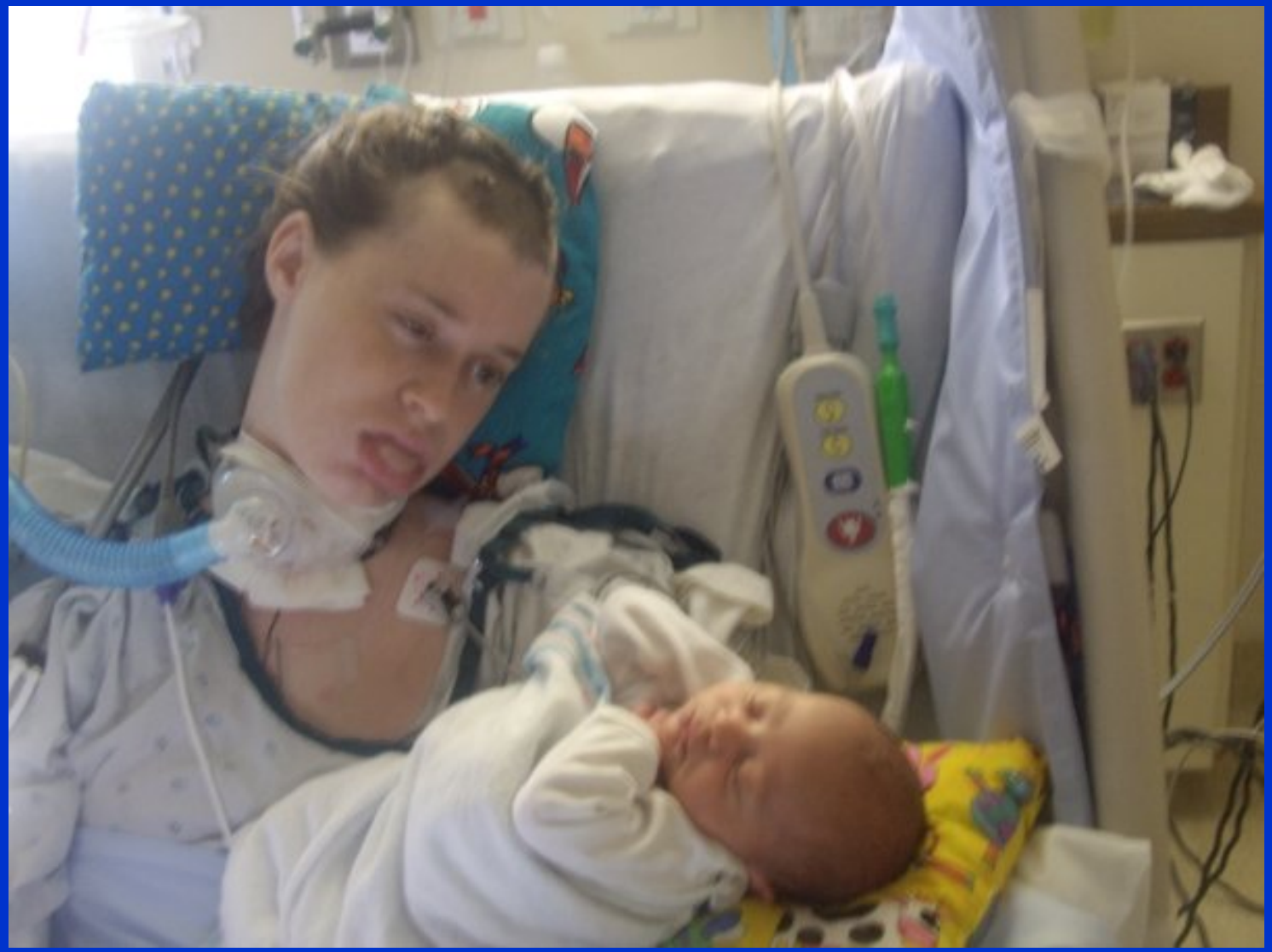
- Abruptio placentae (1–4%)
- Disseminated coagulopathy/HELLP syndrome (10–20%)
- Pulmonary oedema/aspiration (2–5%)
- Acute renal failure (1–5%)
- Eclampsia (<1%)
- Liver failure or haemorrhage (<1%)
- Stroke (rare)
- Death (rare)
- Long-term cardiovascular morbidity

Neonatal complications

- Preterm delivery (15–67%)
- Fetal growth restriction (10–25%)
- Hypoxia-neurologic injury (<1%)
- Perinatal death (1–2%)
- Long-term cardiovascular morbidity associated with low birthweight (fetal origin of adult disease)







Classification and Diagnosis

Classification

- Gestational hypertension
- Pre-eclampsia
- Chronic hypertension
  - Essential
  - Secondary
- Superimposed Pre-eclampsia

Gestational hypertension

- *de novo* hypertension after 20 weeks
- no other features of multisystem disease
- resolution within 3 months post partum

- Hypertension = BP ≥ 140/90 mmHg

Preeclampsia

- a multisystem disorder
- usually first detected by hypertension
- proteinuria common but not essential for a clinical diagnosis of pre-eclampsia in the presence of other organ involvement, including feto-placental unit

Preeclampsia: Diagnosis

de novo hypertension after 20 weeks

and new onset of one or more of:

- proteinuria
- renal insufficiency
- liver disease
- neurological problems
- haematological changes
- pulmonary oedema
- Fetal growth restriction

Pathogenesis

What is meant by the term Pre-eclampsia

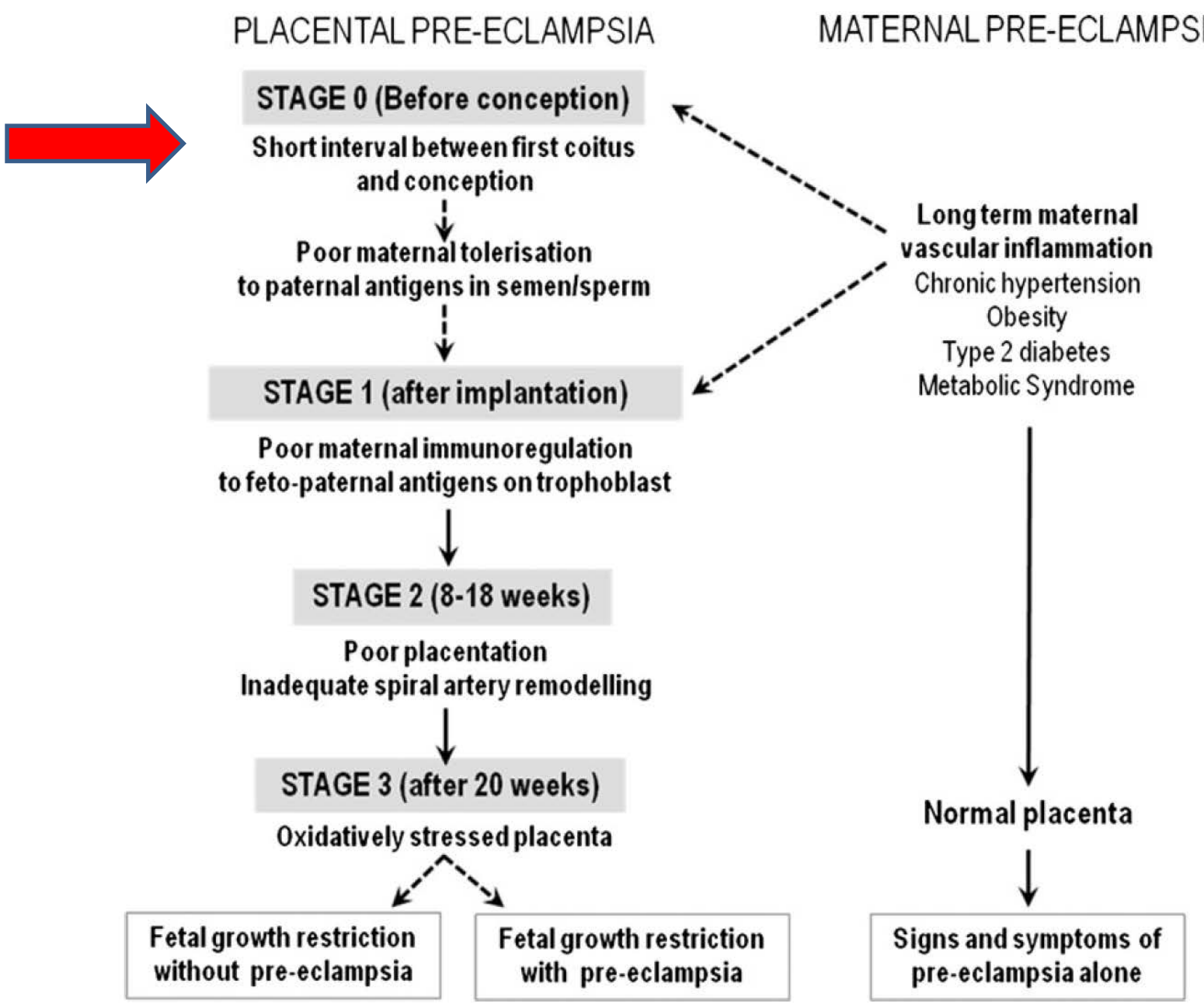
A syndrome – a reversible clinical phenotype; pregnancy induced hypertension and proteinuria

A syndrome is not a disease – it is a situation

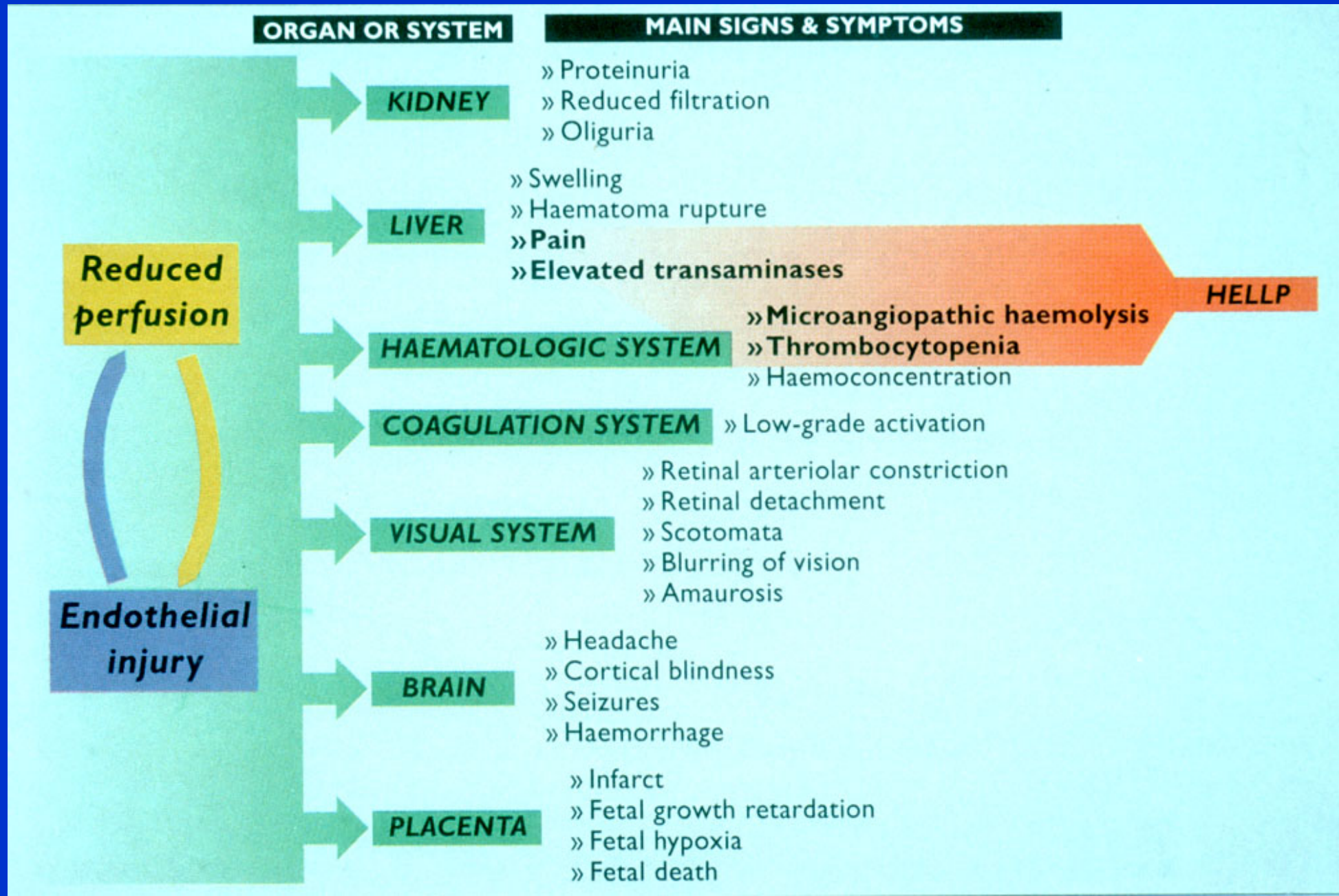
Non-specific, likely to be the endpoint of several pathogeneses.

- Placenta is causative tissue
- Maternal factors can contribute
- Concept of two stage disease

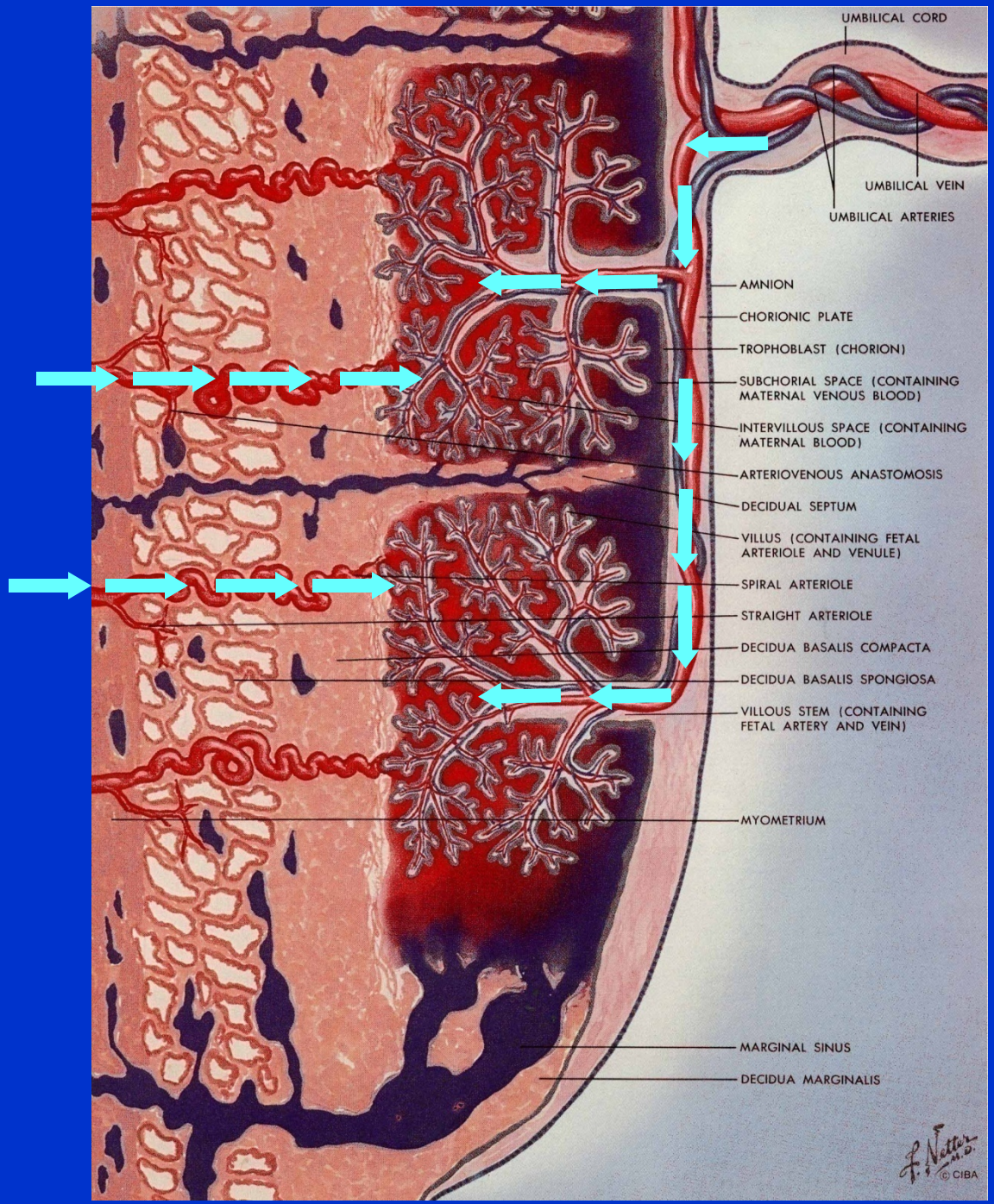
Chris Redman



preeclampsia



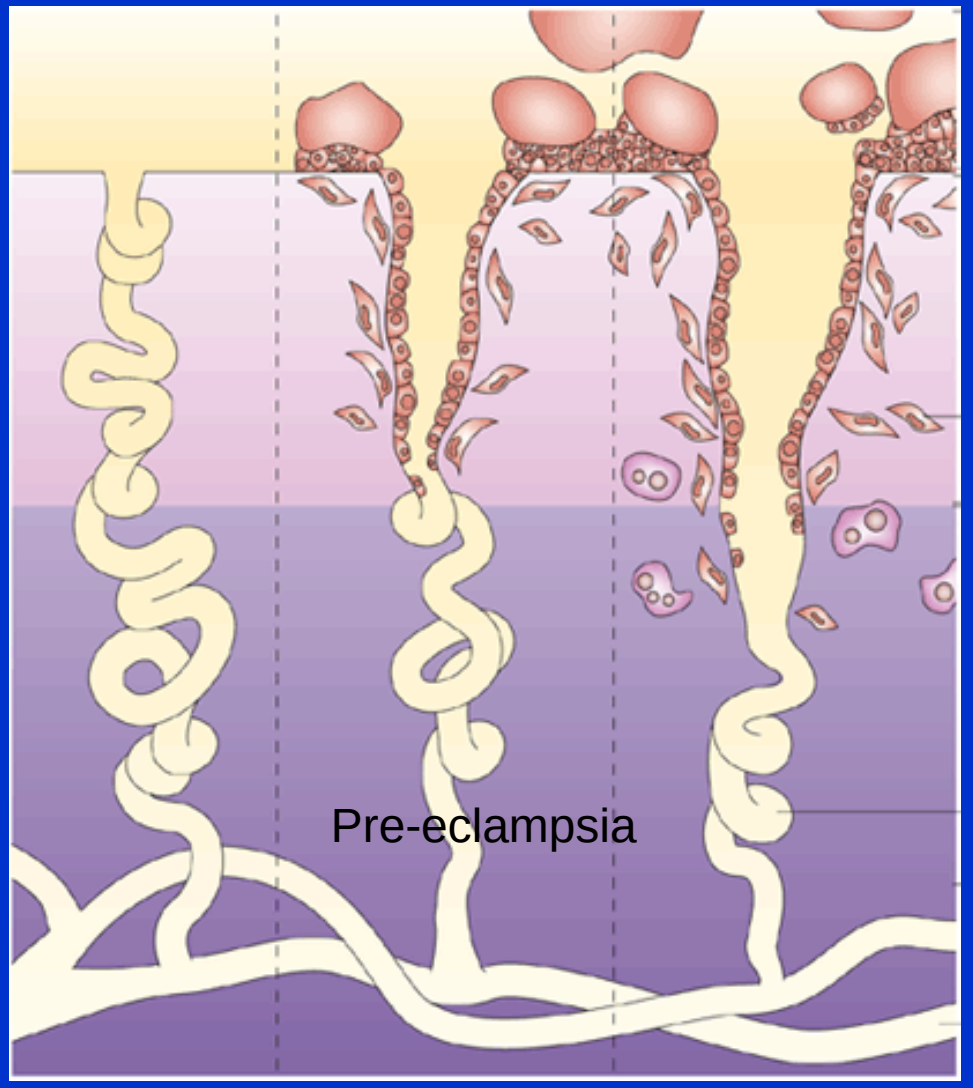
mother



fetus

Impaired Spiral Artery Modification in Preeclampsia (and IUGR)

Non pregnant

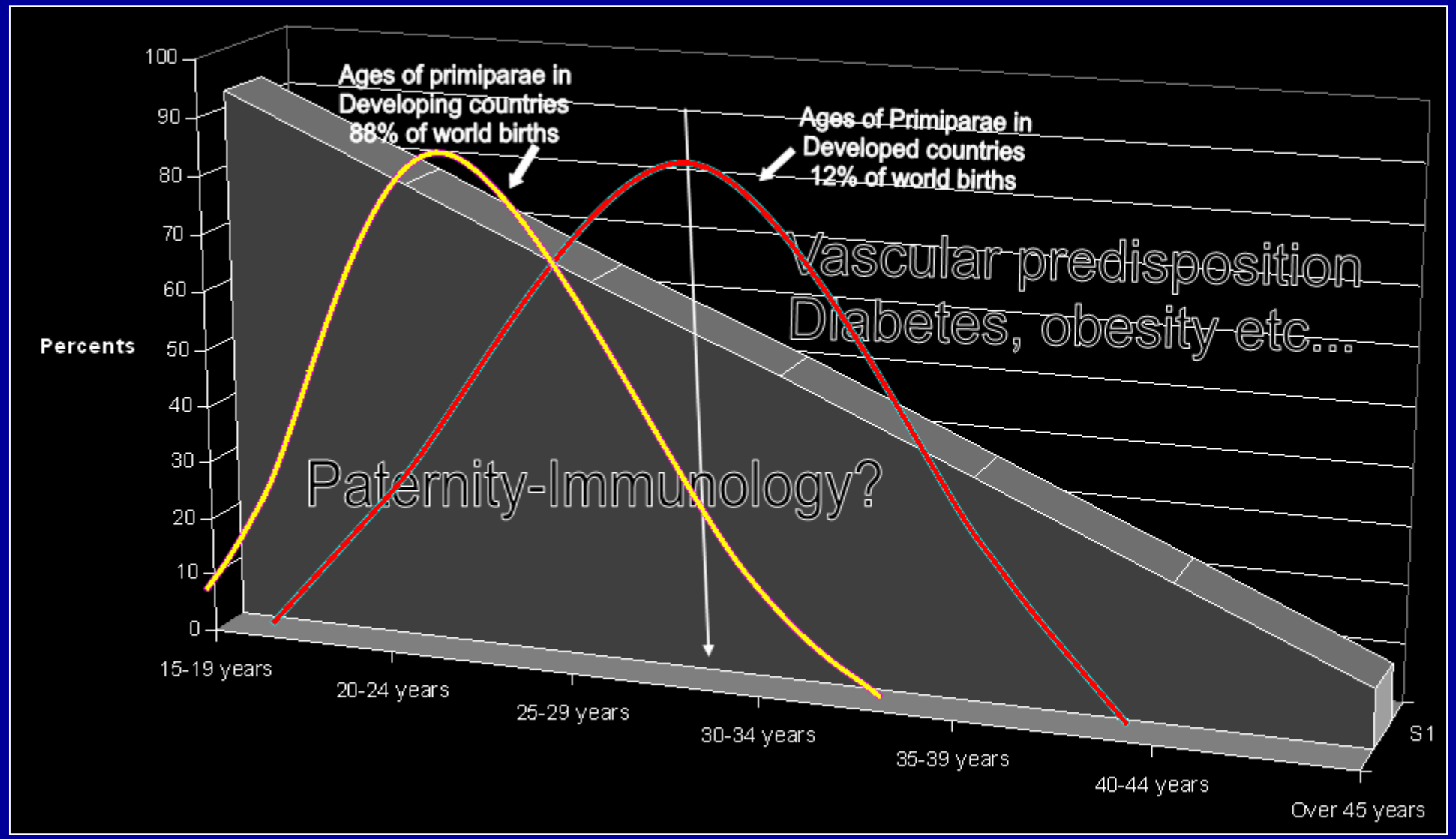


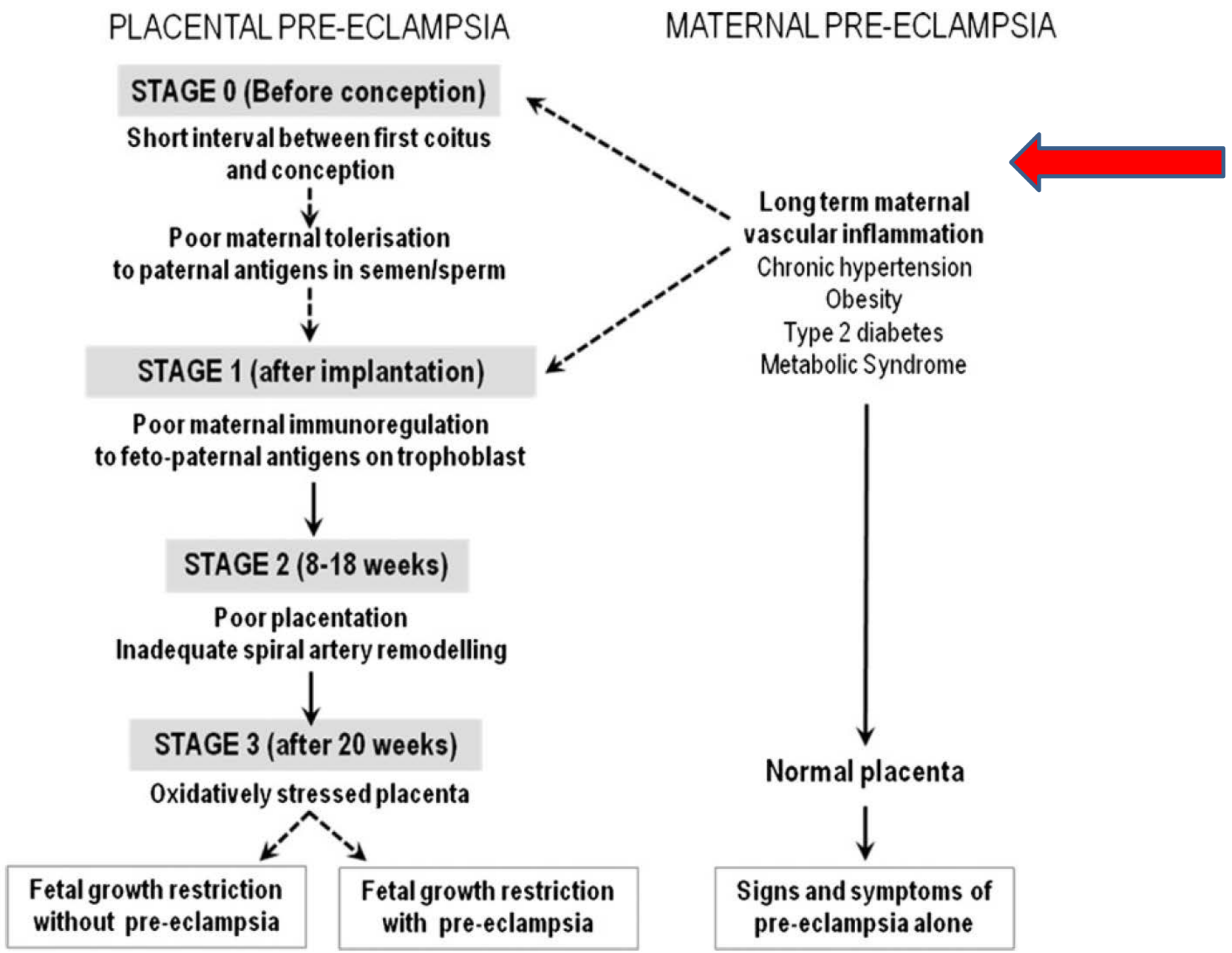
Normal Pregnant

Moffett et al, 2002

ETIOLOGY OF PREECLAMPSIA: MATERNAL VASCULAR PREDISPOSITION, COUPLE DISEASE. MUTUAL EXCLUSION OR COMPLEMENTARITY?

Pierre-Yves Robillard (1), Gustaaf Dekker (2), Gérard Chaouat(3), Thomas C. Hulsey(4)





Preeclampsia
a heterogeneous syndrome

Phenotype spec. pathw.

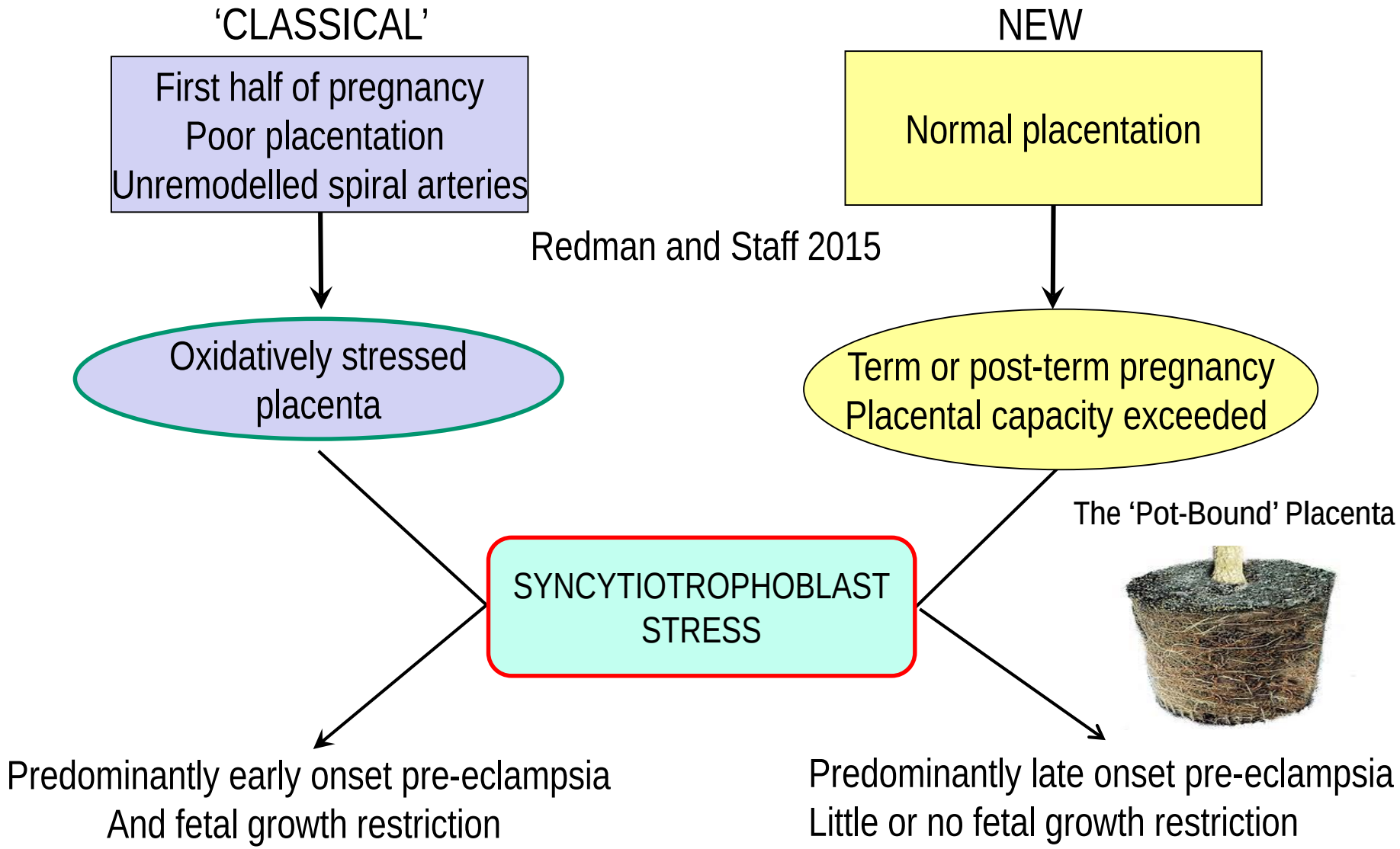
- **Lack of remodelling (IUGR)**
- **Chronic systemic inflammation**
- **Food inflammation**
- **Infection, e.g CMV, dormant microbes**
- **Allostatic load**
- **…….**

- Final common pathway
- **sFlt1/endoglin**
- **ER stress – misfolding proteins**
- **CK's**
- **Complement activ.**
- **'Debris'**

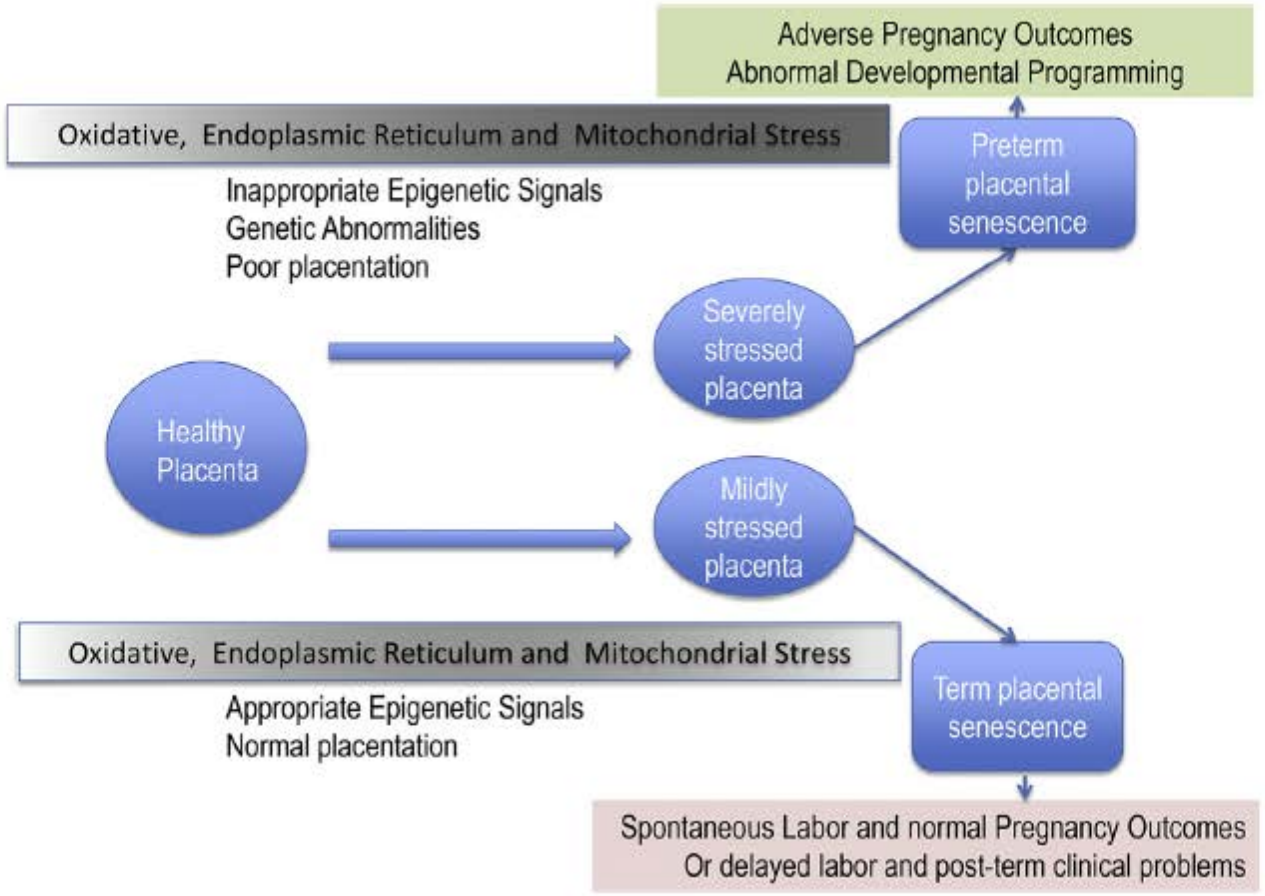
Inflammation &
Pro- versus Anti Angiogenic Factors

Chris Redman - Two Stage Model of Preeclampsia Extended

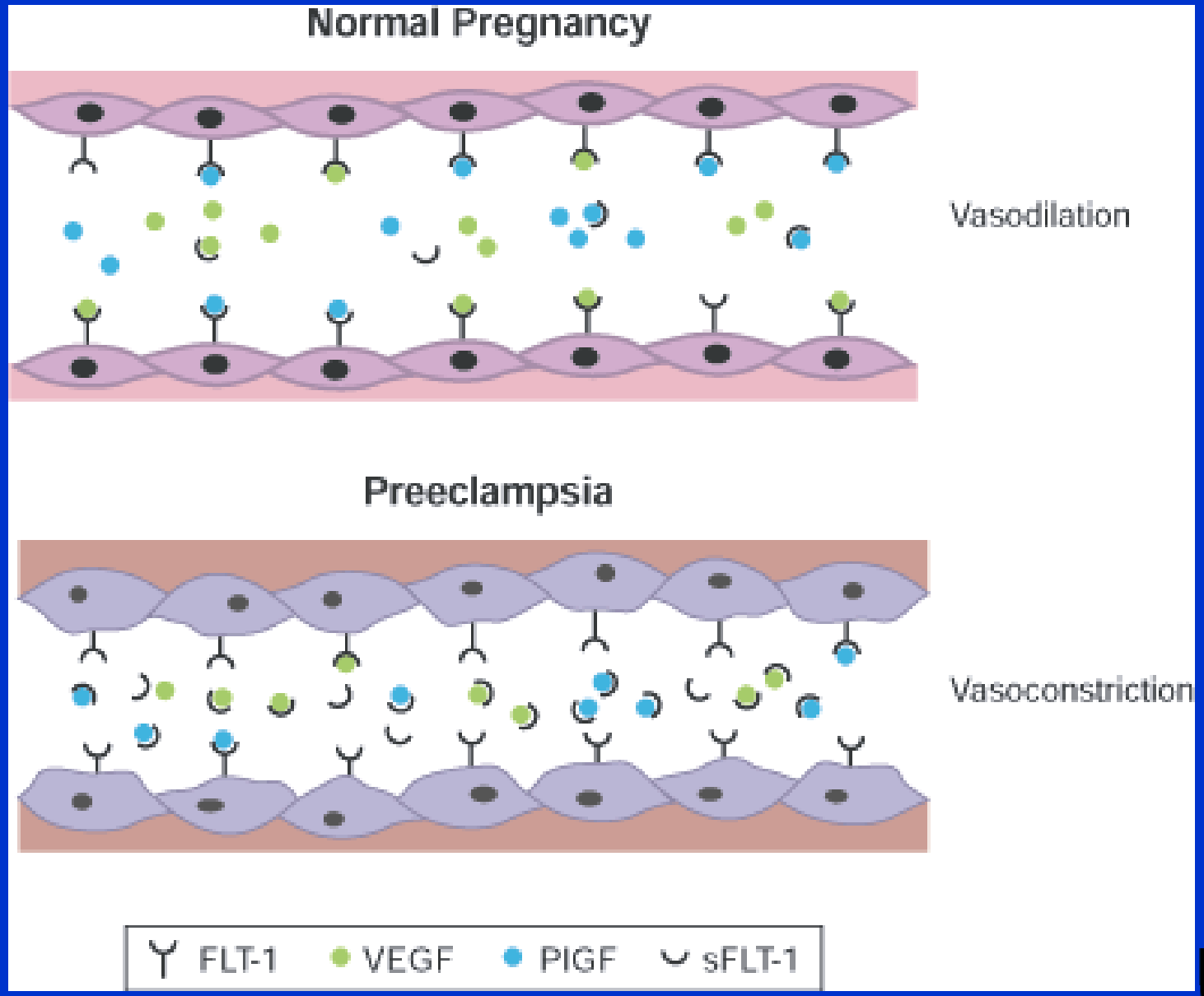
Two Causes of Placental Malperfusion – early and late



Chris Redman Placenta 2017

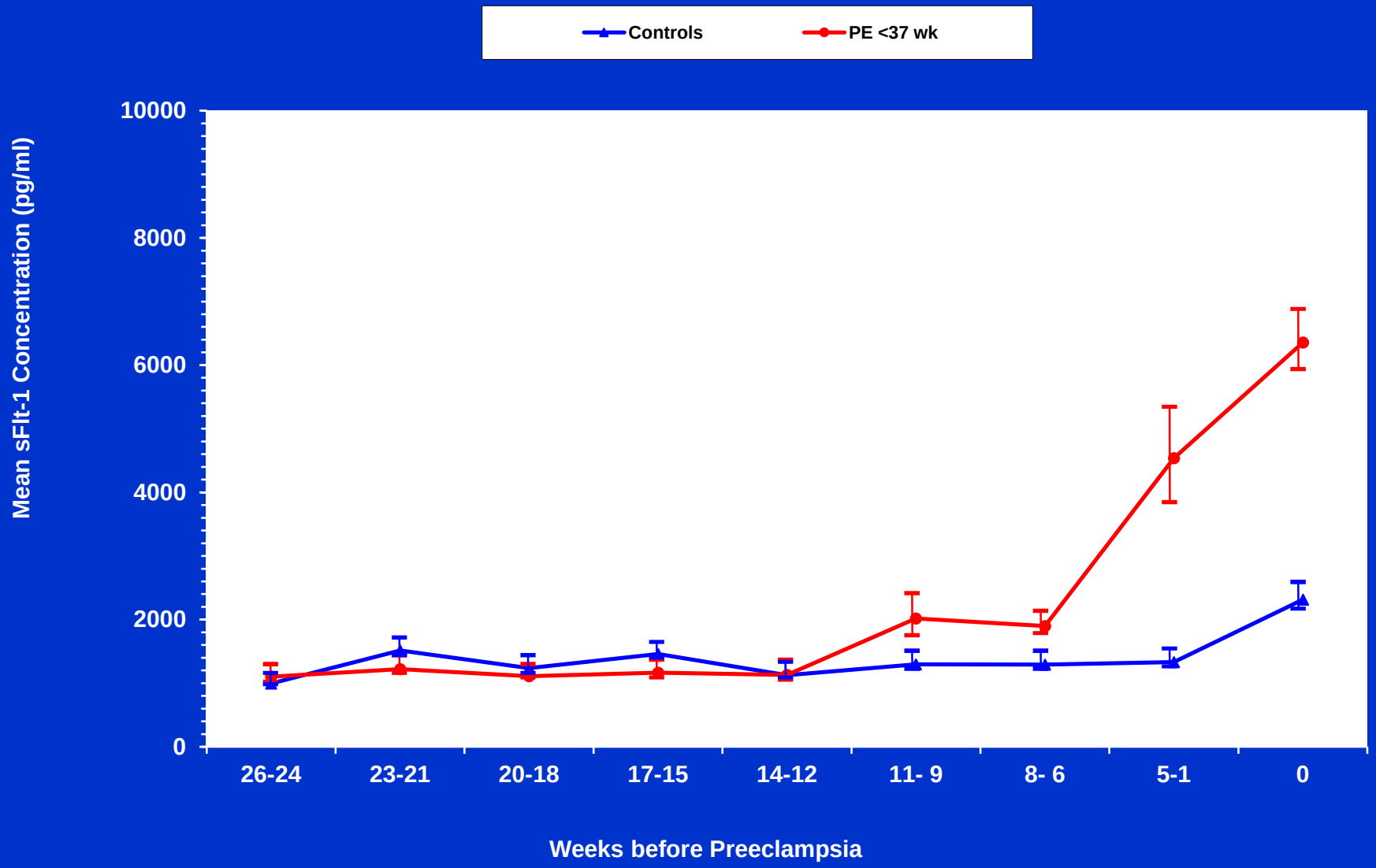


blood vessel

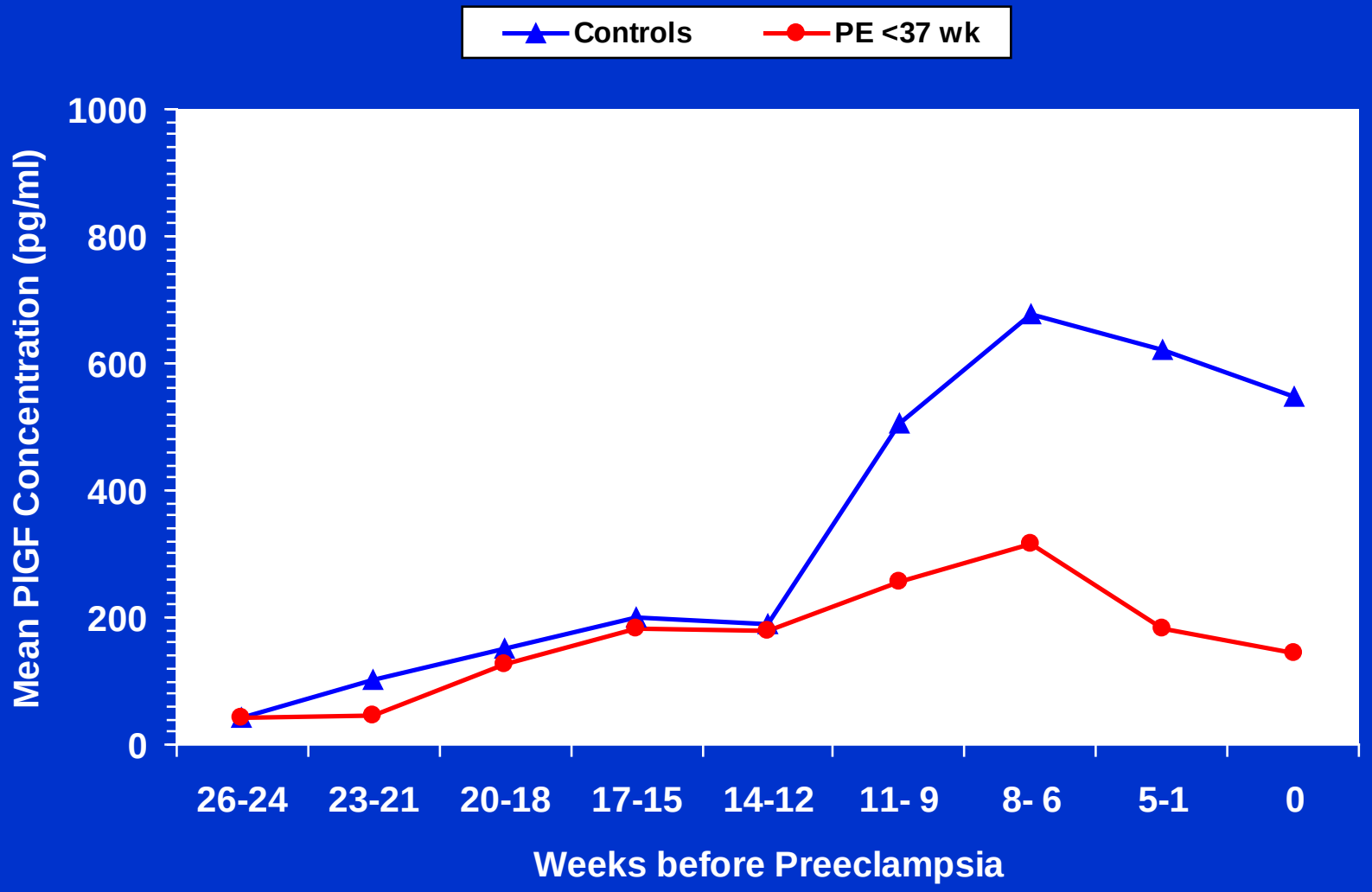


Sick endothelium

Gestational pattern of sFlt1 in the weeks preceding PE



Gestational pattern of PlGF in the weeks preceding PE



Inflammation and Complement

Trophoblast, Pre-eclampsia and ER Stress

ER stress activates an inflammatory response

ER stress activates Nf-kappaB
Generates reactive oxygen species
Increases intracellular Ca2+
Unfolded protein response

ER stress stimulates generation of danger signals
Cell surface expression of calreticulin

An inflammatory response may cause ER stress
Generation of reactive oxygen species
For example action of TNFα/IFNγ

Hasnain et al. Immunol Cell Biol 2012;90:260-70

frontiers in Medicine

REVIEW
published: 29 November 2016
doi: 10.3389/fmed.2016.00060

Check for updates

A Dormant Microbial Component in the Development of Preeclampsia

Douglas B. Kell[1,2,3]* *and Louise C. Kenny*[4,5]

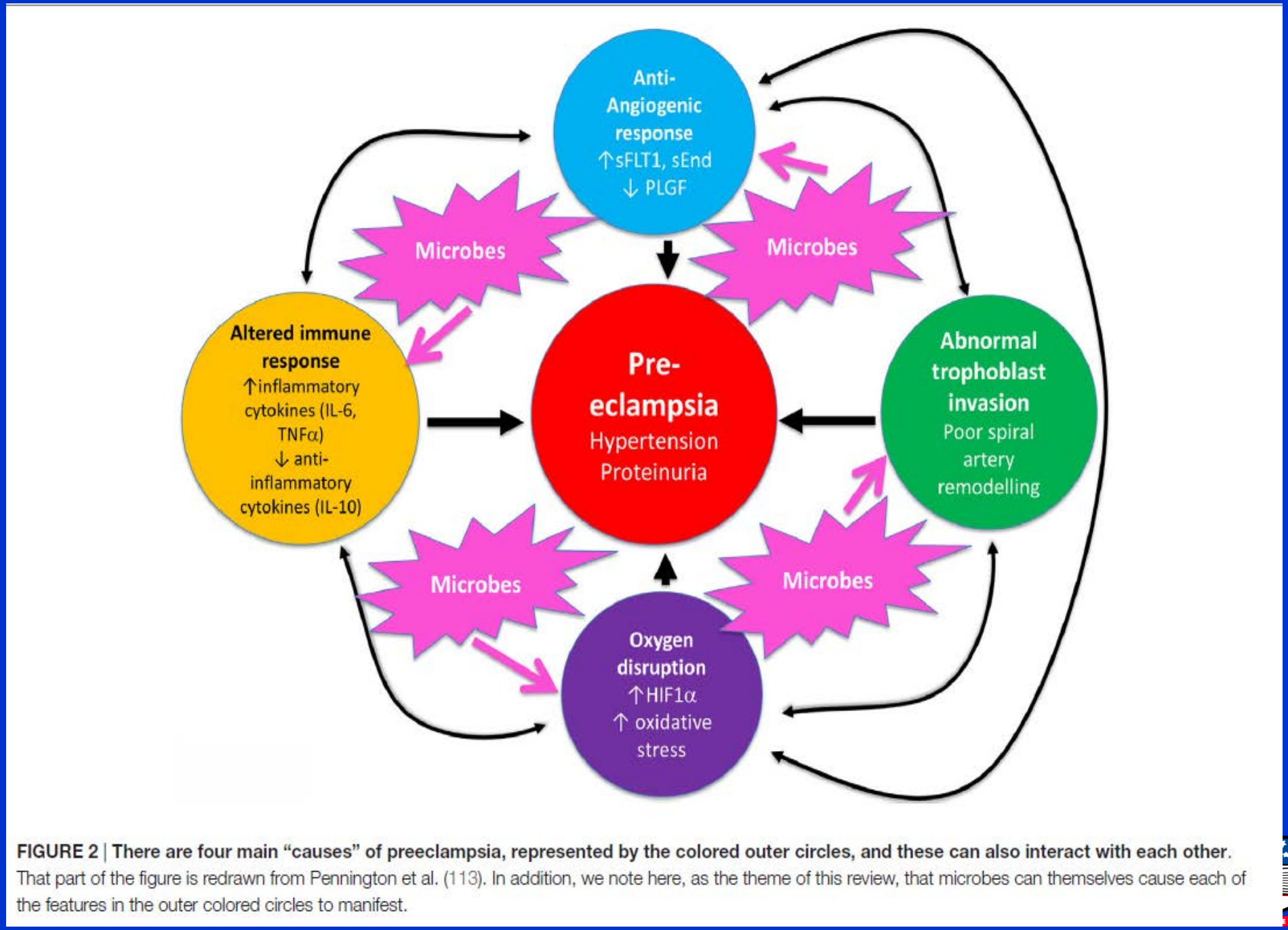


FIGURE 2 | There are four main "causes" of preeclampsia, represented by the colored outer circles, and these can also interact with each other. That part of the figure is redrawn from Pennington et al. (113). In addition, we note here, as the theme of this review, that microbes can themselves cause each of the features in the outer colored circles to manifest.

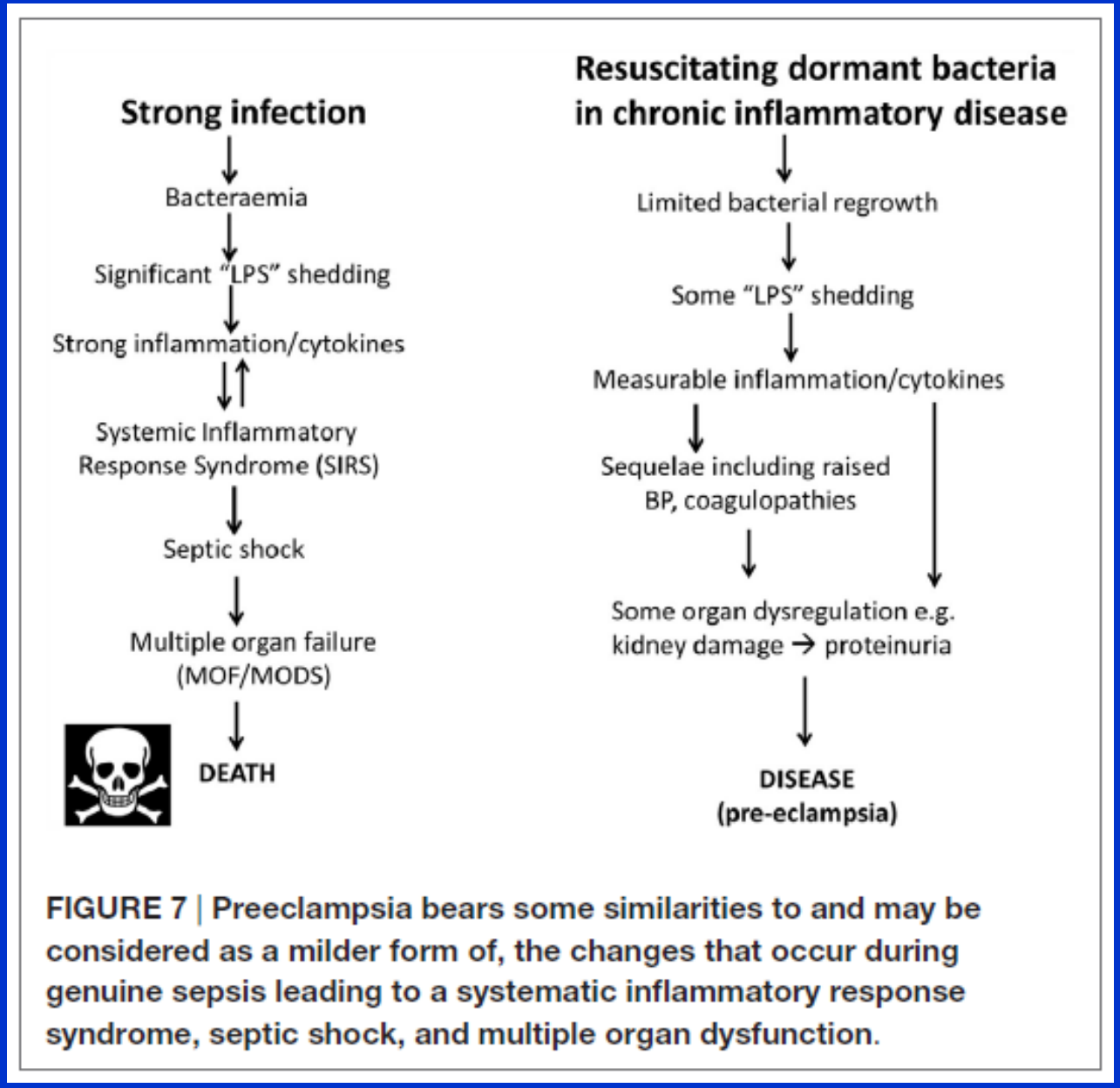


FIGURE 7 | Preeclampsia bears some similarities to and may be considered as a milder form of, the changes that occur during genuine sepsis leading to a systematic inflammatory response syndrome, septic shock, and multiple organ dysfunction.

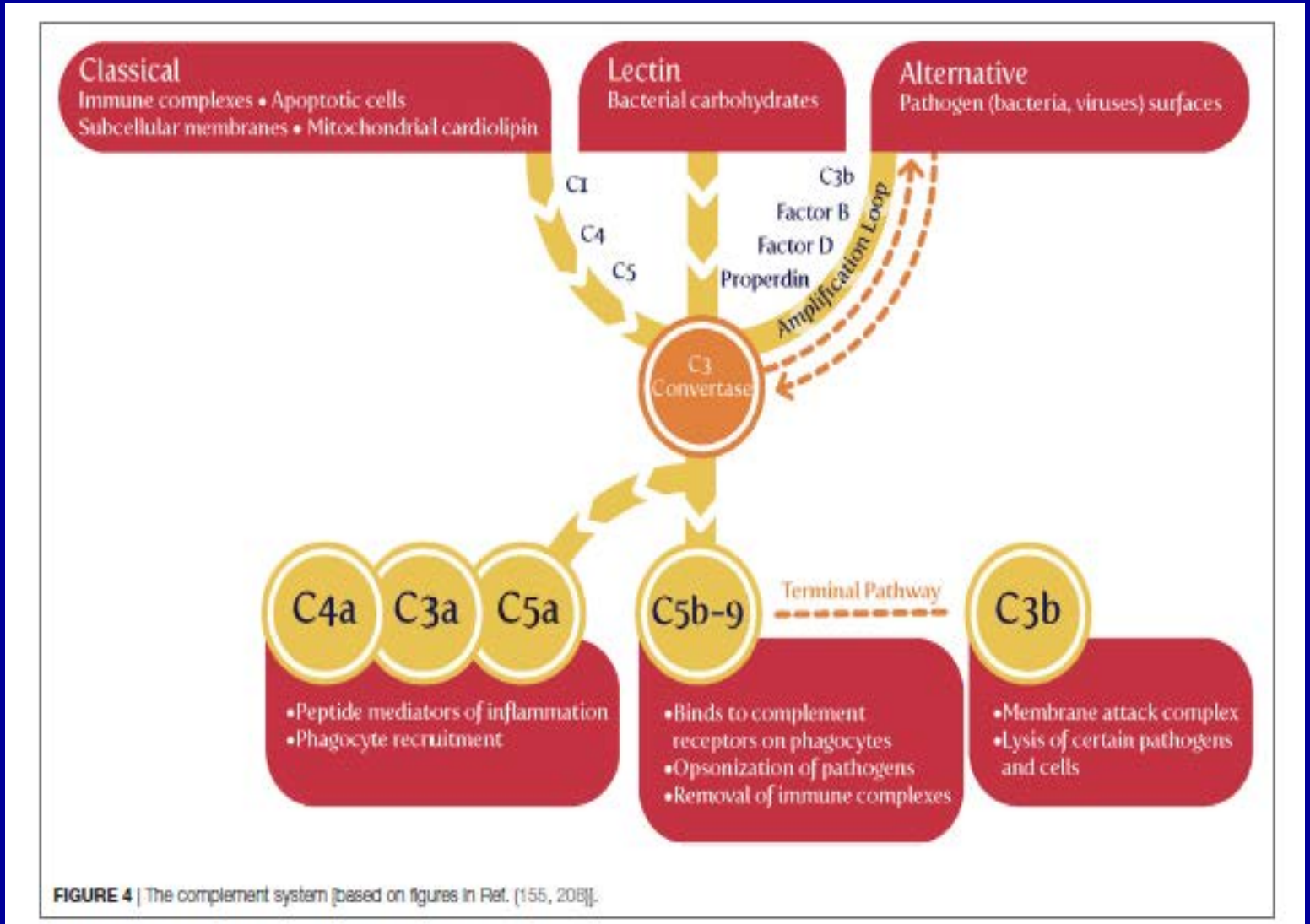


FIGURE 4 | The complement system [based on figures in Ref. (155, 208)].

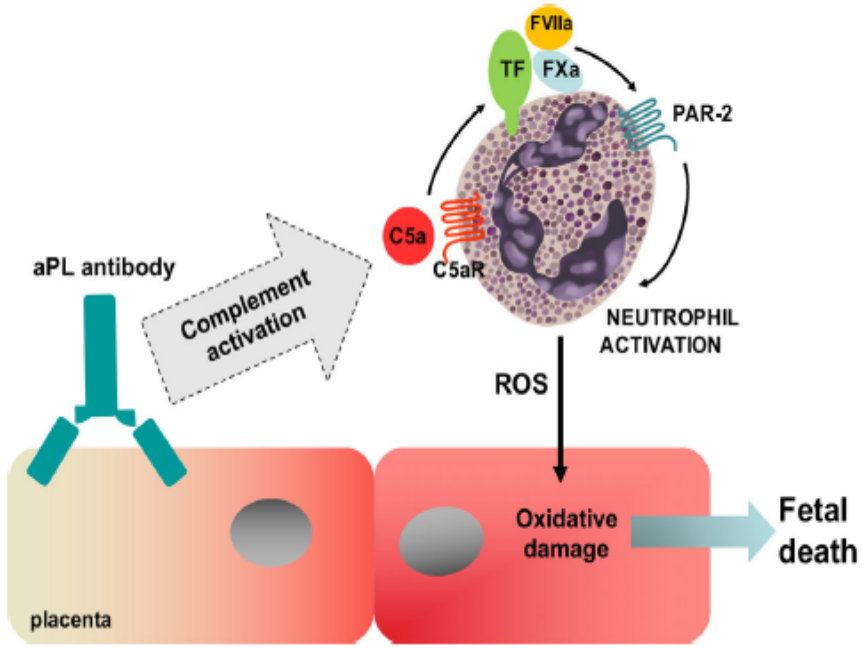


Fig. 4 C5a-induced tissue factor plays a crucial role in placental and fetal injury induced by aPL antibodies. aPL antibodies bind to the placenta and activate the complement cascade. C5a attracts and activates neutrophils to the fetomaternal interface. C5a activates neutrophils through the expression of tissue factor and protease activated receptor-2 (PAR-2). Increased neutrophil activity results in increased oxidative damage of the placenta and fetal loss [66, 67]

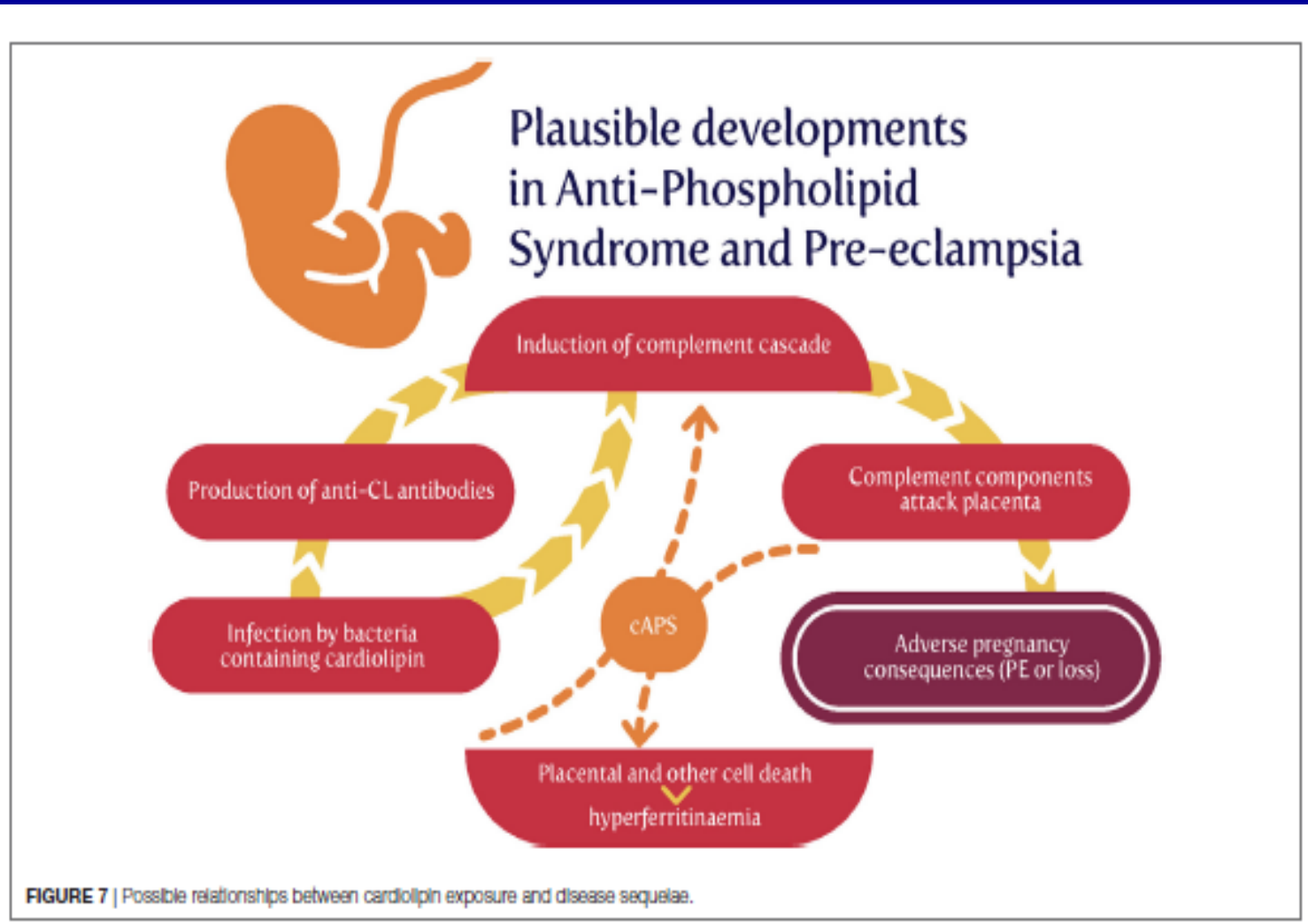


FIGURE 7 | Possible relationships between cardiolipin exposure and disease sequelae.

frontiers in
IMMUNOLOGY

ORIGINAL RESEARCH ARTICLE
published: 09 July 2014
doi: 10.3389/fimmu.2014.00312

Complement activation and regulation in preeclamptic placenta

Anna Inkeri Lokki[1,2,3 *†], *Jenni Heikkinen-Eloranta*[1,4†], *Hanna Jarva*[2,3,5], *Terhi Saisto*[4], *Marja-Liisa Lokki*[6], *Hannele Laivuori*[1,4] *and Seppo Meri*[2,3,5]

[1] *Department of Medical Genetics, Haartman Institute, University of Helsinki, Helsinki, Finland*
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[4] *Department of Obstetrics and Gynaecology, Helsinki University Central Hospital, Helsinki, Finland*
[5] *Division of Clinical Microbiology, Helsinki University Central Hospital Laboratory (HUSLAB), Helsinki, Finland*
[6] *Transplantation Laboratory, Haartman Institute, University of Helsinki, Helsinki, Finland*

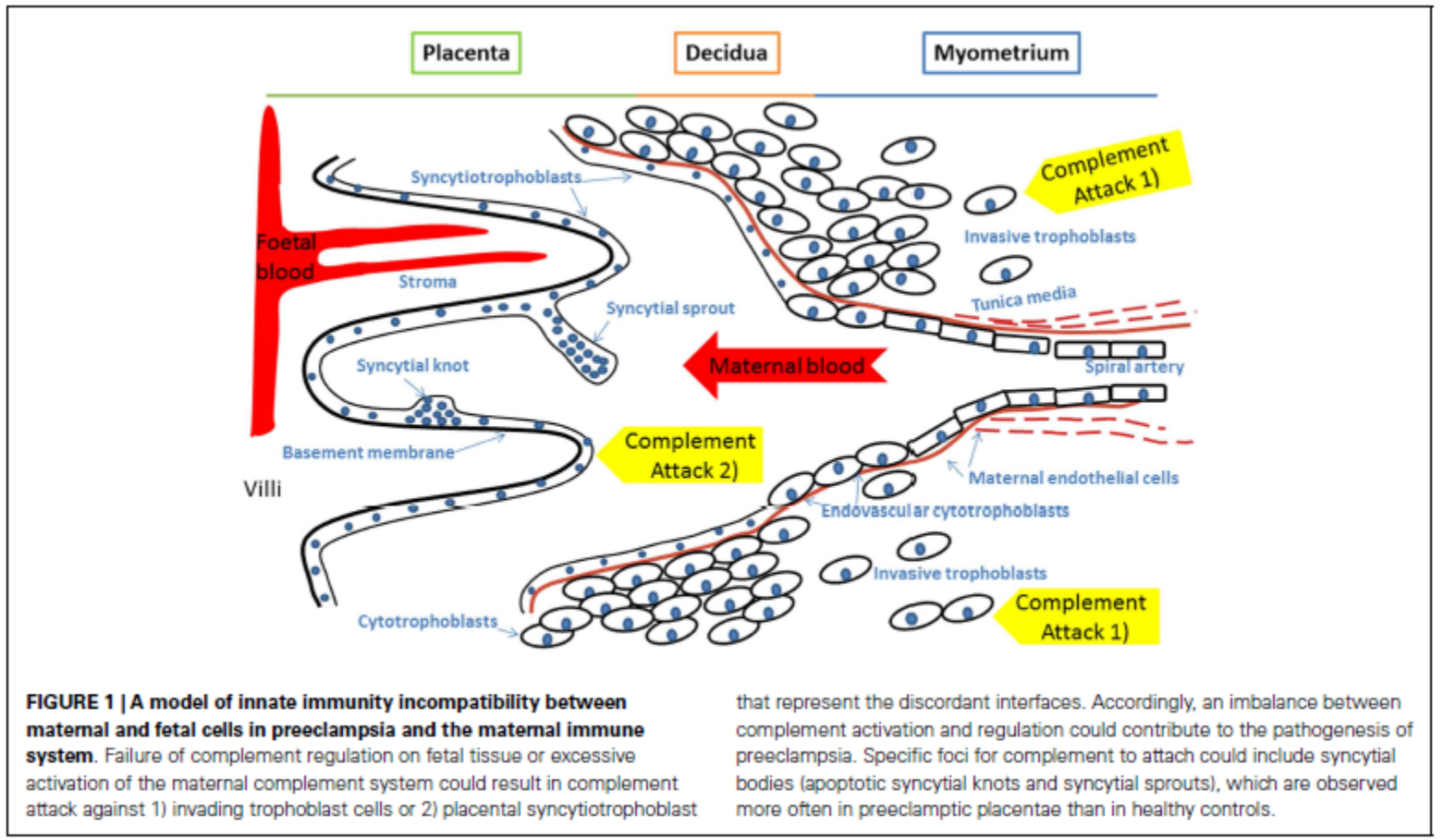

FIGURE 1 | A model of innate immunity incompatibility between maternal and fetal cells in preeclampsia and the maternal immune system. Failure of complement regulation on fetal tissue or excessive activation of the maternal complement system could result in complement attack against 1) invading trophoblast cells or 2) placental syncytiotrophoblast that represent the discordant interfaces. Accordingly, an imbalance between complement activation and regulation could contribute to the pathogenesis of preeclampsia. Specific foci for complement to attach could include syncytial bodies (apoptotic syncytial knots and syncytial sprouts), which are observed more often in preeclamptic placentae than in healthy controls.

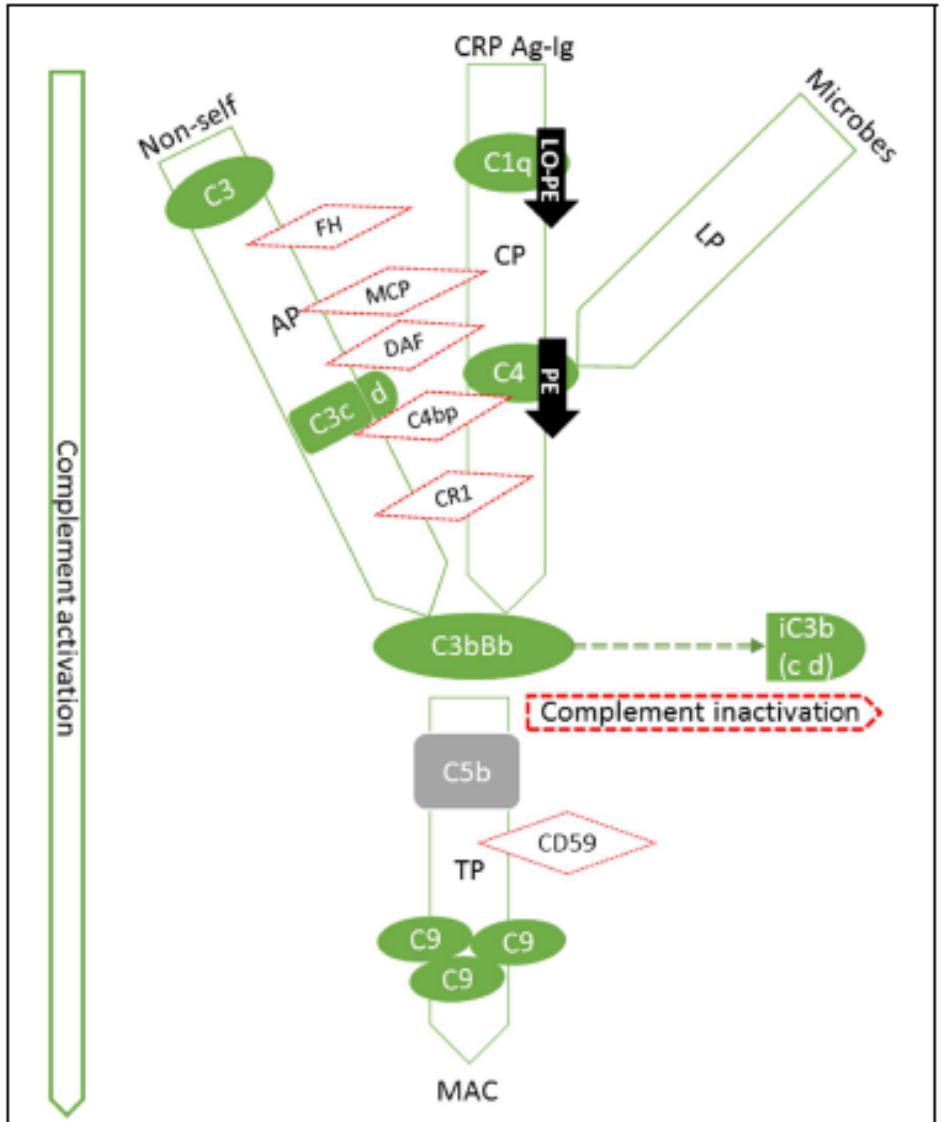

FIGURE 3 | Summary of expression patterns of complement components in the placenta. Our findings are highlighted in black arrows (PE: preeclampsia, LO-PE: late-onset preeclampsia). Pictured are the

Our results support the theory, that C1q has an important role in the maintenance of immune tolerance by clearing apoptotic and self-antigens. C1q has an important ability to recognize altered or exposed structures of self thereby leading to their efficient clearance by phagocytes without lysis and inflammation (22). Direct binding of C1q may occur to various structures, such as to phospholipids or vimentin exposed by vascular endothelia during tissue damage (23). Deficiency in C1q is associated with a major insufficiency in the clearance of apoptotic cells. This causes an SLE-like disease often involving glomerulonephritis (24). In PE, a partially similar function for C1q could be envisioned. Continuing stress and, by definition, the temporary existence of placenta may predispose the STB to cellular damage.

J. Cell. Mol. Med. Vol 22, No 2, 2018 pp. 1034-1046

Complement 5a-mediated trophoblasts dysfunction is involved in the development of pre-eclampsia

Yu Ma [a], Ling-Ran Kong [a], Qian Ge [a], Yuan-Yuan Lu [a], Mo-Na Hong [a], Yu Zhang [b, *], Cheng-Chao Ruan [a, c, *], Ping-Jin Gao [a, c]

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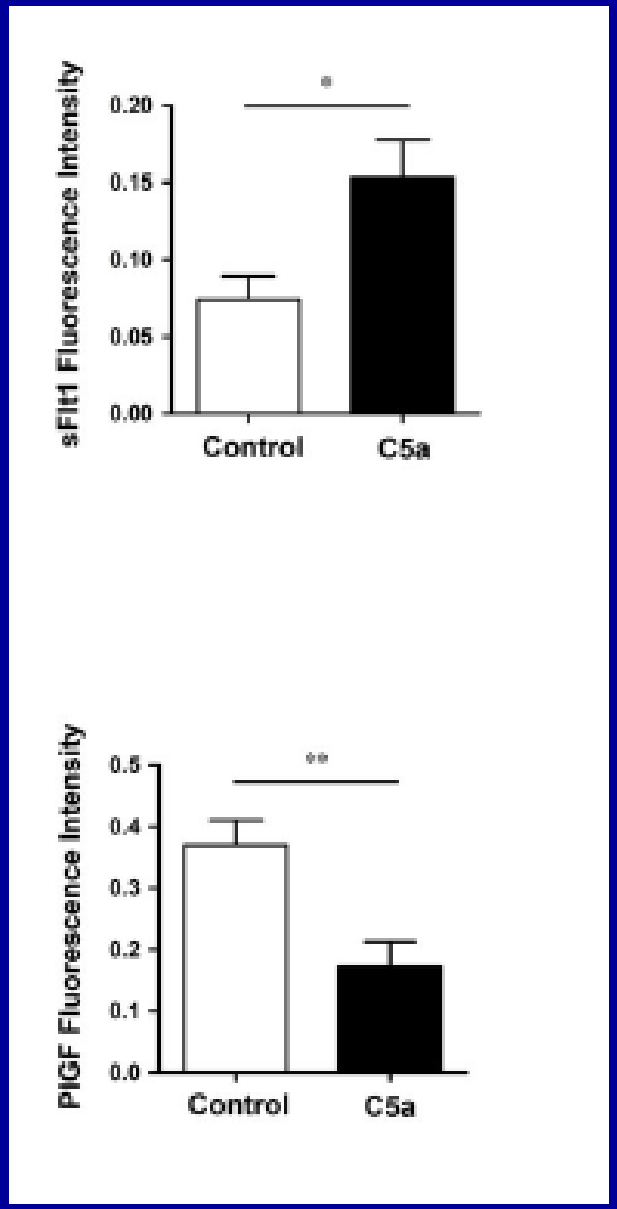
Received: June 6, 2017; Accepted: October 21, 2017

Abstract

Pre-eclampsia (PE) is a life-threatening multisystem disorder leading to maternal and neonatal mortality and morbidity. Emerging evidence showed that activation of the complement system is implicated in the pathological processes of PE. However, little is known about the detailed cellular and molecular mechanism of complement activation in the development of PE. In this study, we reported that complement 5a (C5a) plays a pivotal role in aberrant placentation, which is essential for the onset of PE. We detected an elevated C5a deposition in macrophages and C5a receptor (C5aR) expression in trophoblasts of pre-eclamptic placentas. Further study showed that C5a stimulated trophoblasts towards an anti-angiogenic phenotype by mediating the imbalance of angiogenic factors such as soluble fms-like tyrosine kinase 1 (sFlt1) and placental growth factor (PlGF). Additionally, C5a inhibited the migration and tube formation of trophoblasts, while, C5aR knockdown with siRNA rescued migration and tube formation abilities. We also found that maternal C5a serum level was increased in women with PE and was positively correlated with maternal blood pressure and arterial stiffness. These results demonstrated that the placental C5a/C5aR pathway contributed to the development of PE by regulating placental trophoblasts dysfunctions, suggesting that C5a may be a novel therapeutic possibility for the disease.


sFlt1 Fluorescence Intensity
0.20
0.15
0.10
0.05
0.00
*
Control
C5a
PlGF Fluorescence Intensity
0.5
0.4
0.3
0.2
0.1
0.0
**
Control
C5a

Received: 11 May 2016 | Accepted: 2 September 2016

DOI: 10.1111/aji.12586

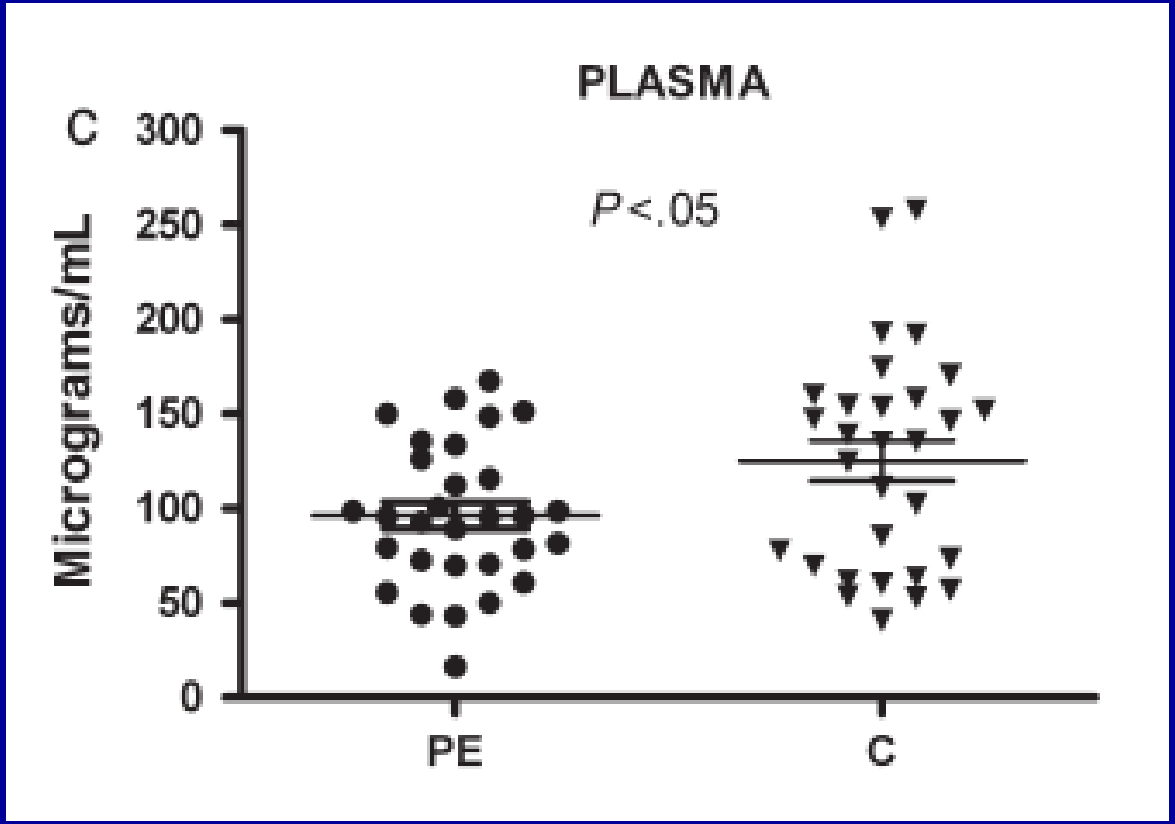
ORIGINAL ARTICLE

WILEY AJRI American Journal of Reproductive Immunology

Complement component C1q as potential diagnostic but not predictive marker of preeclampsia

Chiara Agostinis[1] | Tamara Stampalija[1] | Dionne Tannetta[2] | Claudia Loganes[1] | Liza Vecchi Brumatti[1] | Francesco De Seta[1,3] | Claudio Celeghini[4] | Oriano Radillo[1] | Ian Sargent[2] | Francesco Tedesco[5] | Roberta Bulla[4]

C1 INH levels are lower in pre-eclampsia patients



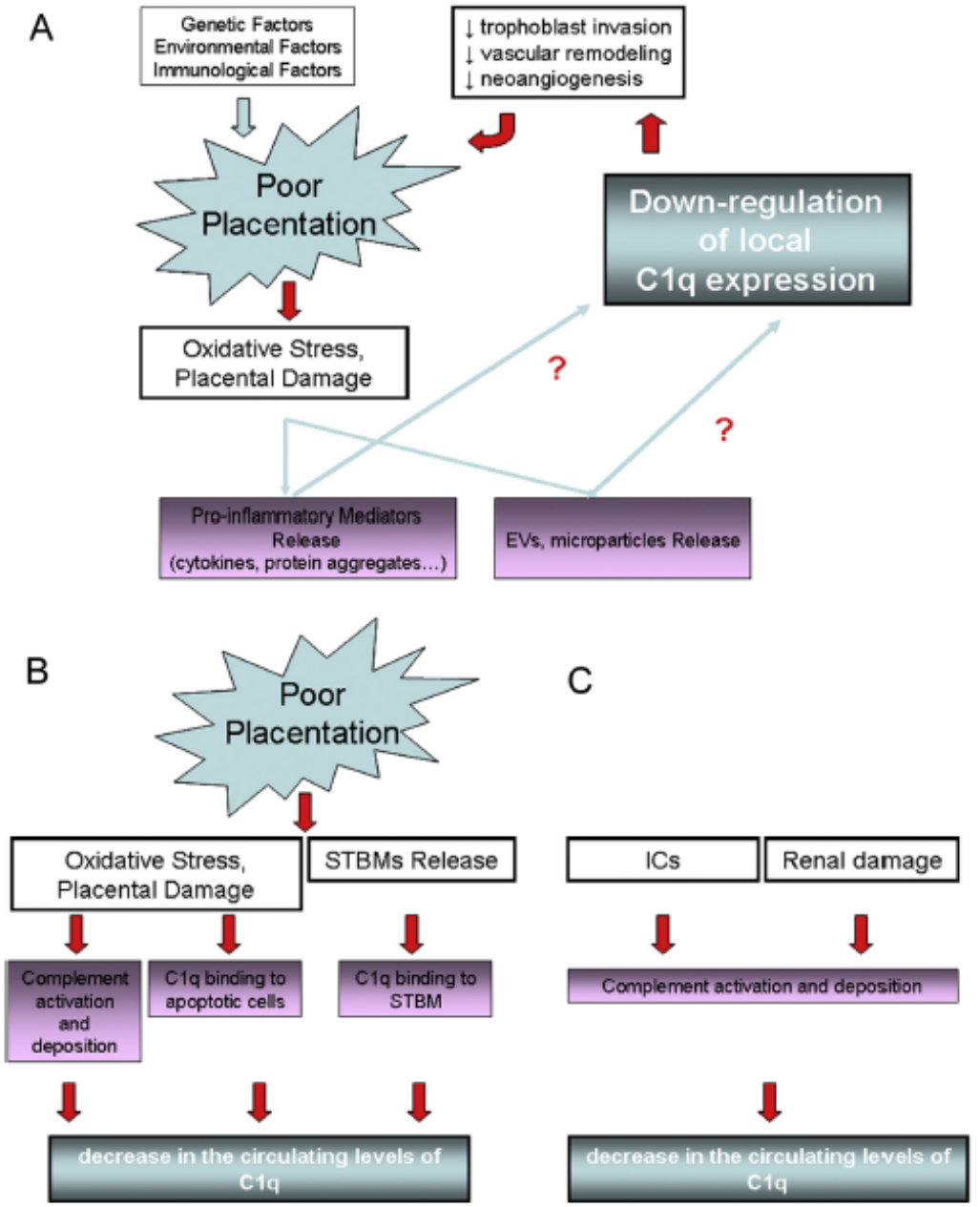
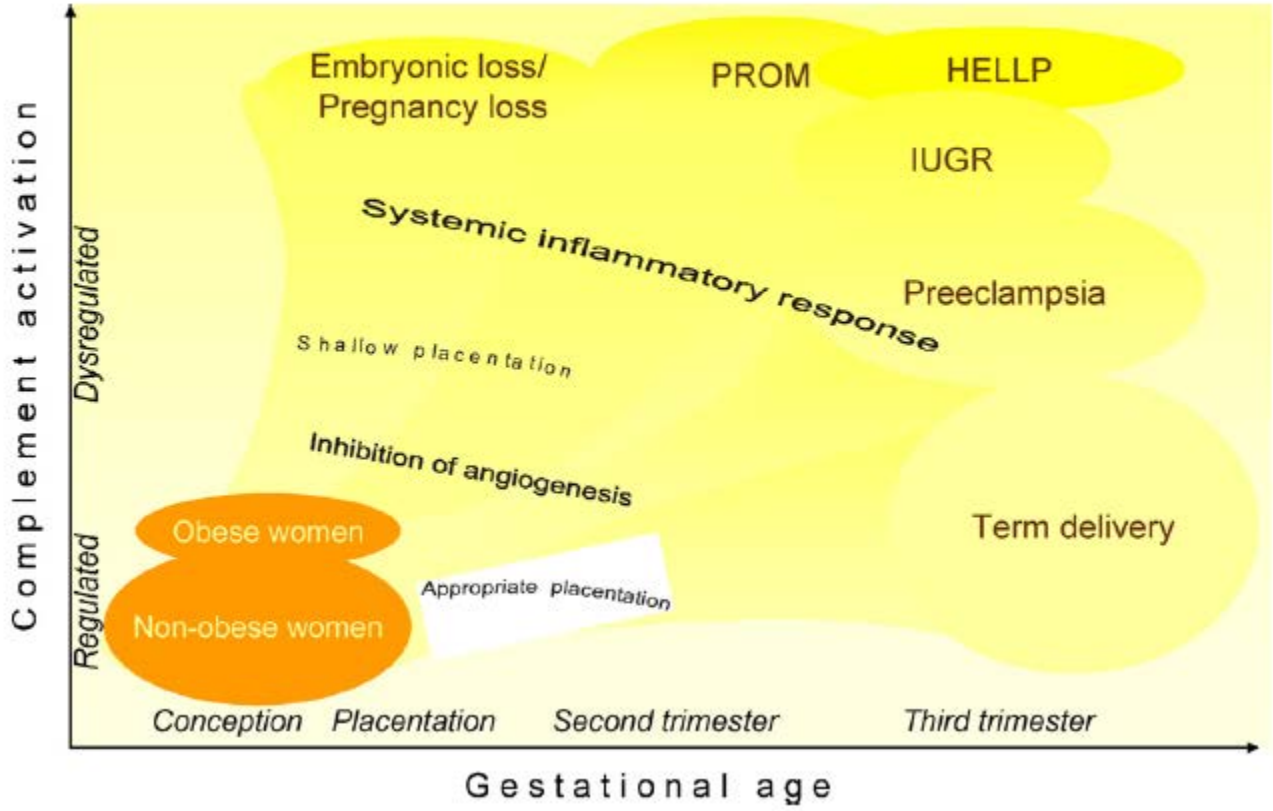


Fig. 3. Hypothetical role of C1q in the pathogenesis of PE.
A) Unknown factors present in PE sera (such as pro-inflammatory mediators or extracellular vesicles or protein aggregates) down-regulate placental expression of C1q. Reduced local production of C1q causes impaired trophoblast invasion, vascular remodeling and neoangiogenesis and, and consequently poor placentation.
B) Placental damage induces activation of the complement system and deposition of C1q and other complement components at placental level. C1q can bind to apoptotic cells, which have been documented by several groups to be present in increased number in the placental villi of pre-eclamptic patients (Allaire et al., 2000; Ishihara et al.,


Embryonic loss/
Pregnancy loss
PROM
HELLP
IUGR
Systemic inflammatory response
Preeclampsia
Shallow placentation
Inhibition of angiogenesis
Term delivery
Obese women
Non-obese women
Appropriate placentation
Complement activation
Dysregulated
Regulated
Conception
Placentation
Second trimester
Third trimester
Gestational age

Agenda

Pharming

Agenda

1. Introduction
2. HAE Therapeutics Overview – Professor Marc Riedl, UCSD
3. HAE US market overview
4. Building the RUCONEST® franchise in HAE
5. rhC1INH: Indications beyond HAE
6. rhC1INH development for Pre-eclampsia – Professor Gustaaf Dekker, University of Adelaide
7. Contrast-induced nephropathy and cardiac protection, delayed graft function, hemorrhagic shock
8. Protein Replacement Therapy in Pompe and Fabry's diseases
9. Pharming's Commercial Potential
10. Summary

Pharming

Contrast-induced Nephropathy and Cardiac Protection, Delayed Graft Function, Hemorrhagic Shock

Professor Bruno Giannetti

Chief Operating Officer, Pharming Group

Pharming

Contrast-induced Nephropathy and Cardiac Protection

- Millions of investigations are carried out each year using contrast medium to enhance views of pathology in vascular systems
- The ability of each patient to clear such media through their kidneys varies
- Renal damage during CT and other contrast imaging is an important risk of such procedures
- Complement activation in renal endothelial structures is often cited as one possible cause of contrast-related kidney damage
- To assess this hypothesis further, Pharming supported an investigator-initiated study started in 2017 at the University Hospital, Basel, led by Dr Michel Osthoff
- This double-blind, placebo-controlled Phase II study is expected to read out in Q3 after safety follow-up
- Possible secondary indication: Troponin T, measured as an indicator of cardiac damage, may give information on protective effect of rhC1INH on the vascular system during such investigations

Pharming

Contrast-induced Nephropathy and Cardiac Protection

Key Parameters for ongoing study in University Hospital Basel:

(Investigator: Dr Michel Osthoff, outline data expected Q3 2018)

- Double-blind, placebo-controlled study
- Σ 80 patients
- Criteria include impaired kidney function
- Treatment: 50U/kg before, and 4 hours after, elective coronarography
- Primary objective: to assess the efficacy of rhC1INH in preventing contrast-induced kidney damage
- Secondary objective: to assess the efficacy of rhC1INH in preventing induced endovascular (and related) cardiac damage
- Primary variable: Neutrophil Gelatinase-Associated Lipocain (NGAL)
- Key secondary variable (marker of cardiac damage): Troponin T

Pharming

Renal and Cardiac Protection

- Depending on the results of the Basel study, follow-up clinical development could be initiated
  - If the primary marker gives a positive signal, there could be clear therapeutic utility to offset risk of renal damage for at-risk patients
  - A formal Phase II study in CIN could be developed and initiated

- If the secondary marker Troponin T is reduced in the RUCONEST® arm, this would be evidence of reduction of the vascular/cardiac stress caused by the endovascular investigation or operation* itself
  - Depending on the strength of such signal, a formal Phase II study in Cardiac Protection could be proposed and endpoints for such studies discussed with the regulatory authorities

** such as a CT scan or a stent, vasodilation/balloon angioplasty or coronarography*

Pharming

Delayed Graft Function

- A type of ischemic reperfusion injury
- Potential organ damage following transplant surgery
- Defined as Acute Kidney Injury following renal transplantation
- 23% incidence in transplant patients, but different to rejection
- Complement activation affecting renal endothelial structures is discussed as one possible cause of damage
- IIS ongoing with University of Wisconsin
- Incidence is 18,000 kidney transplants at risk per year in US, with applications in additional 6,000 heart and/or lung transplants as well, probably requiring chronic therapy

Pharming

Hemorrhagic Shock

- Caused by trauma (gunshot wound, accident etc)
- Complement activation triggered by events including hypoxic cellular damage
- Fluid is drawn from other tissues, and causes organs to shut down - once a vital organ is affected, patient often enters into a cascade of multiple organ failure
- “Golden Hour”: If patient reaches trauma care within 1 hour, 90% chance of survival. If not, 90% chance of death
- To assess this hypothesis, US DoD (Army/USAF) has been conducting large mammal studies on the effect of RUCONEST® on extending the Golden Hour when given as soon as possible after injury (supported by Pharming)
- Data (when available) may support a clinical program

Pharming

Production Capacity Options

Pharming

Expansion of production capacity

- The rabbit-based production of rhC1INH is very scalable; up-scaling can be executed rapidly
- To serve future potential large indications in a more economical way, Pharming will restart its previously-developed and characterized cattle-based production lines of rhC1INH
- Clinical programs could be initiated with RUCONEST® and switched to cattle version during program following conversion studies
- Cattle-derived rhC1INH may have some benefits over the current rabbit version, including an extended serum half-life as result of an improved (even closer to human) glycosylation pattern
- New IP to be filed on the cattle-derived rhC1INH

Pharming

Summary of Production options

- Historic data in hand for cattle-derived rhC1INH and current options:

Analysis	1st Line	2nd Line	Rabbit-derived rhC1INH	Plasma-derived C1INH
rhC1INH in milk (gm per liter)	2.9	4.5	~11	n/a
N-acetylneuraminic acid (sialic acid) (mol/mol)	18.7	24.4	7.9	~30
Specific activity (U/mg)	6	6	6	~4
rhC1INH purity (%)	>99%	>99%	>99%	~80-95%

- Specific activity of cattle-derived and rabbit-derived rhC1INH higher compared to plasma-derived pdC1INH
- Purity of all rhC1INH higher compared to pdC1INH
- Sialic acid content (measure of glycosylation) is much higher for cattle-derived rhC1INH than for rabbit-derived rhC1-INH and slightly lower than natural C1INH – so is much closer to natural human C1-INH
- Cattle-derived rhC1INH has a longer plasma half-life than rabbit-derived rhC1INH

Pharming

Agenda

Pharming

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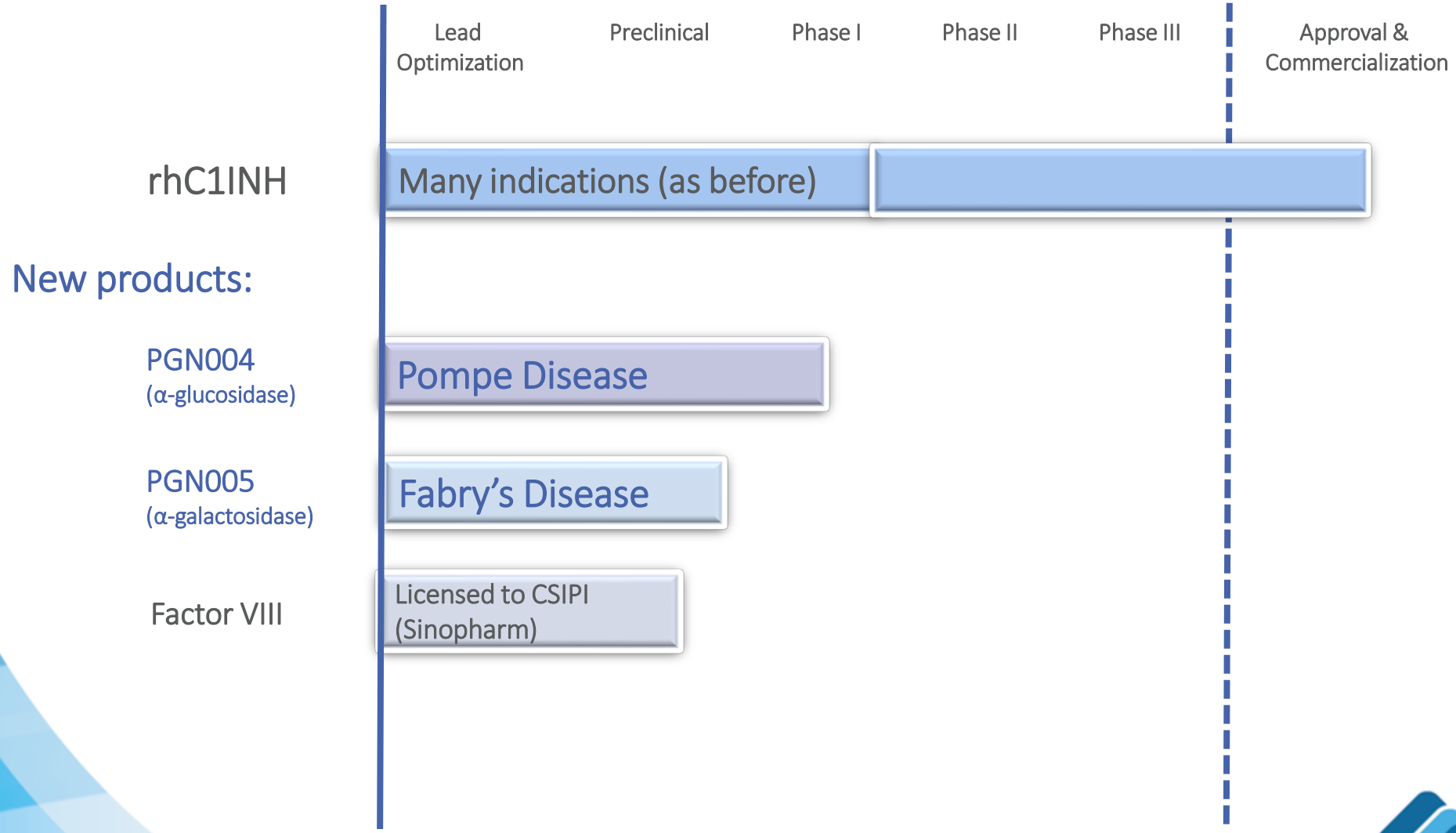
Protein Replacement Therapy in Pompe and Fabry's Diseases

Professor Bruno Giannetti
Chief Operating Officer, Pharming Group

Pharming

Expansion of Pharming to a Multiple Product Franchise



Pharming

α-Glucosidase For Pompe Disease

Pharming

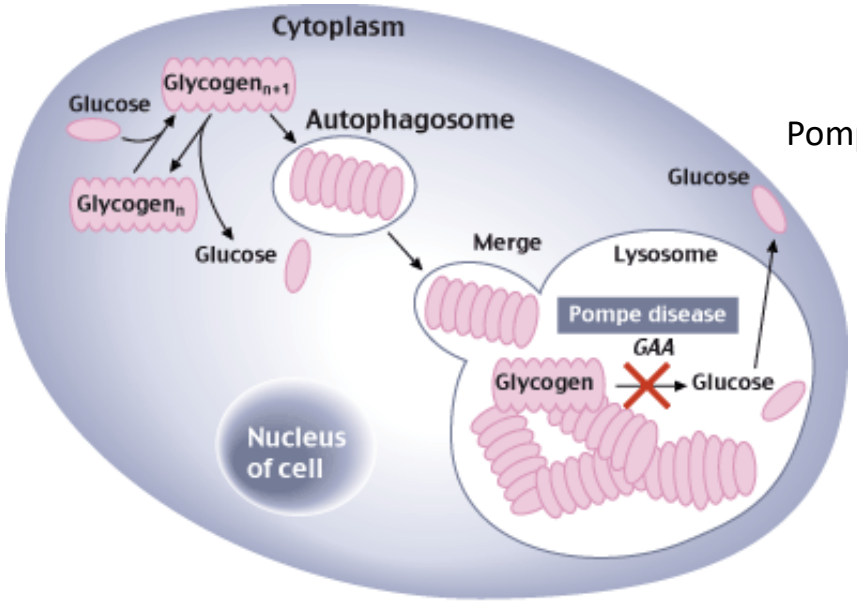
Pompe disease

- Autosomal recessive lysosomal storage disease
- Deficiency of lysosomal acid alpha glucosidase (α-Glu: Single-chain N-glycosylated enzyme, precursor of ~110 kDa, active in the lysosomes, natural substrate: glycogen)
- Estimated 5-10 thousand patients WW
- Infantile onset: untreated fatal in the first year of life
- Late or later onset form occurs after the first one to two years and progresses slowly. Difference to early onset is mainly levels of α-Glu

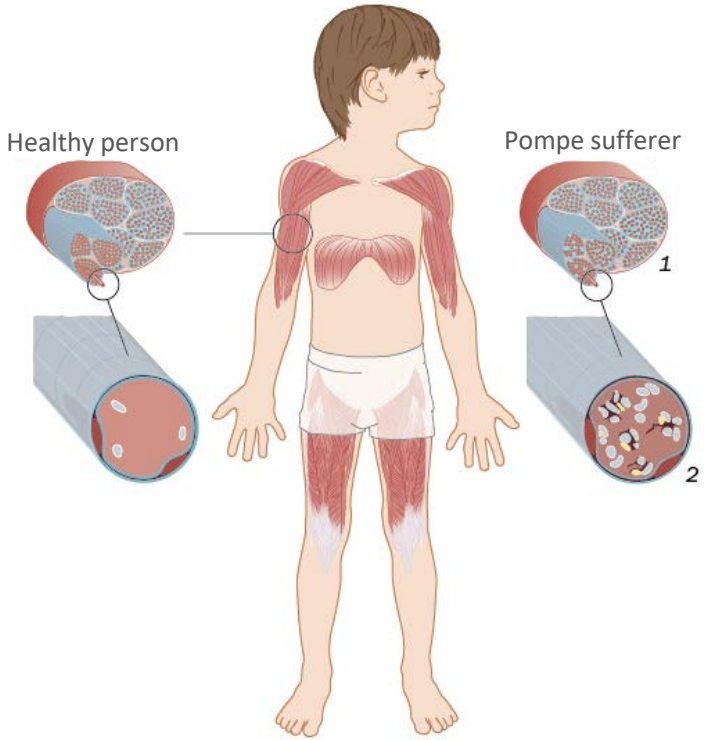
Pharming

Pompe disease

Normal situation



Pompe disease



- Progressive decrease in muscle strength starting with the legs and moving to smaller muscles in the trunk and arms, such as the diaphragm and other muscles required for breathing
- Cardiac failure and respiratory failure are the most common causes of death

Pharming

Therapy of Pompe Disease

- Enzyme replacement with recombinant human α-Glucosidase (rhaGLU)
- Two rhαGLU products on the market (from SANOFI-GENZYME): Myozyme® and Lumizyme®
- Current market size around $1.0~$1.2 billion
- Other products under development using similar CHO-cell derived rhαGLU base
- Current treatment: large (6 hour+) infusions of immunogenic version of α-Glu every 2 weeks
- Current estimation of market penetration 20-50%
- Infusion reactions in 50% of patients, and antibody formation in 80%+ of patients
- Immunogenic side effects in significant portion of patients
- Anaphylaxis/cardiac arrest in 1% of patients
- FDA Boxed Warnings on both products

→ There is still a significant unmet medical need

Pharming

Results of a Phase II clinical study with rabbit-derived α-glucosidase

Skeletal muscle α-glucosidase activities[a]			
	Activity (nmol/h per mg)		
Patient	*Muscle t=0*[b]	*Muscle t=1*[b]	*Muscle t=2*[b]
Patient 1	0.15	4.9	27.0
Patient 2	0.27	2.7	8.0
Patient 3	0.20	2.1	13.0
Patient 4	0.37	2.7	16.0

[a] Normal α-glucosidase activity 8-40 nmol/h per mg (n=29)

[b] t=0, baseline; t=1, 12 weeks after start of treatment with 15 or 20 mg/kg; t=2, 12 weeks after dose adapation to 40 mg/kg

Source: Van den Hout et al., J. Inherit. Metab. Dis., 24 (2001), 266-274

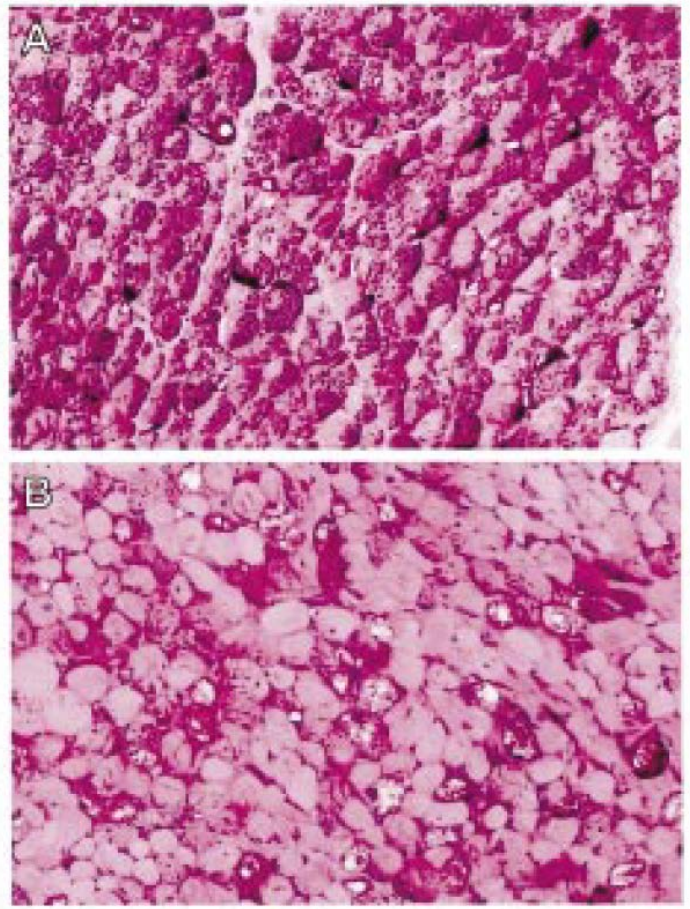


Figure 2 Muscle biopsy (cross-section) from patient 1 obtained before start of treatment with rhAGLU (A) and after 12 weeks of treatment with a dose of 40 mg/kg (B). Sections were stained with PAS to visualize lysosomal glycogen

Pharming

Achievements in developing α-glucosidase (rhαGLU)

- Transgenic rhαGLU lines generated (cDNA and gDNA) and lead lines identified
- Milk expression confirmed (> 5 g/l)
- Glycosylation pattern significantly different from existing products and much closer to human α-glucosidase
  - Natural α-glucosidase has 20 mannose-6 phosphate (M6P) groups to enable cell membrane entry – all approved products have fewer than 4 M6P groups
  - New rabbit line has almost normal M6P number
- All key analytical assays developed (activity, purity, identity)
- Production of validation batches underway
- Initiation of clinical trial supplies
- IND filing/ start of clinical trials planned for 1H2019

Pharming

α-Galactosidase
For Fabry's Disease

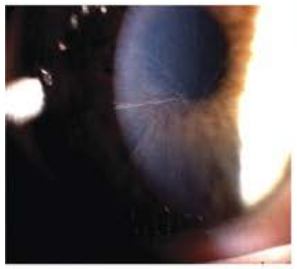
Pharming

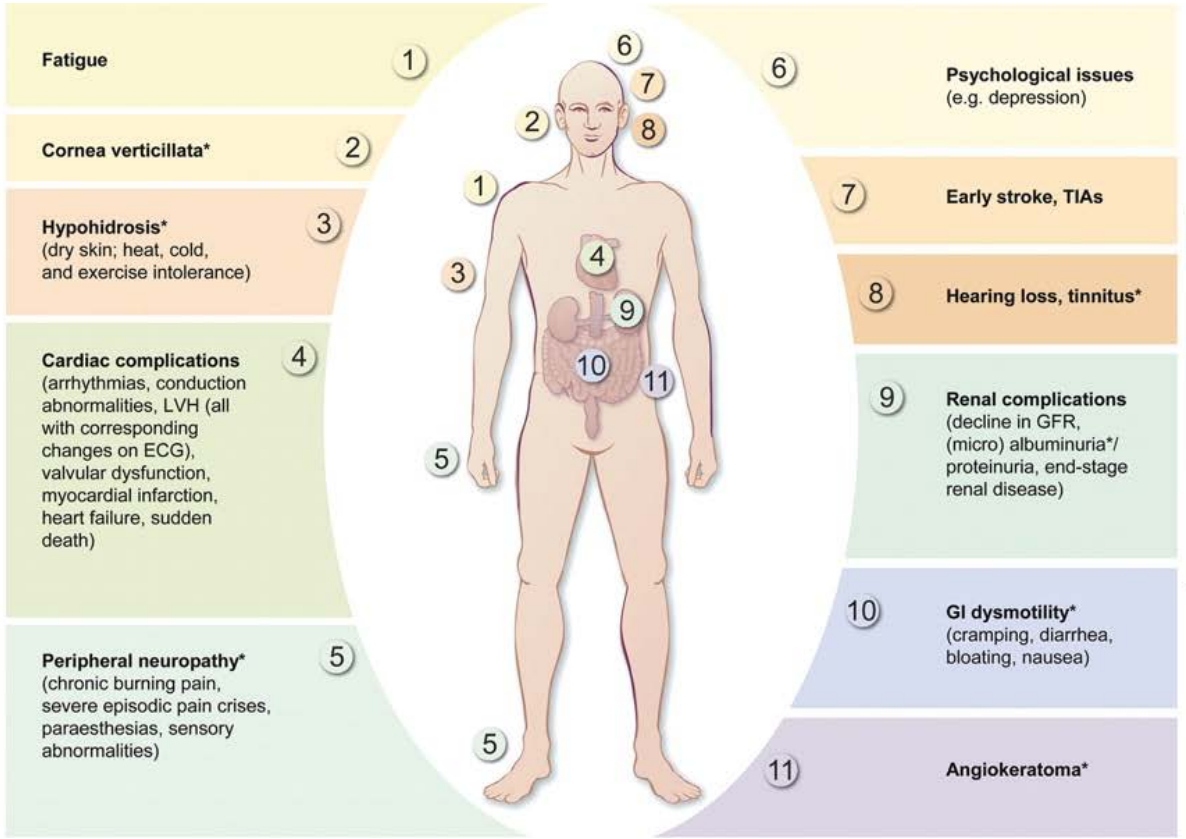
Fabry's Disease

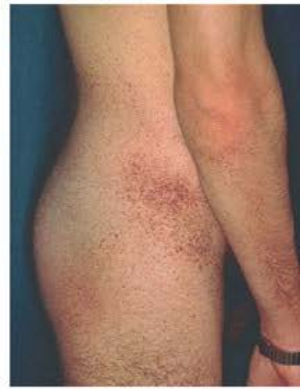
- Lysosomal storage disease
- X-linked recessive disorder
- Deficiency of lysosomal α-galactosidase
- Lysosomal accumulation of globotriaosylceramide within blood vessels, other tissues, and organs
- Historical prevalence 1:40,000 – 1:100,000
- Current therapy poor and immunogenic ($1.2 billion+ market)
- Current products (*Fabrazyme®*, *Replagal®*) have either FDA boxed warnings (US) or are not approved in USA
- Similar problems as for Pompe disease

Pharming

Fabry's Disease







Ref.: Zaheer Y, et al,
http://dx.doi.org/10.1093/eurheartj/ehs166 802-808
First published online: 26 June 2012

Symptoms: renal dysfunction,cardiac abnormalities,cerebrovascular manifestations,dermatological signs,ocular and auditory symptoms, neurological symptoms

Pharming

Therapy of Fabry's Disease

- Symptomatic treatment of GI, renal and cardiac symptoms
- Enzyme replacement with recombinant human α-Galactosidase (rhαGAL) is only causal therapy
- Two rhαGAL products on the market (from SANOFI-GENZYME and SHIRE) - either have boxed warnings (Fabrazyme®) or have not been approved in USA (Replagal®)
- Current estimation market penetration 10% treated with rhαGAL
- Antibody formation
  - IgG in 88% of patients in clinical trials
  - IgE in 3% of patients in clinical trials
  - 1% of anaphylactic shock or severe allergic reactions during infusion

→ There is still a significant unmet medical need

Pharming

Advantages of rhαGAL Produced with the Pharming Platform

- From the experience with RUCONEST® the following advantages can be reasonably expected:
  - Low immunogenicity due to glycosylation pattern
  - Lower likelihood of producing neutralizing antibodies
- Furthermore it is known that rhαGAL can be produced in acceptable yields in rabbits
- rhαGAL transgenic rabbit lines in hand, further optimization ongoing
  - Competitive cost of goods expected

Achievements so far:

- Transgenic rhαGAL lines generated (cDNA and gDNA)
- Milk expression confirmed
- Optimization of yield and identification of lead lines underway
- Glycosylation pattern significantly different from existing products and much closer to human α-galactosidase

Pharming

Milestones for Pipeline expansion

Pre-eclampsia:	Initial clinical Study due to start within Q4 2018
Contrast-induced nephropathy:	DBPC Phase II investigator-initiated study (IIS) ongoing, with data expected in Q3 2018 - may also provide signal on likelihood of reducing/ preventing cardiac damage
Cardiac Protection:	Could be initiated (if CIN study above is positive)
Delayed Graft Function:	Phase II IIS due to start in Q3 2018 (University of Wisconsin)
Hemorrhagic shock:	US Army/ US Air Force studies ongoing for several years in large mammal models
α-glucosidase (Pompe):	Phase I/II study starting 1H2019
α-galactosidase (Fabry's):	Phase I/II study expected to be initiated by 2020

(DBPC = Double blind, placebo-controlled study)

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1. Introduction
2. HAE Therapeutics Overview – Professor Marc Riedl, UCSD
3. HAE US market overview
4. Building the RUCONEST® franchise in HAE
5. rhC1INH: Indications beyond HAE
6. rhC1INH development for Pre-eclampsia – Professor Gustaaf Dekker, University of Adelaide
7. Contrast-induced nephropathy and cardiac protection, delayed graft function, hemorrhagic shock
8. Protein Replacement Therapy in Pompe and Fabry's diseases
9. Pharming's Commercial Potential
10. Summary

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Pharming's Commercial Potential

Robin Wright,
Chief Financial Officer, Pharming Group NV

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What indications can Pharming tackle with rhC1INH?

Important to play to our strengths:

- Some conditions are well controlled or do not represent major unmet needs, such as:
  - asthma
  - lupus erythematosus
  - inflammatory bowel disease
  - some forms of arthritis
- Others require difficult, large studies and would not normally be first on our list:
  - sepsis
  - autoimmune heart disease
  - multiple sclerosis
  - myocardial Infarction
  - stroke
  - glomerulonephritis
- The ideal first use of an C1 esterase inhibitor is in conditions which are caused by vascular inflammation/leakage, such as pre-eclampsia or contrast-induced nephropathy, as C1 esterase inhibitors may slow or stop the leakage process

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Potential for expansion for rhC1INH beyond HAE

- Sales are currently running at about 10% of the $1.8 billion HAE market
- Preliminary facts about the sizes of the indications we are investigating directly or through IIS projects:

Contrast-induced nephropathy:	No approved current treatment available. About 40 million contrast-enhanced exams performed each year in the USA. Approximate total size of prophylactic patient group*: up to 3 million patients per year
Pre-eclampsia	No approved current therapy. Approximately 4 million pregnancies per year in the USA, with around 3% incidence. Approximate total size of US patient group: up to 120,000 patients per year in US, 2.5 million globally
Delayed Graft Function	No current therapy. Approximately 25,000 instances per year in the USA, requiring chronic care if therapy works
Hypovolemic shock	No current therapy. Approximately 2 million instances of severe trauma per year in the USA, with another 2 million in Western Europe, plus ambulance/ hospital/military/paramedic supplies

* *Incidence between 3.3% (Mayo Clinic study) and 14.5% (William Beaumont Hospital study), depending on the relative proportions of certain higher-risk groups such as diabetics and renal-impaired patients*

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Potential for expansion of rhC1INH beyond HAE (continued)

- No ongoing studies at present, but related studies may prove the concepts….

  Cardiac protection: No current therapy – this would be used to reduce/ prevent damage to the vascular system as result of invasive investigative of therapeutic interventions -about 50 million procedures performed each year in the USA, of which a certain percentage may be relevant for intervention

- ….and there are sizeable markets in our other pipeline products:

  α-glucosidase (Pompe): Current market size approximately $1 billion – all products have boxed warnings

  α-galactosidase (Fabry's): Market size approximately $1.2 billion – all products have boxed warnings

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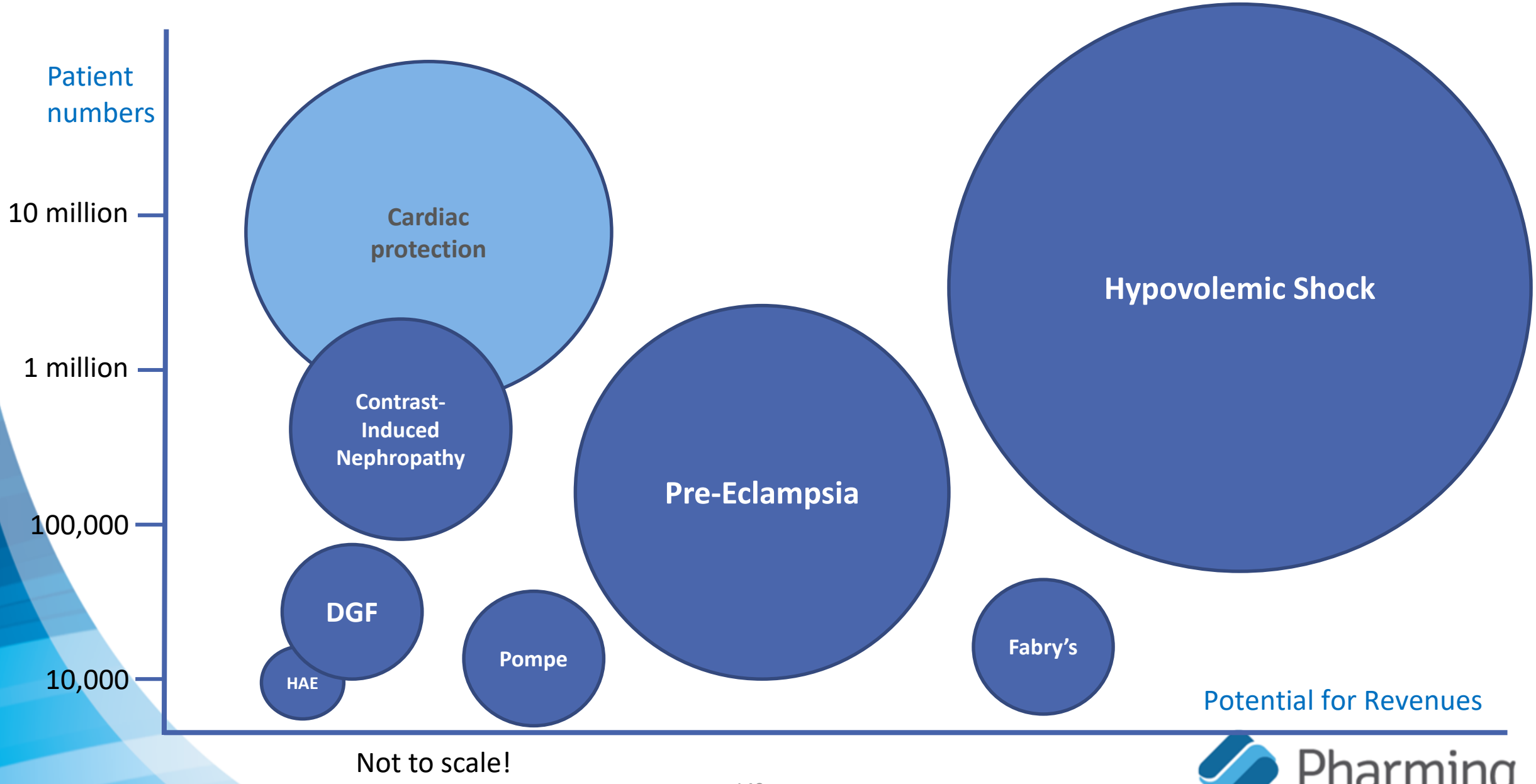
Potential addressable future markets



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Developing a RUCONEST® franchise

- Improving HAE patient convenience with smaller, liquid formulations which can be administered intravenously, subcutaneously, intracutaneously or intramuscularly as the patient wishes
- Removing pain from the process with simple reloadable IC device
- Expanding RUCONEST® into new large indications:
  - Pre-eclampsia: We will file our IND for rhC1INH in pre-eclampsia in the next couple of months
  - Contrast-induced Nephropathy – if data is positive, a formal Phase II study to develop this indication will be initiated
  - Cardiac protection: If positive signal for fast-acting Troponin, a clinical development program could be designed
  - Hemorraghic shock: Following evaluation of pre-clinical results, a clinical development program could be designed
- New IP on the new indications and cattle-derived rhC1INH

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Building Pharming beyond RUCONEST®

α-glucosidase and α-galactosidase

- Market potential for Pharming is over $1 billion per year in each indication
- Attractive market:
  - All current products have severe shortcomings and boxed warnings, but together sell for over $1 billion
  - Second generation products likely to have their own shortcomings
  - Many patients are not on therapy because of antibody formation or adverse reactions
- α-glucosidase for Pompe disease now finalising last parts of manufacturing file and upscaling production to produce clinical trial material
- IND and start of clinical trials to begin 1H2019
- α-galactosidase for Fabry in mid preclinical development; expected to reach IND filing stage in 2020

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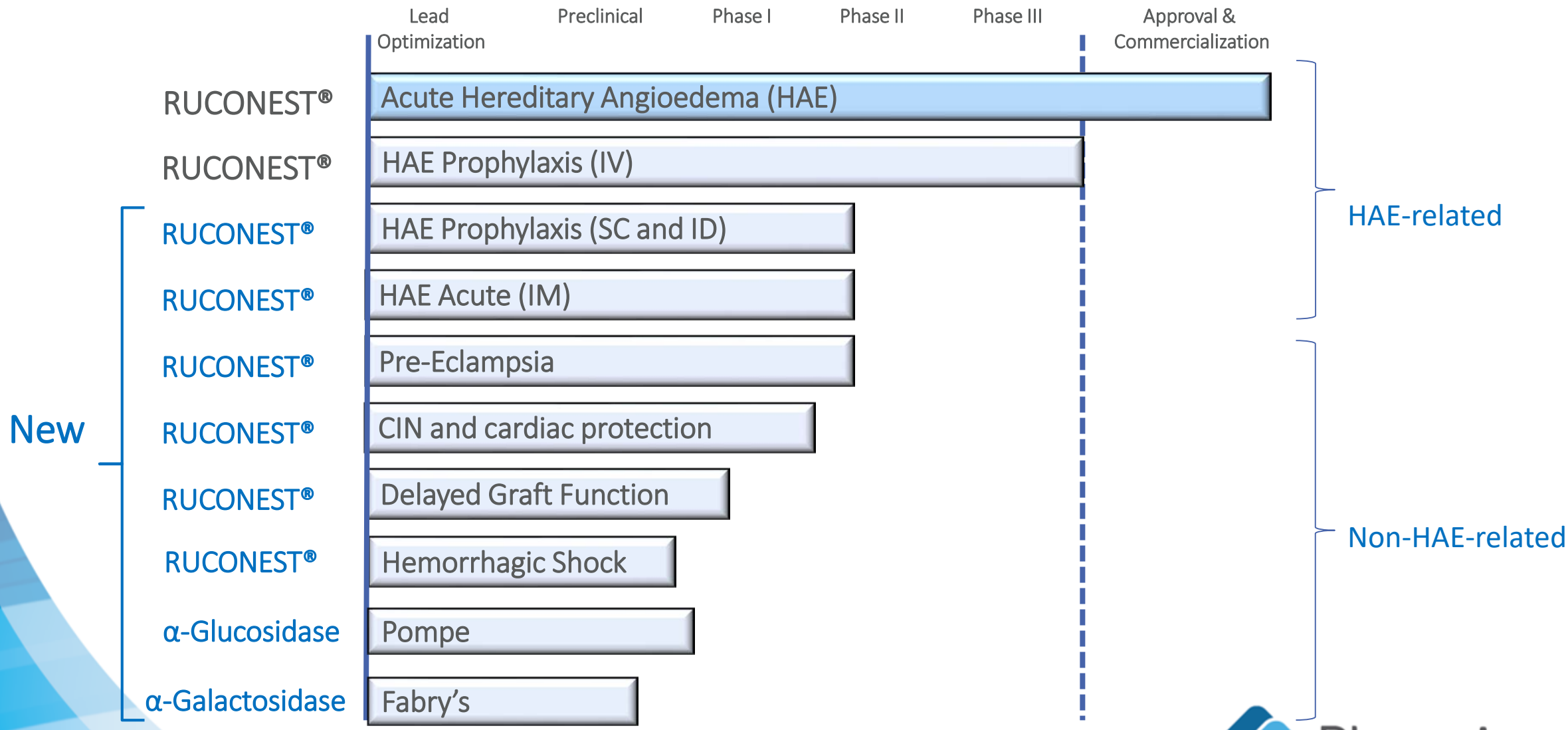
Expansion of RUCONEST® to a multiple market franchise



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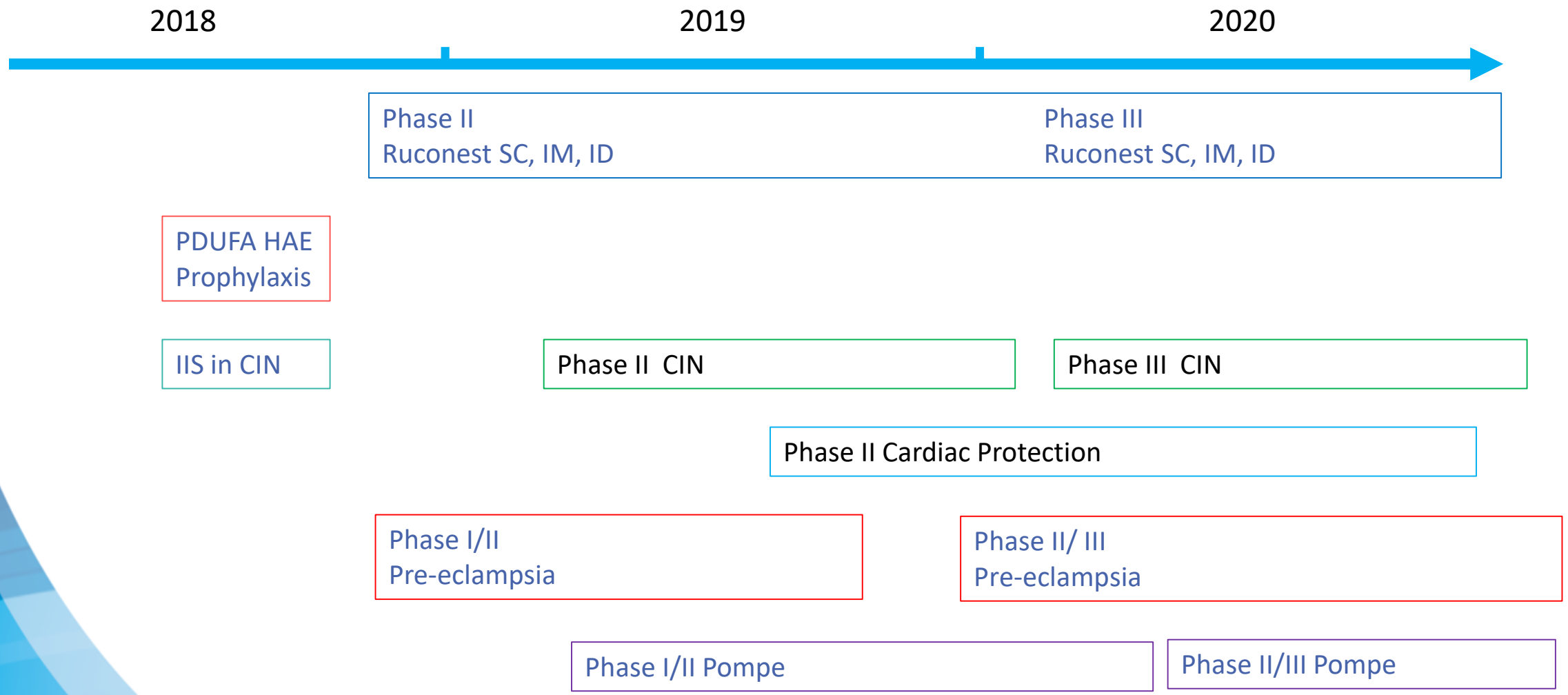
Potential for significant Newsflow over the coming years

Assumed solely for purpose of diagram: positive results of studies



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Pharming over the next few years

An excellent growth prospect across the board

- Now, profitability and positive cashflows achieved from commercialisation of lead product in the $1 billion acute HAE market which enables investments in expansion
- Increased HAE market potential once we can promote RUCONEST also for prophylaxis following FDA approval (action date 21 September 2018)
  - Need to increase convenience, so Pharming has initiated development of quicker/fewer/ easier injections, and pain-free administration options
- Multiplication of commercial potential and value if ANY of the new rhC1INH indication studies show positive results
  - Largest indications each have blockbuster sales potential and limited if any therapeutic options
  - Difficult for plasma-derived C1 competitors to scale up to supply any of these indications
  - New IP makes it difficult for early competition
- Significant additional commercial potential from positive results from clinical studies in Pompe disease and (later) Fabry's disease

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