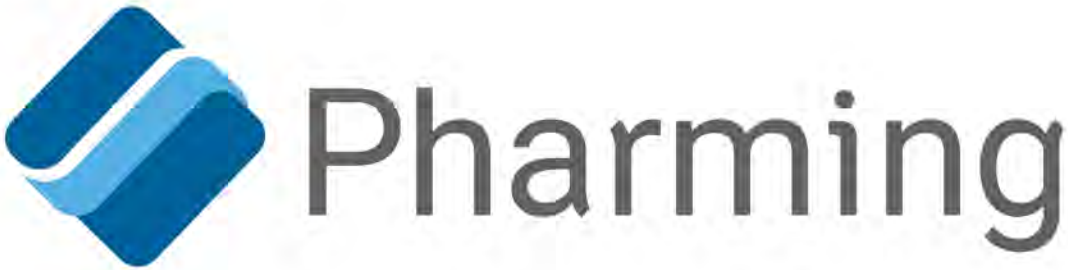
Pharming

Pharming Group

Sijmen de Vries
Chief Executive Officer

Bruno Giannetti
Chief Medical Officer

Robin Wright
Chief Financial Officer

Mireille Sanders
Senior Vice President, Operations

Anurag Relan
Vice President, Clinical Research/Medical Affairs

Pharming Forum Day

26 October 2019

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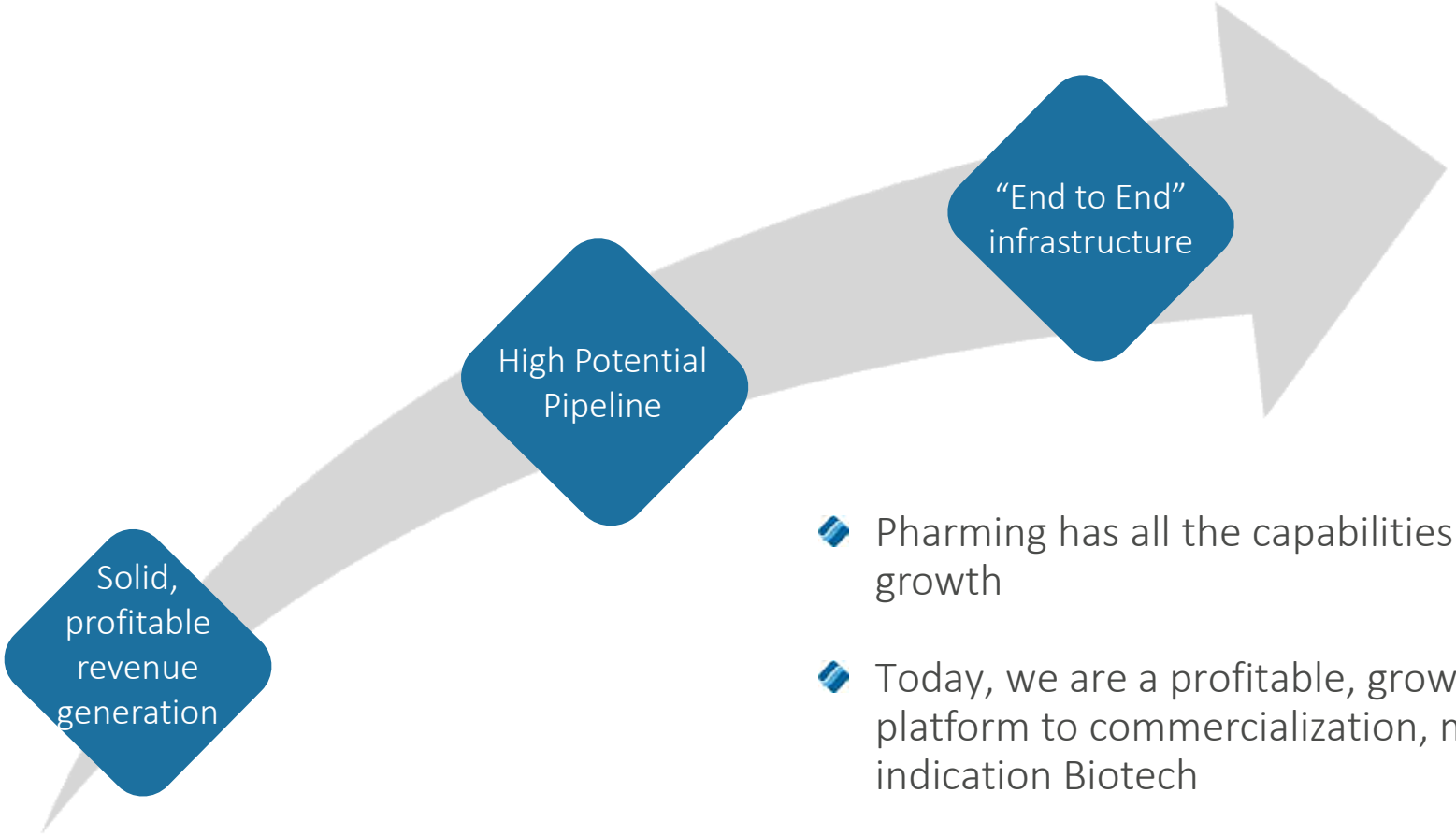
Company Overview

- **Public Company:** Euronext: PHARM: ~€750million (~$820 million)
- **Domiciled:** the Netherlands, ~206 employees globally
- **Current Focus:** Rare and Ultra-rare disease development and commercialization
  - Marketed product: **RUCONEST®**
  - Recombinant human C1-esterase inhibitor (enzyme replacement therapy)
  - For acute angioedema attacks in patients with hereditary angioedema (HAE)
  - Marketed in USA, EU, LatAm, Korea and Israel with other territories coming
- **Profitable and cash flow positive with 9m 2019 net sales of €123M and expecting continued growth in sales**

Pharming today and into the future



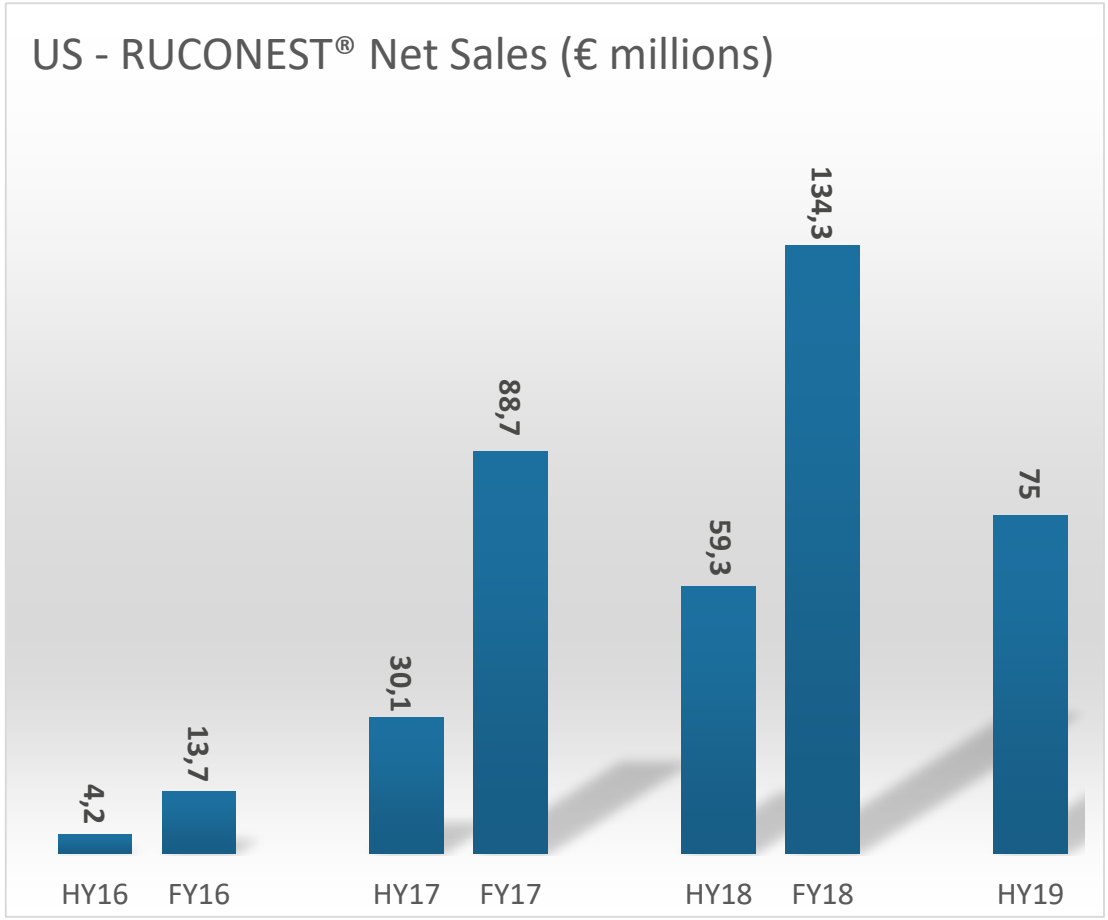
- Pharming has all the capabilities needed for sustainable, high growth
- Today, we are a profitable, growing and fully integrated, from platform to commercialization, multiple product, multiple indication Biotech
- From this we can drive lasting additional growth by developing innovative solutions in select rare, ultra-rare and specialty diseases

Solid, profitable revenue generation

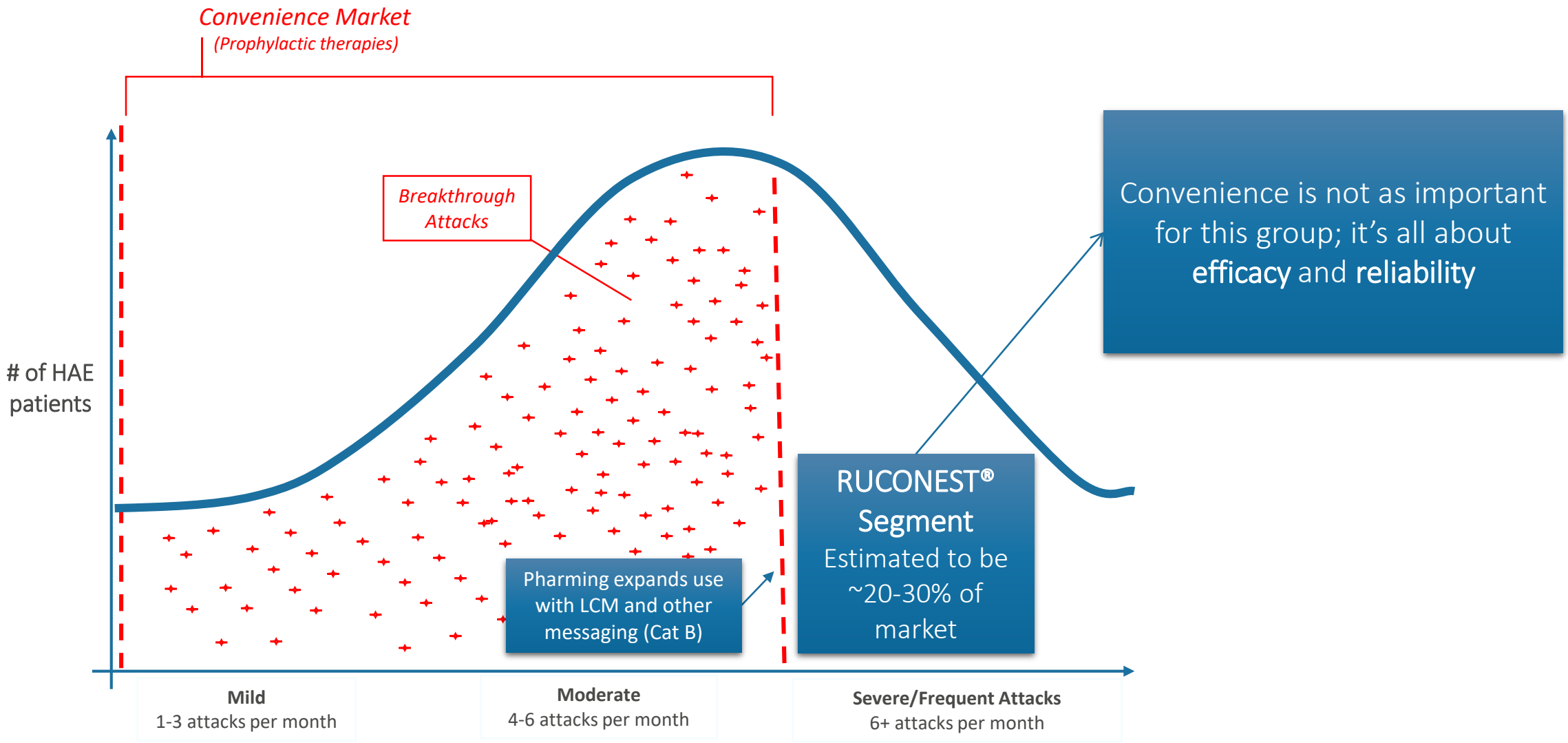
RUCONEST® : Strong Execution of Commercial Strategy

- HAE is a complex, serious disease with many idiosyncrasies and a varied market. The current approved therapies all address certain specific segments/phenotypes of HAE.
- RUCONEST® as the only recombinant PRT serves a segment the other therapies are unable to serve in an adequate way, due to its dosing and method of administration
- Pharming, as a result of the solid RUCONEST®; business, has a strong balance sheet with growing cash position
- With Q3 results, we are almost at the full year 2018 level

Pharming is in a very strong position to execute and grow



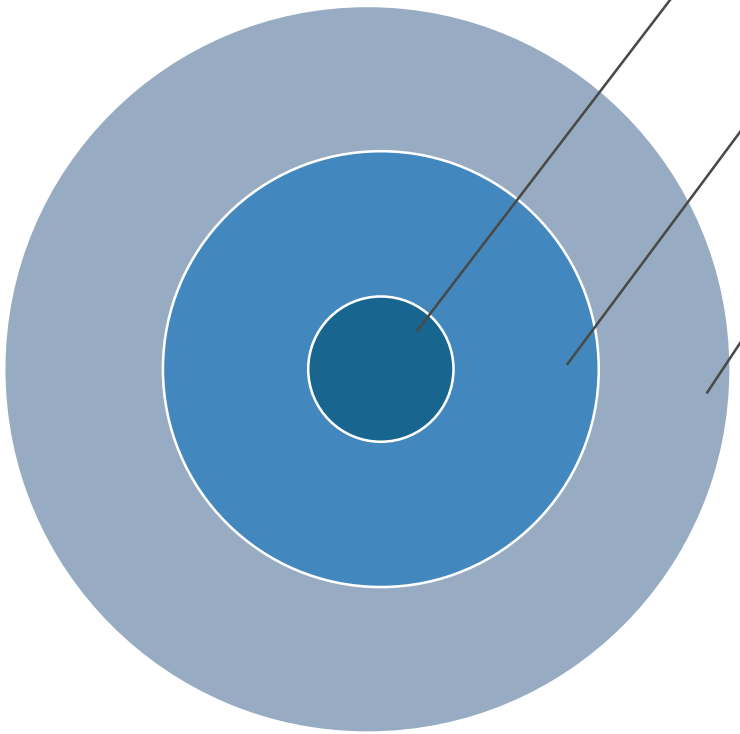
RUCONEST®: Patient Segmentation



1. Banerji A, et al. Allergy Asthma Proc. 2018;39:212-223

High Potential Pipeline

Investment Strategy: Focus, Leverage our Strengths



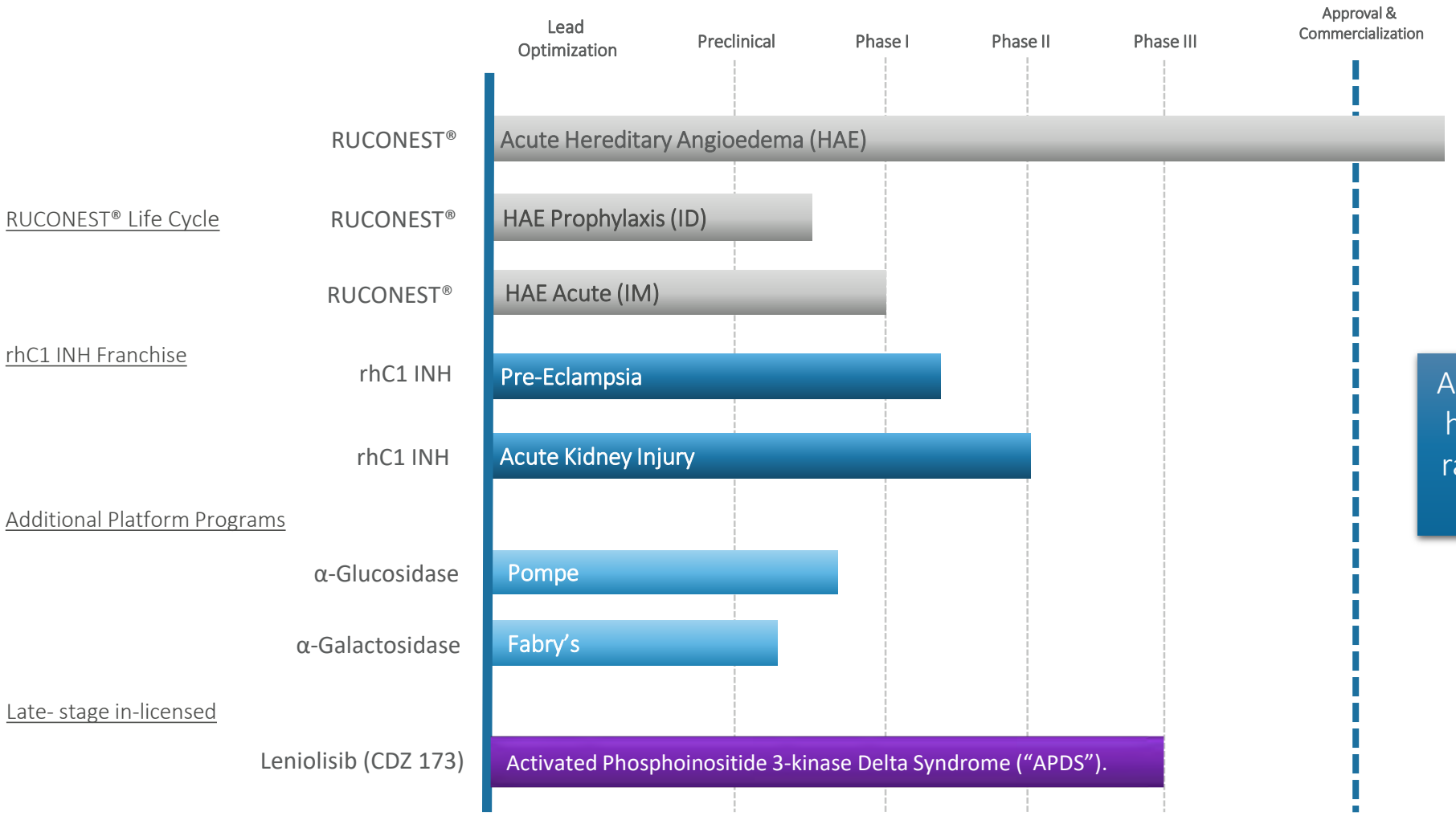
Continued Investment in HAE

Investment in new indications for rhC1INH such as Pre-eclampsia and AKI for C1INH

Licensing/acquisition of additional rare/ultra-rare asset near-to-market

Active Business Development aimed at capital efficient and smart investments that leverage commercial infrastructure ahead of maturation of new indications/ new internal pipeline projects

High Potential Pipeline



All development plans have strong scientific rationale and address high unmet needs

From Milk to Medicine

Mireille Sanders MSc

Sr VP Operations

From Milk to Medicine

Milking & Skimming/ Upstream processing (USP)

Downstream Processing (DSP)

Fill & Finish (F&F)

Packaging & Labeling

Production

Transport

Storage

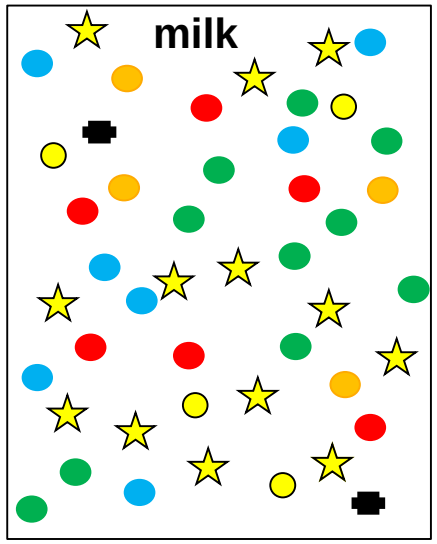
Step 1: USP

- 4x per week milking
- Skimming of milk
- Shelf-life 4 years

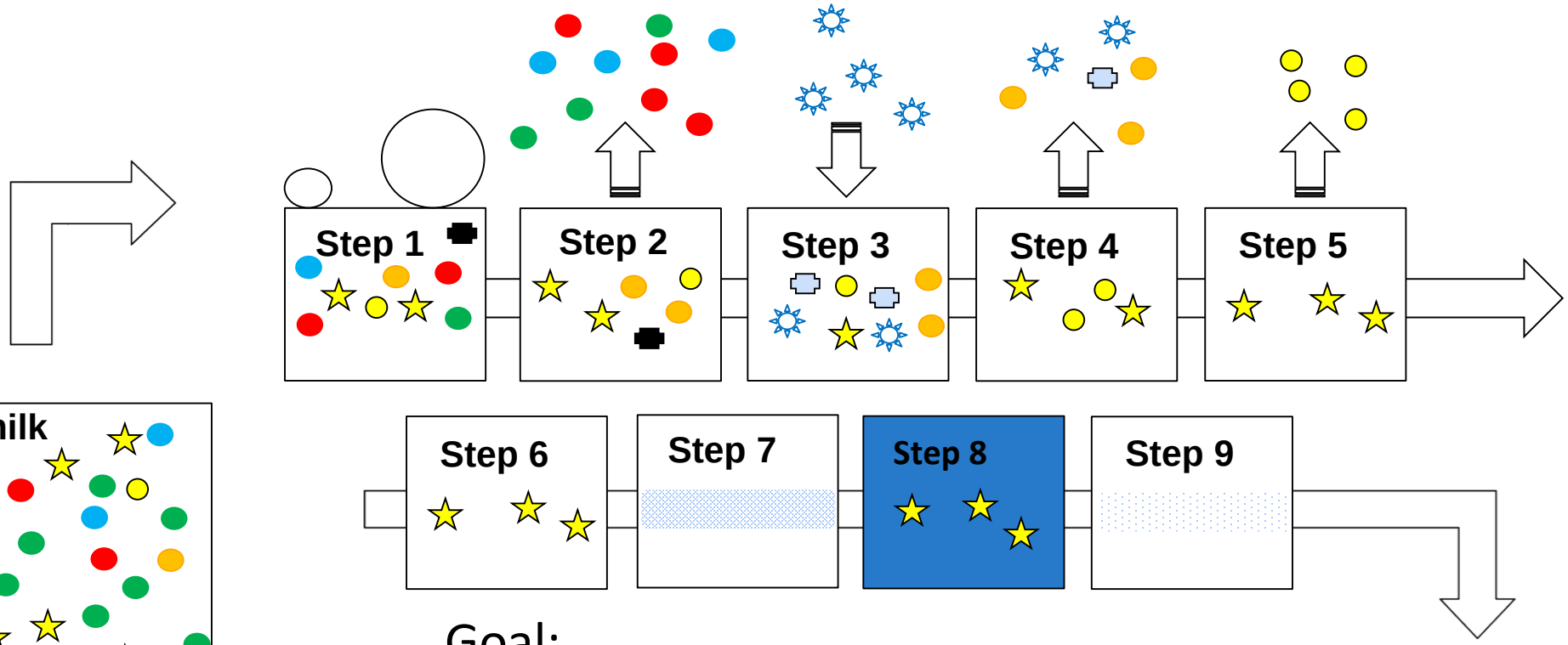
Step 2 and 3: Transport and Storage

- Transport of freezers
- Controlled storage at ≤ -60 °C

Step 5: Downstream Processing

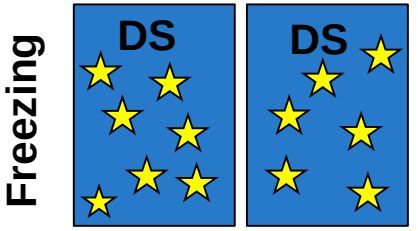


~90 bags



Goal:

- Purification
- Virus inactivation/removal
- Concentration
- Formulation

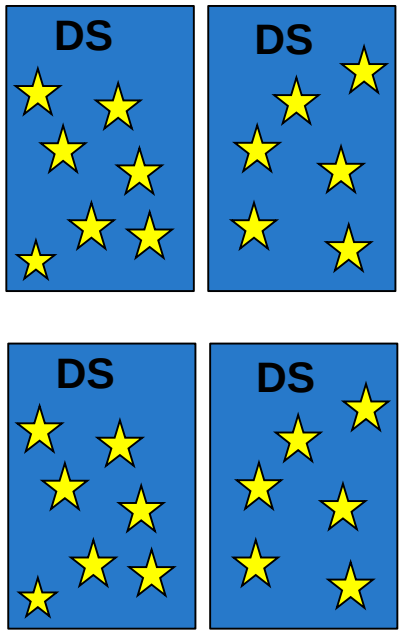


2 bags
Drug Substance (DS)

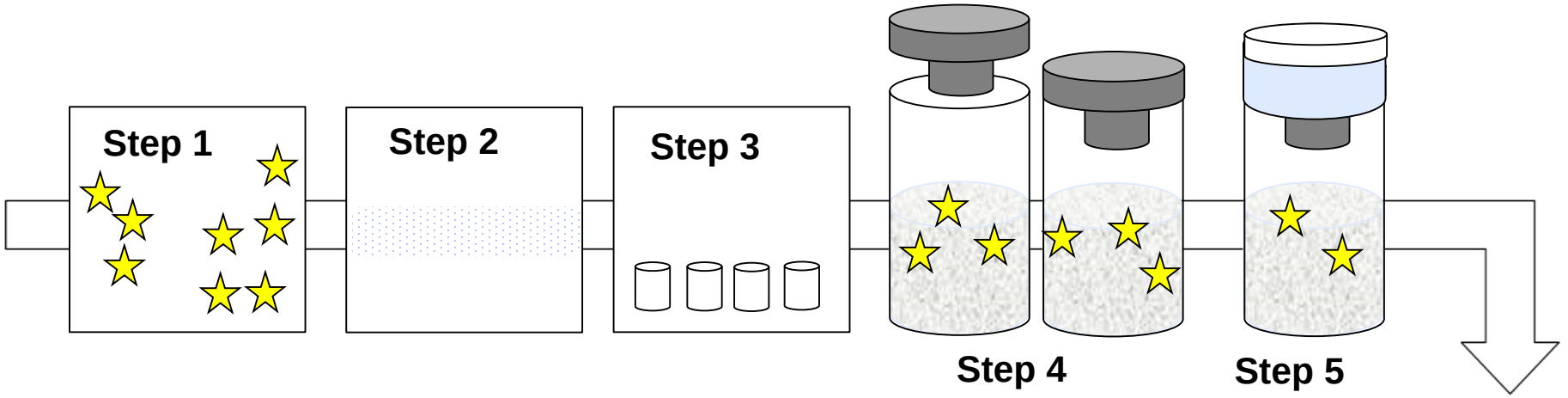
Step 5: Downstream Processing

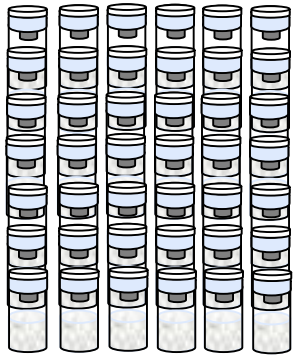
Step 6: Transport

Step 7: Fill & Finish



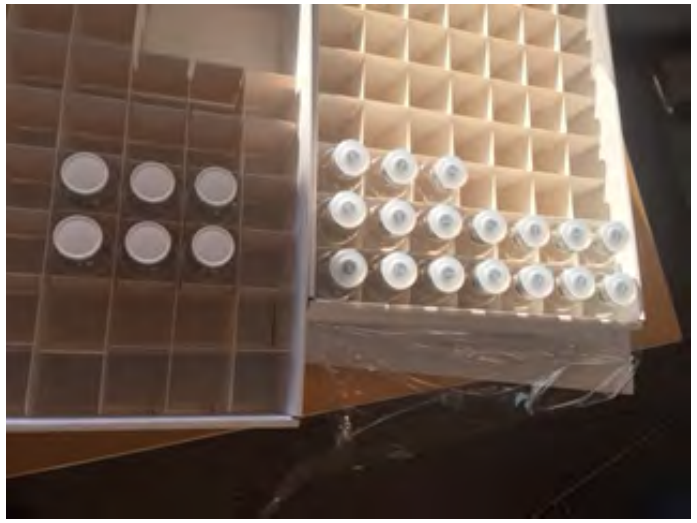
4 bags



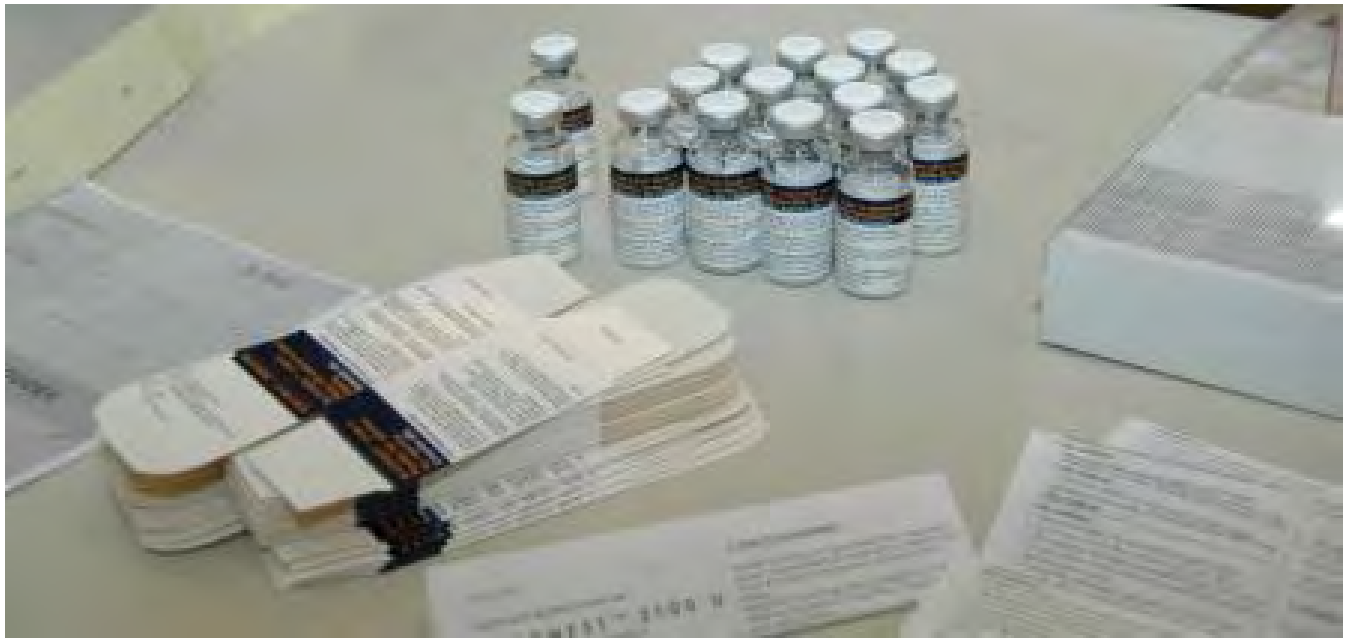


~2500 vials

Step 7: Fill & Finish

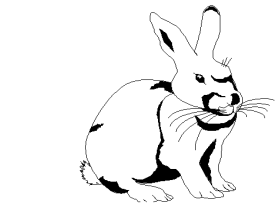


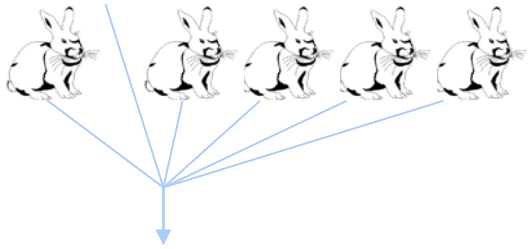
Step 9: Packaging & Labeling

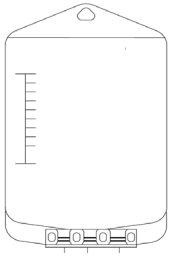


From Milk to Medicine

USP







Day milk pool

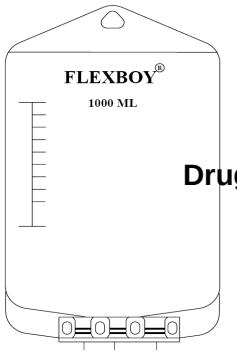
Skimming

Milk bag

DSP

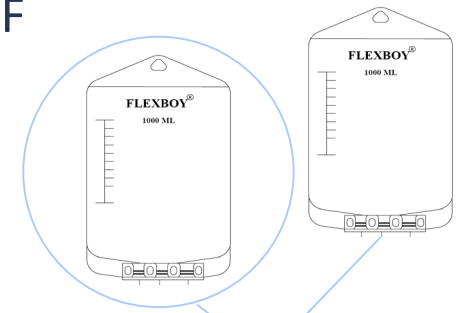
Milk batch

1 bag skimmed milk
≈ 10 treatments



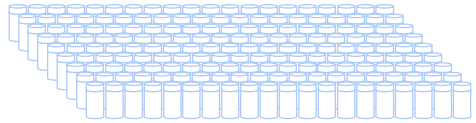
Drug Substance batch

F/F



Pooled DS

Fill & Finish



Drug Product batch

RUCONEST® in Hereditary Angioedema

Prof. Bruno Giannetti MD PhD

Overview of HAE

Genetic and Biochemical Background

Clinical Picture HAE

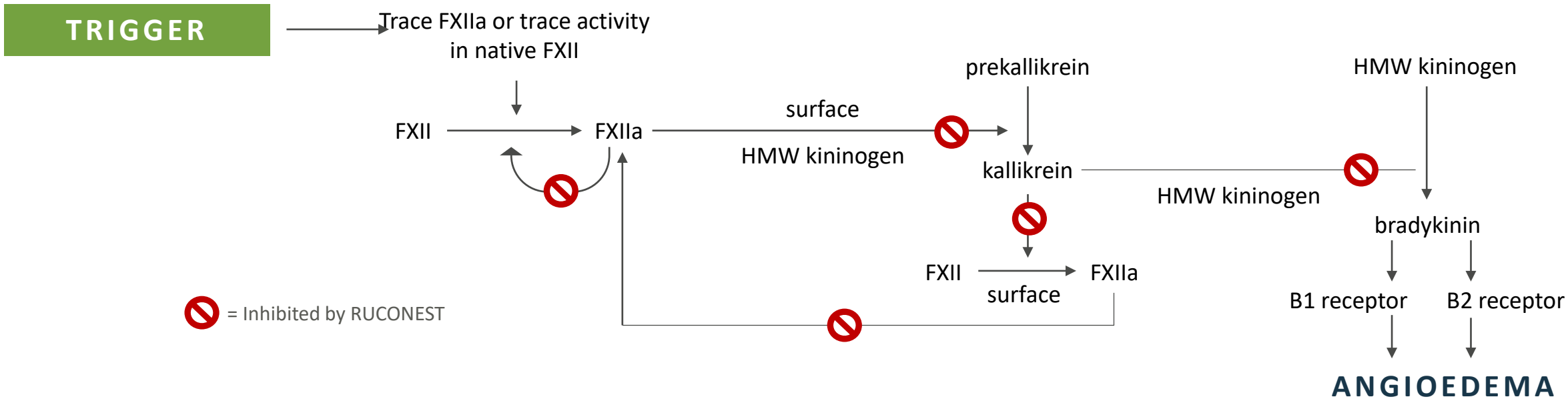
RUCONEST® (C1 esterase inhibitor [recombinant])

Recombinant Technology

Clinical Data

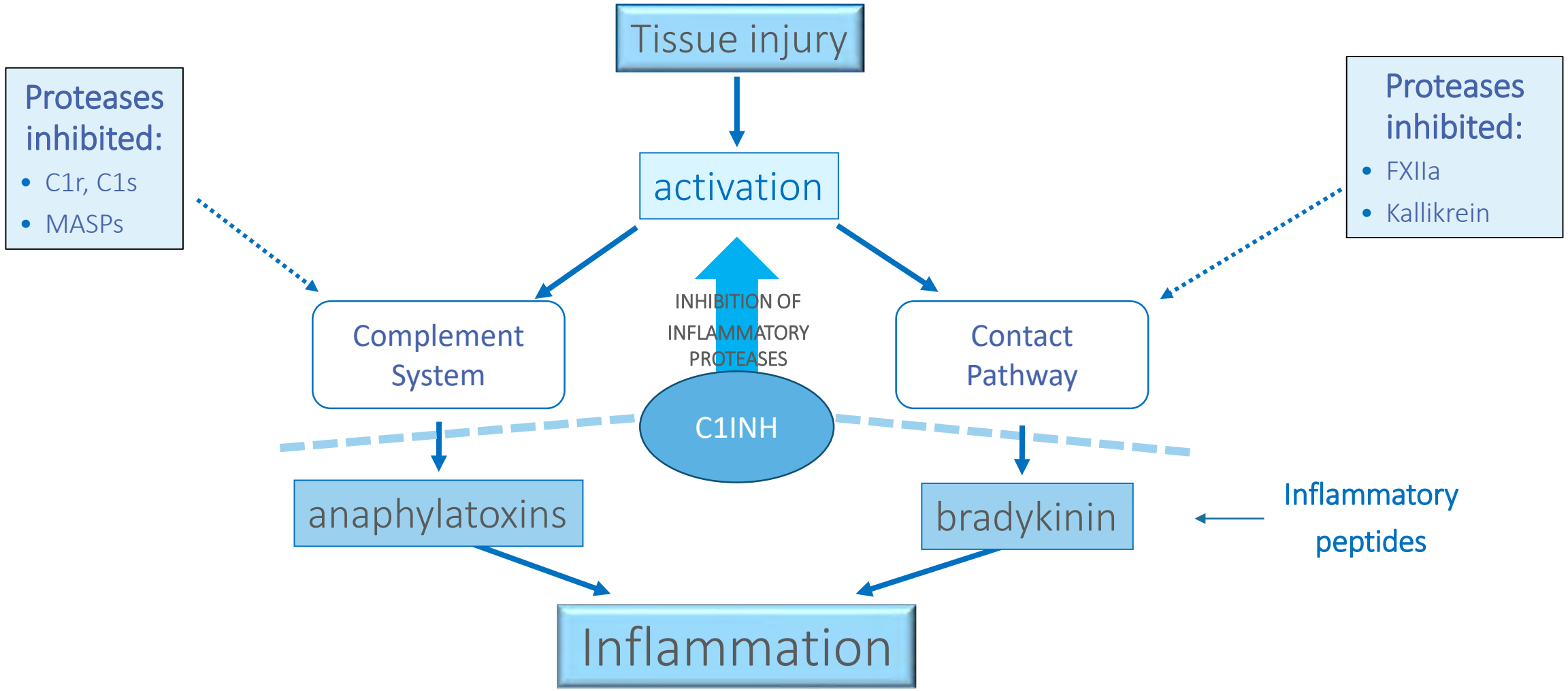
Latest Developments

The Complement Cascade - Contact Pathway



RUCONEST is a recombinant C1-INH that targets HAE at the source.[1,2]

The Complement Cascade - Overview



HAE – A C1INH Deficiency

TYPE I

- Characterized by low levels (below 50% of normal) and low inhibitory function of C1-INH
- Approximately 85% of HAE C1-INH cases

TYPE II

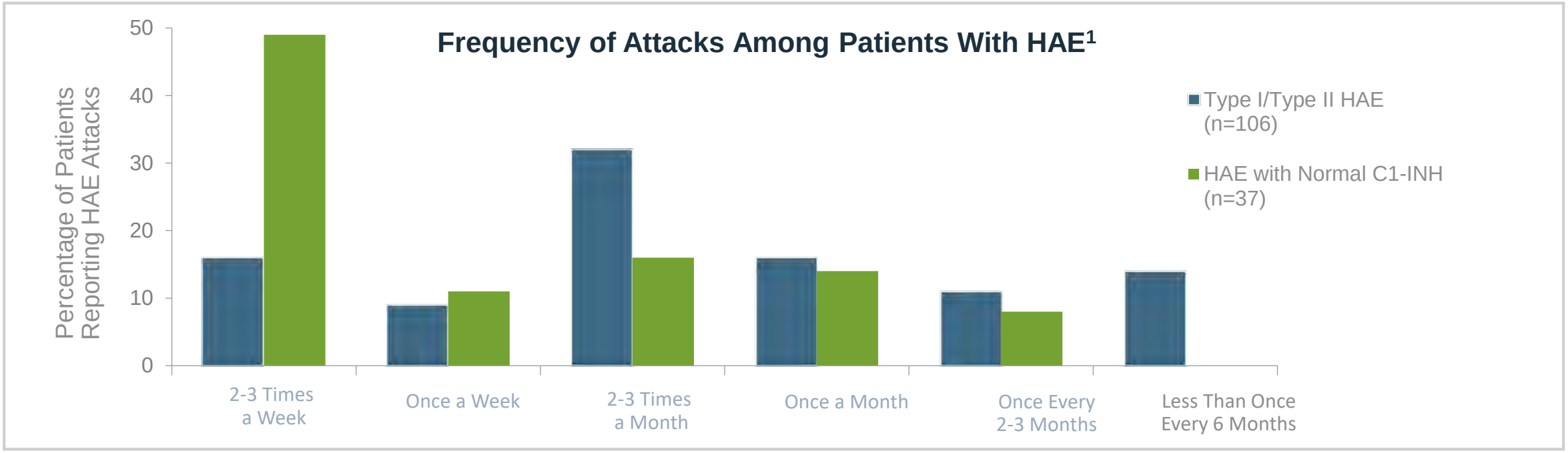
- Associated with normal or elevated antigenic levels of C1-INH with low functional activity
- Approximately 15% of HAE C1-INH cases

HAE With Normal C1-INH

- Previously known as type III HAE
- Most cases are due to unknown cause
- Due to various mutations in FXII gene, resulting in increased activity of FXII, leading to a high generation of bradykinin

HAE occurs in about 1 in 50,000 people.

HAE Attacks Vary in Frequency, Severity and Localization

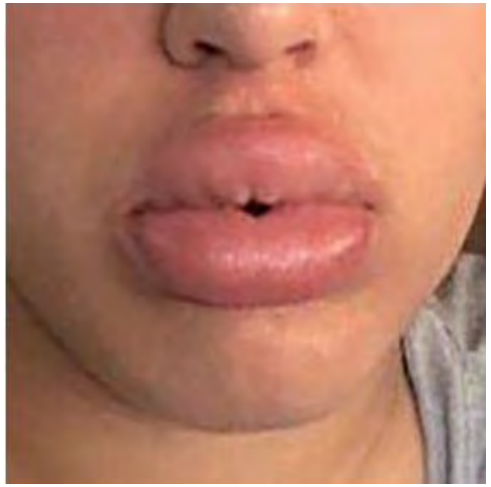


*According to the results of a 2015 survey (n=77).

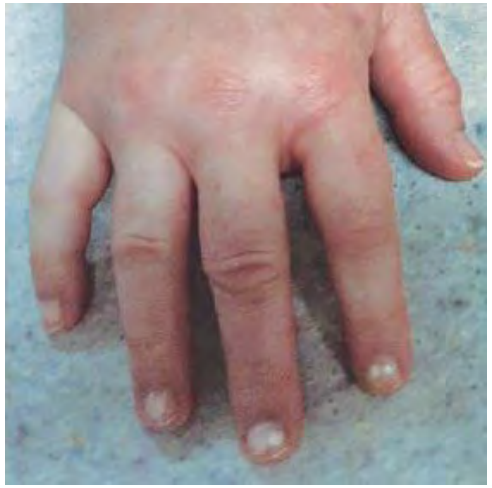
- HAE causes repeated episodes of unexplained swelling that can occur at any time, in almost any part of the body
- Nearly all patients with HAE described their symptoms during an attack as **"moderately severe"** or **"very severe"**

HAE Attacks – Clinical Examples

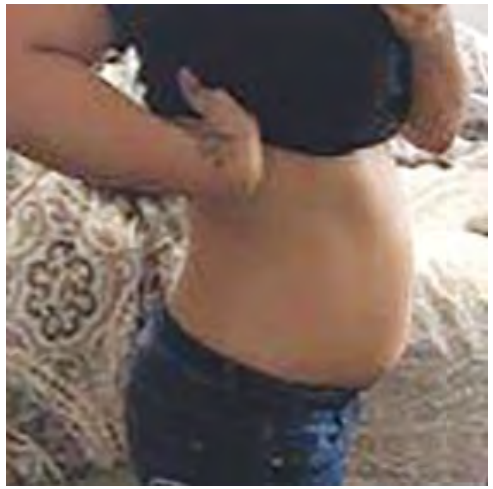
Facial swelling
during an HAE attack



Hand swelling
during an HAE attack



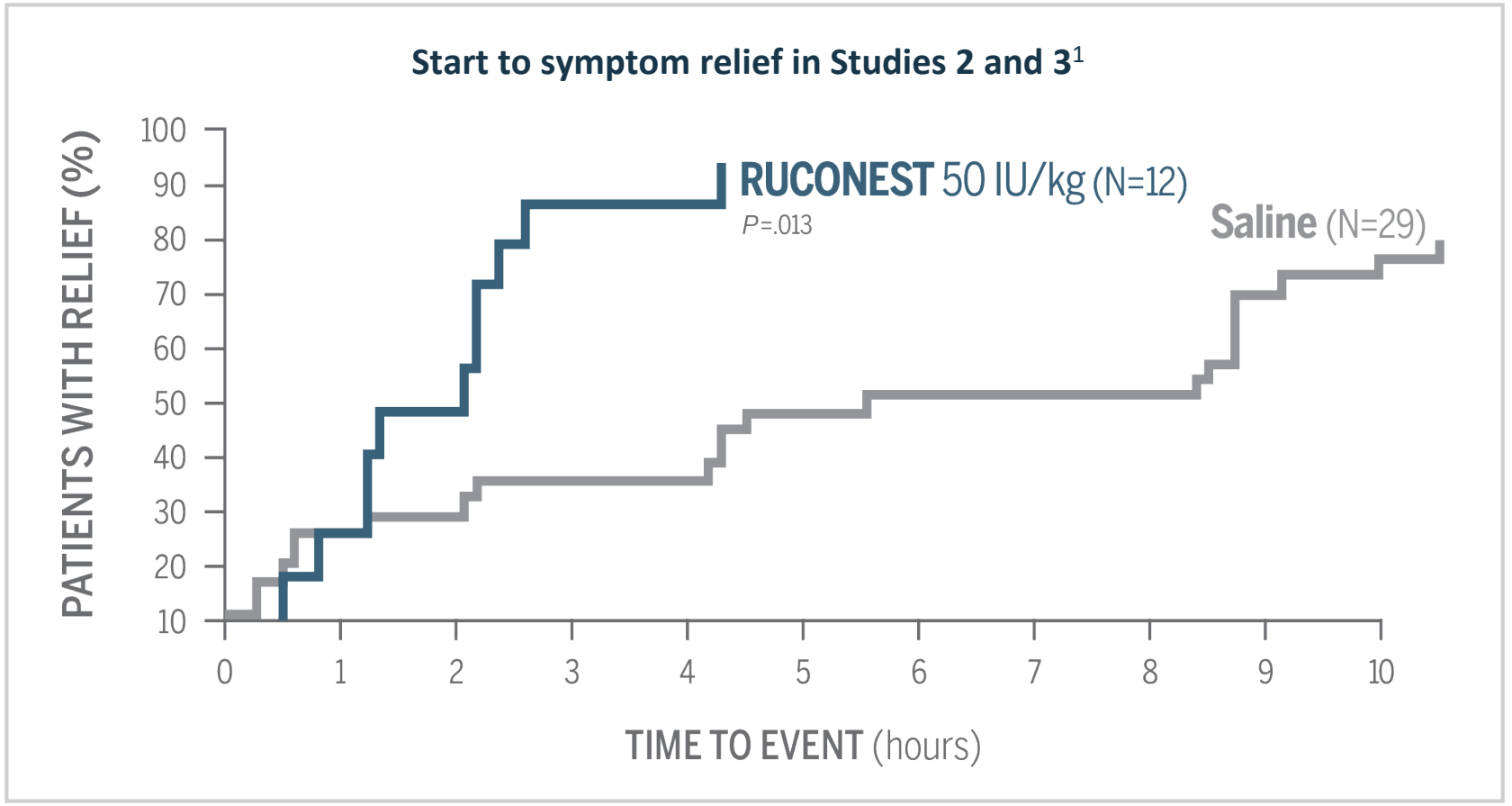
Abdominal swelling
during an HAE attack



Swelling can start in one area and spread to another. Sometimes, this can become life-threatening.
It's important to treat all HAE swells at the first sign of symptoms

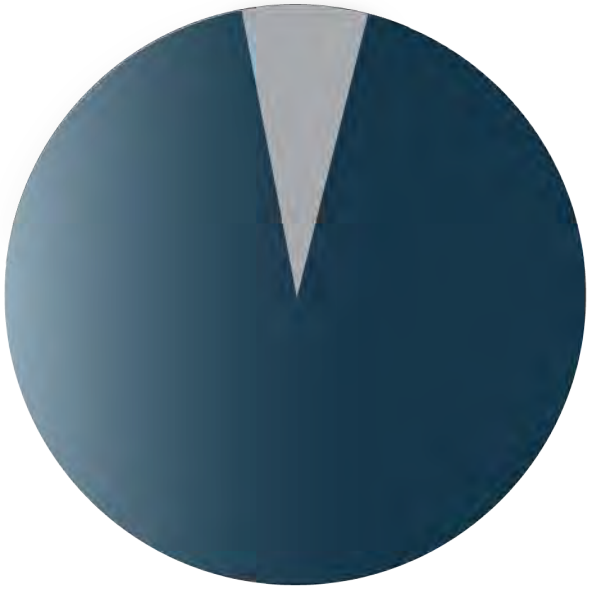
SELECTED DATA ON TREATMENT OF ACUTE HAE ATTACKS

RUCONEST Provided Rapid Symptom Relief from Acute Attacks



Riedl MA, et al. *Ann Allergy Asthma Immunol.* 2014;112(2):163-169.e1.

One Dose of RUCONEST Stopped Most Acute Attacks



97 %

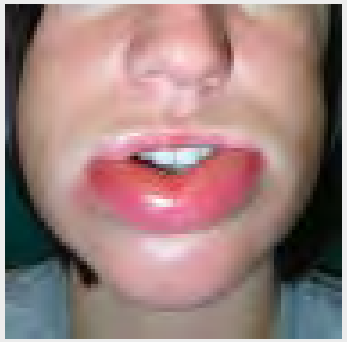
of attacks needed JUST ONE DOSE of RUCONEST 50 U/kg

(open-label extension phase, n=44 [170 attacks])

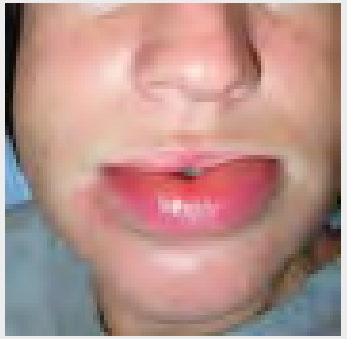
~9 out of 10 patients achieved symptom relief in the pivotal clinical trial with just one dose (n=44)

One Dose of RUCONEST Stopped Most Acute Attacks

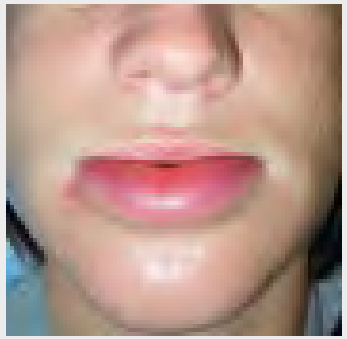
Patients enrolled in clinical studies were required to be experiencing a moderate to severe HAE attack prior to starting RUCONEST



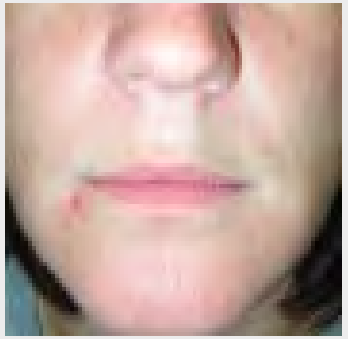
TIME OF
taking RUCONEST



1 HOUR
after taking RUCONEST



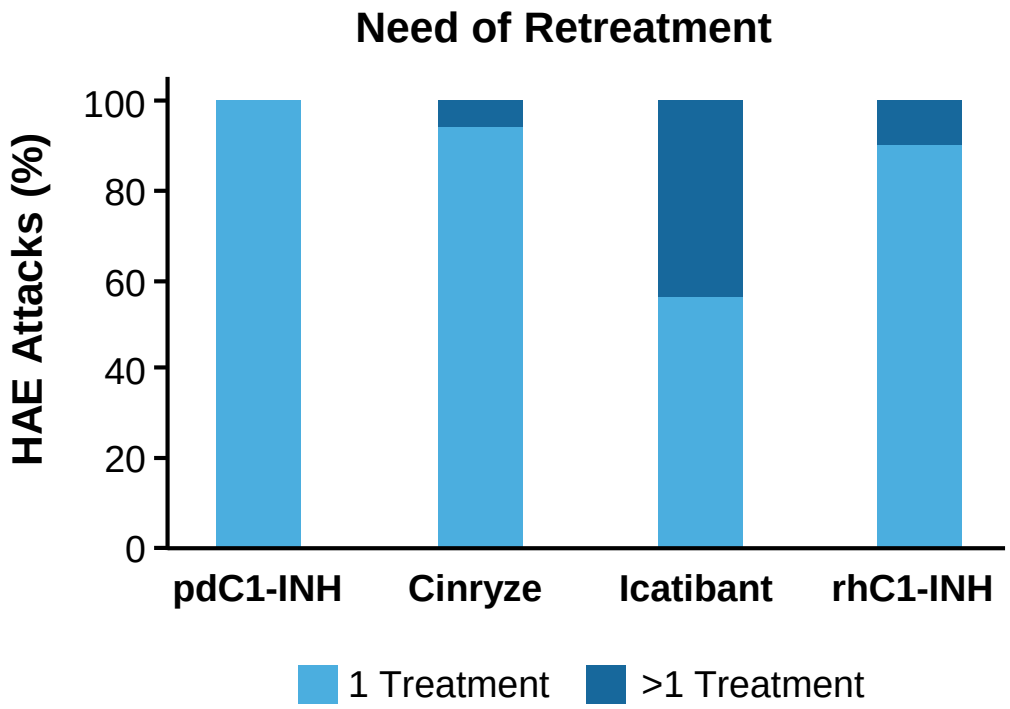
4 HOURS
after taking RUCONEST



24 HOURS
after taking RUCONEST

Additional Dosing Requirements

- 79% of HAE attacks were treated with 1 dose of therapy
- Icatibant had the highest number of treated attacks requiring >1 dose (44%)



HAE = hereditary angioedema; pdC1-INH = plasma-derived C1 esterase inhibitor; rhC1-INH = recombinant human C1 esterase inhibitor.
Magerl M, Zampeli V, Buttgereit T, Maurer M. Magerl M, et al. Presented at the 4th GA²LEN Global Urticaria Forum, Berlin Germany, December 5-6, 2018.

RUCONEST: The First and Only Plasma-free C1-INH

- 97% of acute attacks were successfully treated with **just one dose**
- Relief that lasted **for at least three days**
- High dose of C1-INH **to treat the root cause of HAE**
- Symptom relief that’s proven **rapid and reliable**
- Recombinant design with a **dependable supply**
- **Individualized nurse support**

SELECTED DATA ON PROPHYLAXIS OF ACUTE HAE ATTACKS

Prophylaxis For HAE Phase 2: Study Design

Pharming

Double-blind, multicenter, crossover study

Patient population:

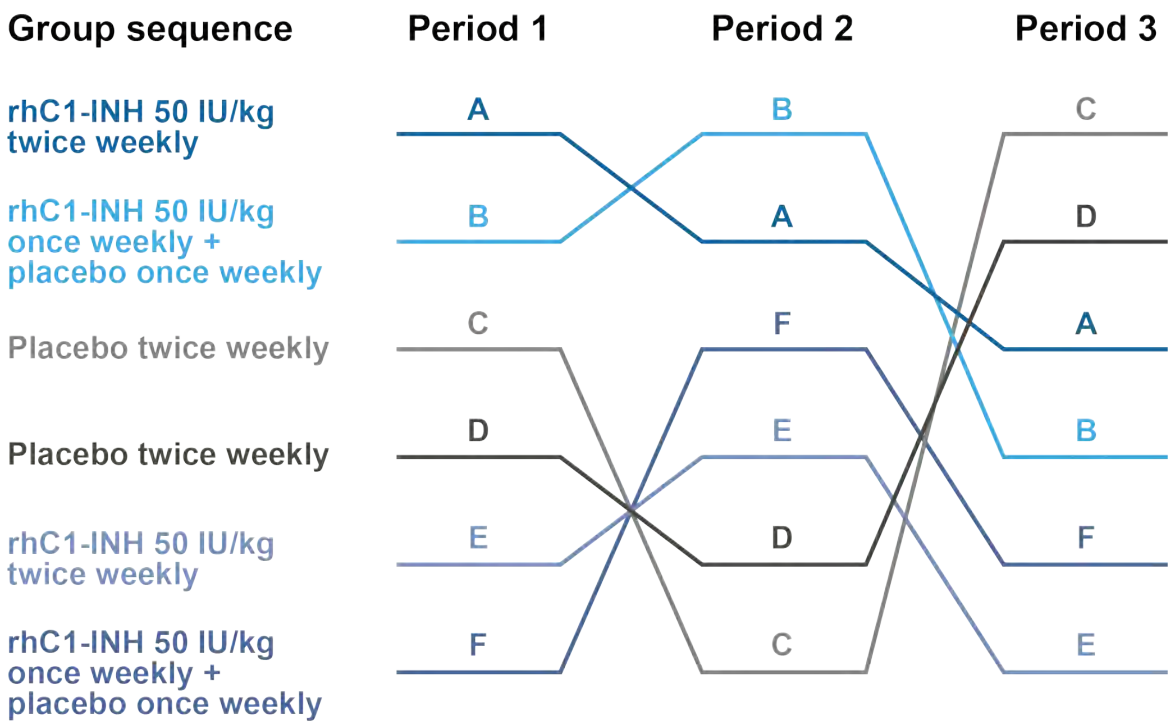
- ≥13 years of age
- Functional C1-INH <50% of normal using a chromogenic assay
- Frequent HAE attacks*

Randomly assigned to 1 of 6 treatment sequences, each consisting of 3 separate 4-week treatment periods separated by a 1-week washout period

- rhC1-INH 50 IU/kg† twice weekly
- rhC1-INH 50 IU/kg† once weekly + placebo once weekly
- Placebo twice weekly

Rescue medications permitted for breakthrough HAE attacks‡

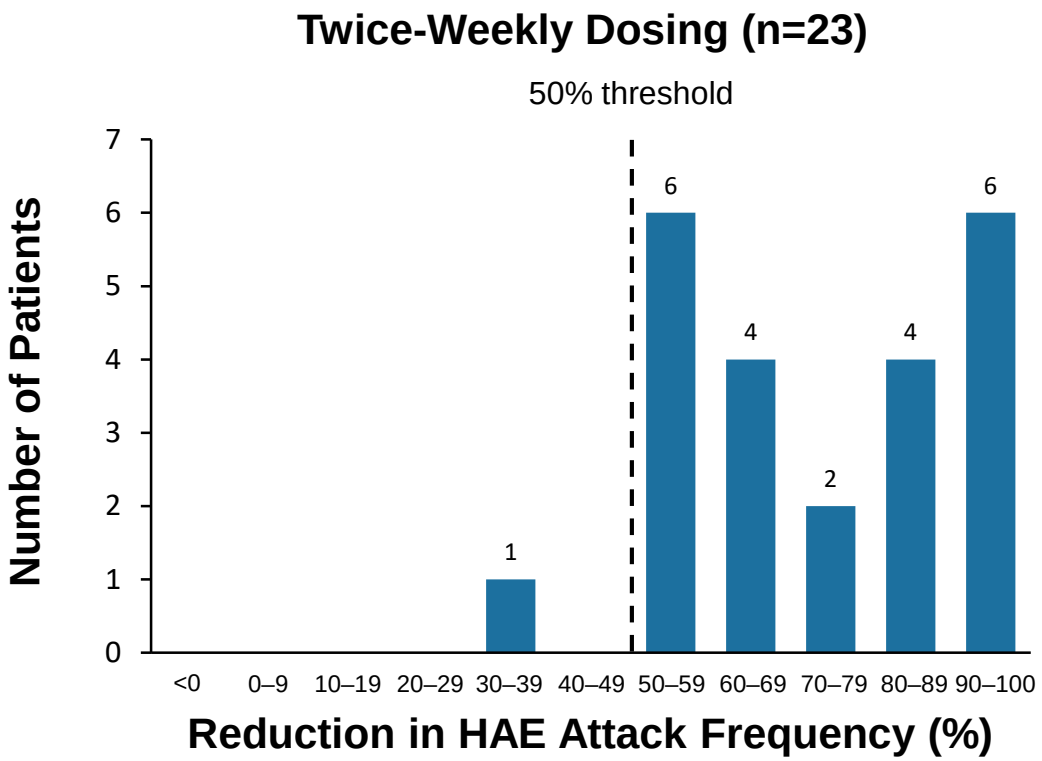
- pdC1-INH only permitted for laryngeal HAE attacks

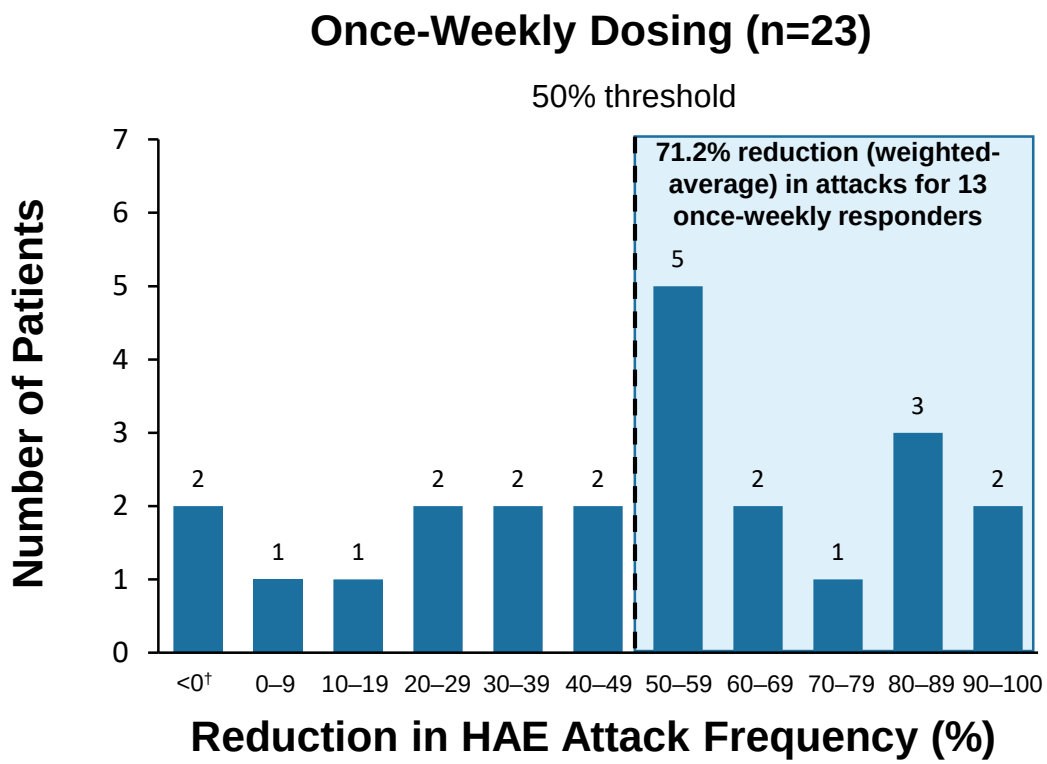


- *≥4 attacks per month for ≥3 consecutive months. †50 IU/kg for patients <84 kg; 4200 IU for patients ≥84 kg.
- ‡Rescue medications could include open-label rhC1-INH, HAE-specific medications (eg, icatibant), or symptomatic medications (eg, narcotics).
- C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; pdC1-INH = plasma-derived C1 esterase inhibitor; rhC1-INH = recombinant human C1 esterase inhibitor.
- Riedl MA, et al. *Lancet.* 2017;390(10102):1595-1602.

Clinical Response Frequency (PP Population)

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

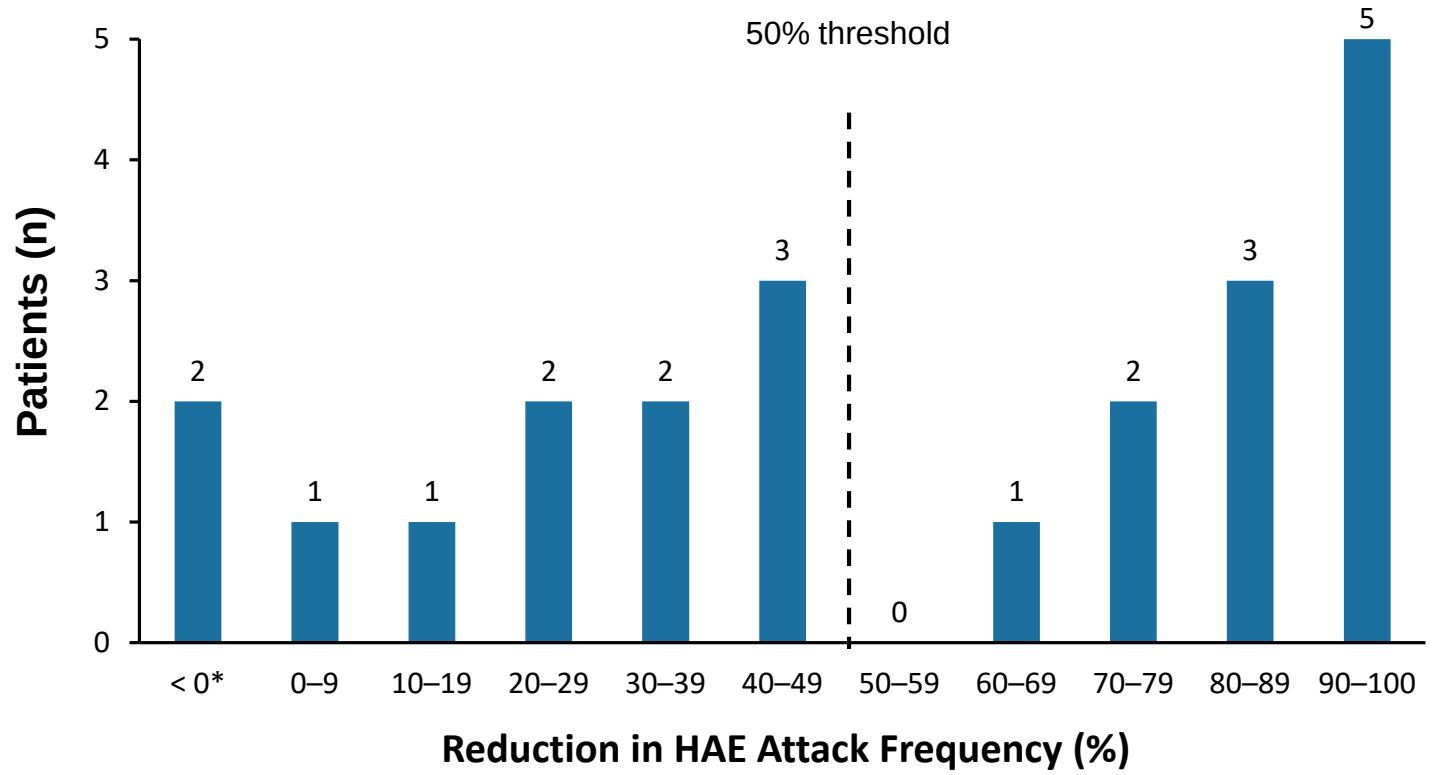




- *Defined as a ≥50% reduction in the number of HAE attacks that occurred during rhC1-INH treatment versus attacks that occurred during placebo treatment
- †Two patients had an increase in HAE attack frequency while receiving once-weekly rhC1-INH prophylaxis (one patient had an increase of 40%, and one 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.

Plasma-Derived C1-INH Prophylaxis: Clinical Response

- Prophylaxis with plasma-derived C1-INH (n=22) resulted in varying reductions in HAE attack frequency



- *2 patients had an increase in HAE attack frequency while receiving plasma-derived C1-INH prophylaxis.
- C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema.
- FDA Briefing Document. Blood Products Advisory Committee Meeting. http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4355B2-1b.htm. Published May 2008. Accessed July 26, 2016.

Possible Mode of Action of rhC1-INH in HAE Prophylaxis

Normalize C1-INH levels for irreversible binding to target proteases (factor XII, kallikrein)[1-3]

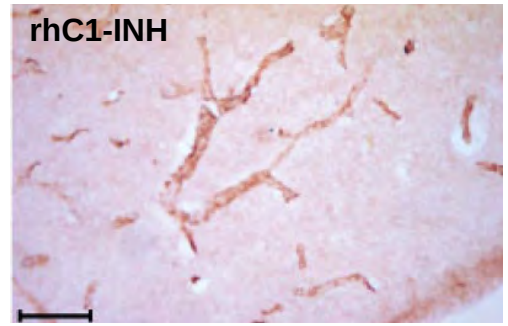
Differences in glycosylation between pdC1-INH and rhC1-INH lead to high affinity of rhC1-INH for MBL[4]

- Localization vs extravasation
- Reduction of endothelial cell activation[3,5]

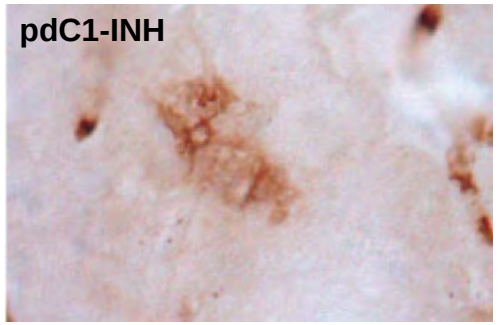
Platelets

- Known to store C1 inhibitor and release from granules[6]
- Patients with HAE have low platelet C1-INH levels[6,7]

Immunohistochemical localization of rhC1-INH and pdC1-INH in mouse cortex after focal ischemia and 30 minutes of reperfusion[4]



Localized in brain capillaries



Diffuse staining in brain parenchyma

C1-INH = C1 esterase inhibitor; HAE = hereditary angioedema; MBL = mannose binding lectin; MOA = mechanism of action; pdC1-INH = plasma-derived C1 esterase inhibitor; rhC1-INH = recombinant human C1 esterase inhibitor.

1. Plosker GL. *BioDrugs*. 2012;26(5):315-323. 2. Farrell C, Hayes S, Relan A, et al. *Br J Clin Pharmacol*. 2013; 76(6): 897-907.
3. Hofman ZL et al. *J Allergy Clin Immunol.* 2016;138(2):359-366. 4. Gesuete R, et al. *Ann Neurol*. 2009;66(3):332-342.
5. Kajdácsi E et al. *J Allergy Clin Immunol*. 2014;133(6):1686-1691. 6. Schmaier AH, et al. *J Clin Invest*. 1985;75(1):242-250. 7. Schmaier AH, et al. *Blood*. 1993;82(2):465-474.

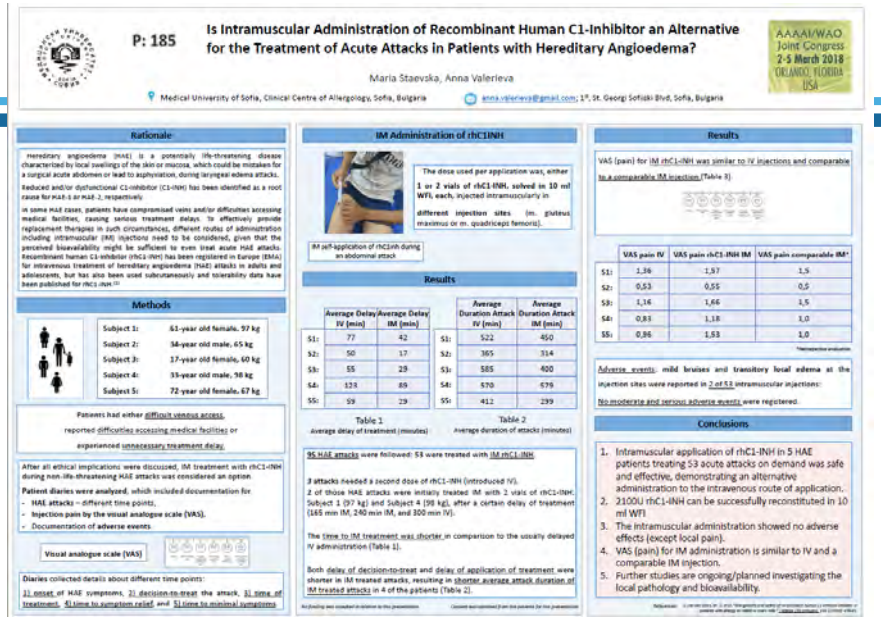
SPECIAL CASES/RECENT RESULTS

Is IM Administration of rhC1-INH an Alternative for the Treatment of Acute Attacks in Patients With HAE?

Staevska M, Valerieva A.

AAAAI/WAO Joint Congress.

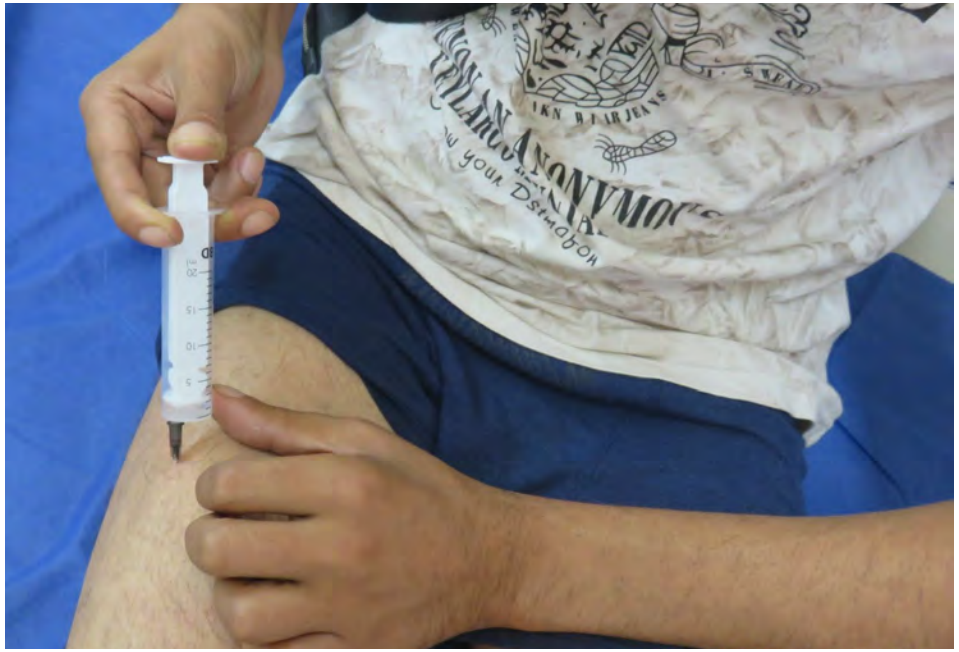
March 2-5, 2018; Orlando, FL



AAAAI = American Academy of Allergy, Asthma & Immunology; HAE = hereditary angioedema; IM = intramuscular; rhC1-INH = recombinant human C1 esterase inhibitor; WAO = World Allergy Organization.

IM rhC1-INH Self-Administration

- 1 to 2 vials of rhC1-INH; each vial reconstituted in 10 mL of water for injection
- Injected into musculus gluteus maximus or musculus quadriceps femoris (1 vial per site)



- 5 patients with difficult venous access, difficulties accessing medical facilities, or unnecessary treatment delay
  - Patient 1: 61-year-old female; 97 kg
  - Patient 2: 34-year-old male; 65 kg
  - Patient 3: 17-year-old female; 60 kg
  - Patient 4: 33-year-old male; 98 kg
  - Patient 5: 72-year-old female; 67 kg
- 95 HAE attacks
  - 53 treated with IM rhC1-INH; 42 with IV rhC1-INH
  - 3 attacks initially treated with IM rhC1-INH required a second dose (administered IV)
- Patients completed patient diaries

HAE = hereditary angioedema; IM = intramuscular; IV = intravenous; rhC1-INH = recombinant human C1 esterase inhibitor.

Staevska M, et al. Presented at the American Academy of Allergy, Asthma & Immunology/World Allergy Organization Joint Congress (AAAAI/WAO), Orlando, FL, March 2-5, 2018.

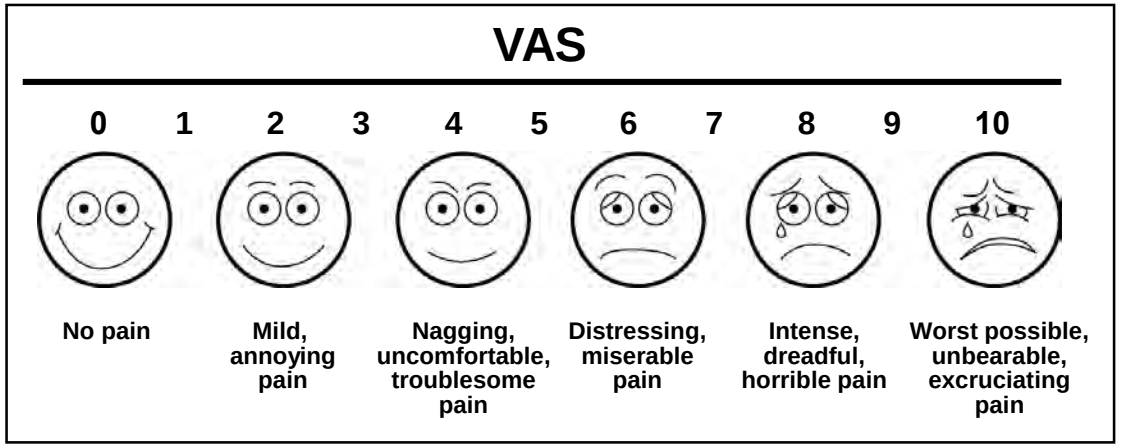
Delay in Treatment and HAE Attack Duration

- The time to IM rhC1-INH treatment was shorter versus time to IV rhC1-INH treatment
- Mean delay in treatment was shorter with IM administration for all 5 patients
- IM-treated HAE attacks had shorter mean duration in 4 of 5 patients

Patient	Mean Delay in Treatment (min)		Mean Duration of Attacks (min)	
	IV	IM	IV	IM
1	77	42	522	450
2	50	17	365	314
3	55	29	585	400
4	123	89	570	579
5	59	29	412	299

IM = intramuscular; IV = intravenous; rhC1-INH = recombinant human C1 esterase inhibitor.
Staevska M, et al. Presented at the American Academy of Allergy, Asthma & Immunology/World Allergy Organization Joint Congress (AAAAI/WAO), Orlando, FL, March 2-5, 2018.

Comparison of Pain With IM Versus IV Administration



Patient	rhC1-INH Administration Mean Pain Score		Non–rhC1-INH Comparable IM Injection*
	IV	IM	
1	1.4	1.6	1.5
2	0.5	0.6	0.5
3	1.2	1.7	1.5
4	0.8	1.2	1.0
5	1.0	1.5	1.0

- IM rhC1-INH pain ratings were similar to IV rhC1-INH and nondrug–comparable IM injection
- Mild bruising and transient edema at the injection site were reported in 2 of 53 IM injections
- No moderate or serious AEs were reported

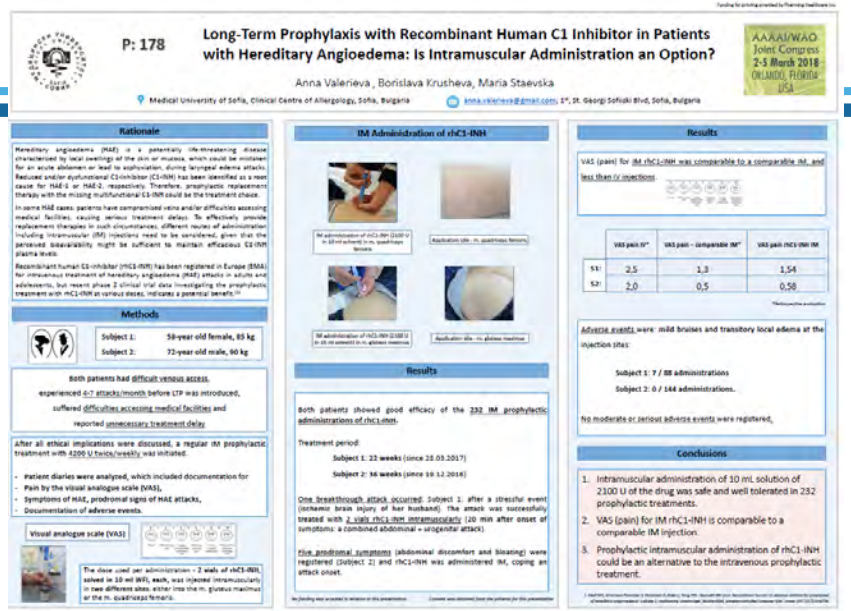
*Retrospectively evaluated.
AEs = adverse events; HAE = hereditary angioedema; IM = intramuscular; IV intravenous; rhC1-INH = recombinant human C1 esterase inhibitor; VAS = visual analog scale.
Staevska M, et al. Presented at the American Academy of Allergy, Asthma & Immunology/World Allergy Organization Joint Congress (AAAAI/WAO), Orlando, FL, March 2-5, 2018.

Long-Term Prophylaxis With rhC1-INH in Patients With HAE: Is IM Administration an Option?

Valerieva A, Krusheva B, Staevska M.

AAAAI/WAO Joint Congress.

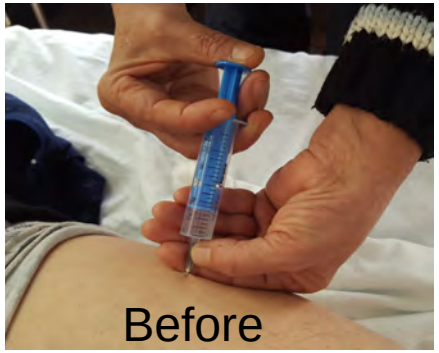
March 2-5, 2018; Orlando, FL

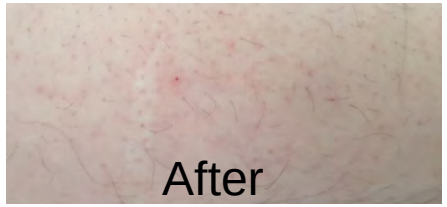


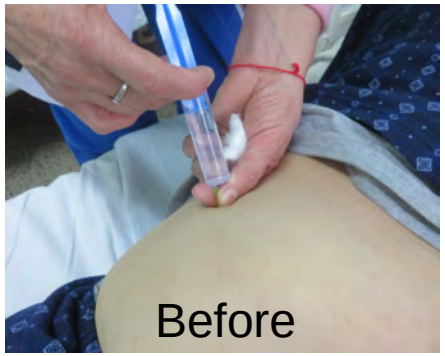
AAAAI = American Academy of Allergy, Asthma & Immunology; HAE = hereditary angioedema; IM = intramuscular; rhC1-INH = recombinant human C1 esterase inhibitor; WAO = World Allergy Organization.

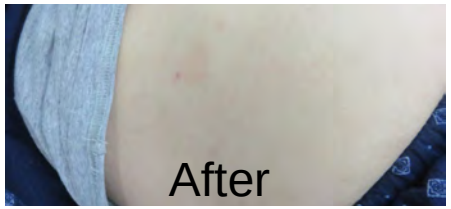
IM Administration of rhC1-INH

- 2 vials rhC1-INH 2100 IU; each vial reconstituted in 10 mL of water for injection
- 1 vial injected into musculus gluteus maximus; 1 vial injected into musculus quadriceps femoris









- 2 patients with difficult venous access and 4 to 7 HAE attacks/month before prophylaxis was introduced had difficulties accessing medical facilities and experienced unnecessary treatment delay
- Treated with IM prophylaxis 4200 IU twice weekly:
  - Patient 1: 58-year old female; 85 kg
  - Patient 2: 72-year old male; 90 kg
- 232 IM administrations of rhC1-INH
  - Treatment duration was 22 and 36 weeks for patient 1 and 2, respectively
- Patients completed patient diaries

HAE = hereditary angioedema; IM = intramuscular; rhC1-INH = recombinant human C1 esterase inhibitor.
Valerieva A, et al. Presented at the American Academy of Allergy, Asthma & Immunology/World Allergy Organization Joint Congress (AAAAI/WAO), Orlando, FL, March 2-5, 2018.

Efficacy of IM rhC1-INH Prophylaxis

- 1 breakthrough HAE attack occurred
  - Abdominal/urogenital attack in Patient 1 after stressful event; successfully treated with IM rhC1-INH 4200 IU administered 20 minutes after onset of attack
- Five events prodromal symptoms reported
  - Symptoms of abdominal discomfort and bloating in Patient 2
  - Treated with IM rhC1-INH
- IM rhC1-INH pain ratings were less versus IV rhC1-INH administration and similar to nondrug–comparable IM injection
- Mild bruising and transient edema at injection site
  - Patient 1: 7 events with 88 doses
  - Patient 2: 0 events with 144 doses
  - No moderate or serious AEs reported

Patient	rhC1-INH Administration Mean Pain Score		Non–rhC1-INH Comparable IM Injection*
	IV	IM	
1	2.5	1.5	1.3
2	2.0	0.6	0.5

*Retrospectively evaluated.
AEs = adverse events; HAE = hereditary angioedema; IM = intramuscular; IV = intravenous; rhC1-INH = recombinant human C1 esterase inhibitor.
Valerieva A, et al. Presented at the American Academy of Allergy, Asthma & Immunology/World Allergy Organization Joint Congress (AAAAI/WAO), Orlando, FL, March 2-5, 2018.

rhC1-INH for Short-Term Prophylaxis in Patients With HAE*

Zanichelli A, Staevska M, Jesenak, M, et al.

ACAAI Annual Scientific Meeting.

November 15-19, 2018; Seattle, WA

Clinical Communications

Recombinant human C1 esterase inhibitor as short-term prophylaxis in patients with hereditary angioedema

Anna Valerieva, MD, PhD[a], Maria Staevska, MD, PhD[a], Milos Jesenak, MD, PhD, MBA, MHA[b,c], Katarina Hrubiskova, MD[c], Marta Sobotkova, MD[d], Radana Zachova, MD[d], Roman Hakl, MD[e], Sladjana Andrejevic, MD, PhD[f], Tobias Sulter, MD[g], Vesna Grivcheva-Panovska, MD, PhD[h], Ljerka Karadza-Lapic, MD, PhD[i], Daniel Soteres, MD, MPH[j], Ralph Shapiro, MD[k], Jeffrey Rumbyrt, MD[l], Raffi Tachdjian, MD, MPH[m], Vinay Mehta, MD[m], F. Ida Hsu, MD[m], and Andrea Zanichelli, MD[n]

Clinical Implications

- Limited data are available on recombinant human C1 esterase inhibitor as short-term prophylaxis. A case series of 51 patients (70 procedures) indicated that recombinant human C1 esterase inhibitor short-term prophylaxis administered within several hours before a medical/dental procedure was efficacious and well tolerated.

TO THE EDITOR:

Hereditary angioedema (HAE), an inherited deficiency of functional C1 esterase inhibitor (C1-INH), is characterized by recurrent episodes of disabling and often painful swelling in subcutaneous and/or submucosal tissues.[1] HAE attacks are generally unpredictable, but triggers for an attack can include having a dental or medical procedure (eg, surgery), other trauma, or stress.[1,2] A preemptive management plan for patients undergoing these types of situations may reduce the risk of HAE attacks.[2] Recommendations include administration of short-term prophylaxis in patients with HAE before invasive medical procedures, especially those involving the upper airways or digestive tract, with C1-INH concentrate typically the medication of choice.[2]

Recombinant human C1-INH (rhC1-INH) is a C1-INH concentrate indicated in the United States and the European Union for the treatment of acute attacks in adults and adolescents with HAE, and several studies have demonstrated that rhC1-INH is efficacious and well tolerated.[3–7] Weight-based dosing is recommended for rhC1-INH (<84 kg, 50 IU/kg ≥84 kg, 4200 IU). rhC1-INH has also been shown to be efficacious and well tolerated as long-term prophylaxis in patients with frequent attacks of HAE.[8] However, data are needed on the efficacy and safety of rhC1-INH as short-term prophylaxis. The objective of the present study was to assess rhC1-INH as short-term prophylaxis in patients with HAE/angioedema due to C1 inhibitor deficiency.

In this retrospective study, patients diagnosed with C1 inhibitor deficiency from the United States and Europe were treated with rhC1-INH before medical procedures or stressful life events. Patients from this study population who were not receiving long-term prophylaxis and underwent medical procedures or stressful life events without short-term prophylaxis were included as part of a self-control group, and these procedures were included in the control analyses. HAE attacks were recorded through 7 days postprocedure/event.

Fifty-one patients from 7 countries (Bulgaria [n = 11], Czech Republic [n = 7], Croatia [n = 2], North Macedonia [n = 10], Serbia [n = 3], Slovakia [n = 11], and the United States [n = 7]) were included in this study. Most of the study population was female (n = 32; 62.7%), with a median age and weight of 44 years (range, 17-73 years) and 74.0 kg, respectively. Most patients had type I HAE (n = 47; 92.2%). Overall, the patients in this case series had a median of 14 attacks annually. Twelve (23.5%) of the 51 patients were receiving long-term prophylaxis and received either danazol (n = 10; dose range, 100-300 mg of varying frequency [eg, daily, every other day, 6 times per week]) or tranexamic acid (n = 2; dose range, 1000-2000 mg/d). For 1 of these 12 patients, the prophylactic dose was increased from danazol 200 mg/d to 600 mg/d for 1 day before and 2 days after surgery.

A total of 70 procedures were recorded for the 51 patients, for which the median rhC1-INH dose given was 3075 IU (range, 2100-4200 IU). More than half the administrations of rhC1-INH were in conjunction with dental procedures (52.9%); there was 1 case of a stressful life event (Table 1). Most (97.3%) dental procedures in patients administered rhC1-INH were characterized as high risk, and included tooth extraction, oral surgery, and cutting of soft tissues. Nineteen (27.1%) of the 70 procedures were from 12 patients receiving long-term prophylaxis. The rhC1-INH prophylaxis was administered a median of 60 minutes before the procedures; in most cases (n = 48; 68.6%), the rhC1-INH was administered 10 to 65 minutes before the procedure. Of these 48 procedures in which rhC1-INH was administered within 10 to 65 minutes preprocedure, 25 were dental (52.1%), 16 were surgical (33.3%), and 7 were endoscopy (14.6%). A subset of patients served as a self-control set of procedures and included 16 patients who had undergone 26 procedures with no long- or short-term prophylaxis preprocedure. Most of these 26 control procedures were dental (n = 17; 65.4%) or surgical (n = 6; 23.1%; Table 1).

Overall, 97.1% of the 70 procedures with rhC1-INH short-term prophylaxis administration were attack-free during the 2 days after the procedure, compared with 23.1% of the 26 procedures in the self-control group (Figure 1). For the 2 HAE attacks (peripheral [hand, knee]) that occurred within 2 days postprocedure in the rhC1-INH group, rhC1-INH was administered 230 minutes and 24 hours or more preprocedure, respectively. Within 7 days postprocedure, 88.6% of the 70 cases with rhC1-INH short-term prophylaxis administration were attack-free, compared with 19.2% of the 26 control cases (Figure 1). For the 6 rhC1-INH cases in which an attack occurred between 2 and 7 days postprocedure, the timing of rhC1-INH administration preprocedure was 60 minutes or less (n = 3), 120 minutes (n = 1), 280 minutes (n = 1), or not reported (n = 1). When the 19 procedures for the patients on

*Valerieva A, et al. *J Allergy Clin Immunol Pract.* Published online ahead of print August 19, 2019. doi: 10.1016/j.jaip.2019.08.011.

ACAAI = American College of Allergy, Asthma, and Immunology; HAE = hereditary angioedema; rhC1-INH = recombinant human C1 esterase inhibitor.

Patient Population

- Retrospective analysis of rhC1-INH administration before medical procedures or stressful life events
  - Control cases included patients who weren't receiving long-term prophylaxis and did not receive short-term prophylaxis
- HAE attacks were recorded through 7 days postprocedure/event
- Included 51 patients from 7 countries
  - 70 procedures with rhC1-INH prophylaxis
    - 51 procedures with no long-term prophylaxis
  - 26 control procedures

Parameter	Patients (N=51)
Age, y, median (range)	44 (17-73)
Female, n (%)	32 (62.7)
Weight, kg, median	74.0
HAE type, n (%) Type I Type II C1-INH-AAE	 47 (92.1) 3 (5.9) 1 (2.0)
HAE attacks/y, median	14
Patients on long-term prophylaxis, n (%) Danazol Tranexamic acid	12 (23.5) 10 (19.6) 2 (3.9)

C1-INH-AAE = acquired angioedema due to acquired C1 esterase inhibitor deficiency; HAE = hereditary angioedema; rhC1-INH = recombinant human C1 esterase inhibitor.
Valerieva A, et al. *J Allergy Clin immunol Pract.* Published online ahead of print August 19, 2019.
Data on file Pharming Healthcare Inc. 2019.

Procedures, Dose, and Timing of rhC1-INH Short-Term Prophylaxis Administration

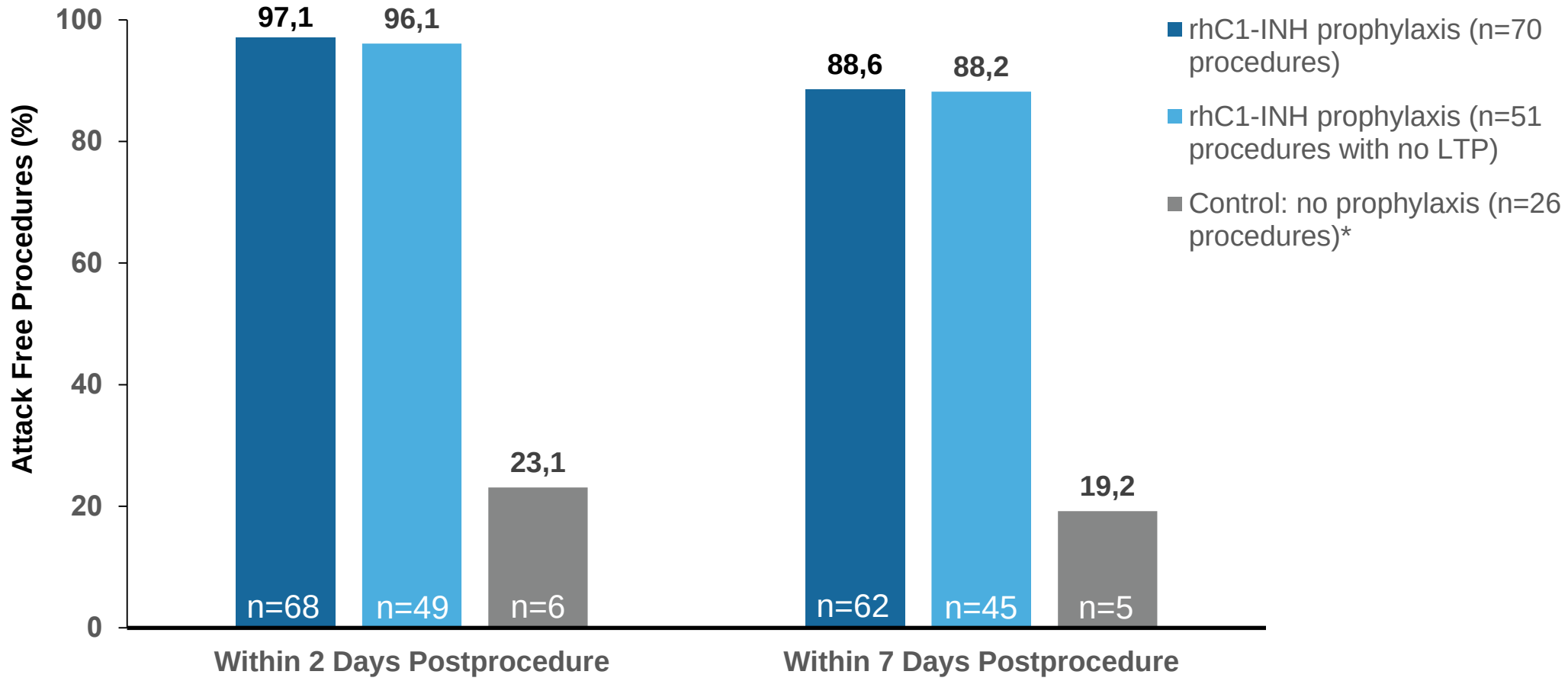
Category	Cases, n (%)	
	rhC1-INH Prophylaxis (n=70)	Self-Control Group* (n=26)
Dental procedure†	37 (52.9)	17 (65.4)
High-risk	36 (97.3)	16 (94.1)
Low-risk	1 (2.7)	1 (5.9)
Surgical procedure	21 (30.0)	6 (23.1)
Endoscopy procedure	11 (15.7)	2 (7.7)
Stressful life event	1 (1.4)‡	1 (3.8)‡

*Cases in self-control group in which patients did not receive long-term or short-term prophylaxis.
†Dental procedures characterized as high-risk for the rhC1-INH group: tooth extraction(s) (n = 24), dental procedure NOS (n = 6), root canal (n = 3), cavity/filling under local anesthesia (n = 1), dental veneer (n = 1), and dental abrasion (n = 1), and for the self-control group: tooth extraction(s) (n = 14), cavity obturation (n = 1), and root canal (n = 1). For both groups, teeth cleaning was classified as low-risk (1 in each group).
‡Stressful life event was identified as an adventure holiday in the mountains and classified as a "procedure" for ease of presentation. The same patient went on 2 adventure holidays in the mountains, 1 year apart. During the first stressful life event, the patient did not receive short-term prophylaxis (self-control group); for the second event, the patient received rhC1-INH as short-term prophylaxis (rhC1-INH prophylaxis group).
NOS = not otherwise specified; rhC1-INH = recombinant human C1 esterase inhibitor.
Valerieva A, et al. *J Allergy Clin immunol Pract.* Published online ahead of print August 19, 2019.

Median rhC1-INH dose: 3075 IU (range, 2100-4200 IU)

In 68.6% of cases (48/70), rhC1-INH was administered 10 to 65 minutes prior to procedure

Efficacy Outcomes



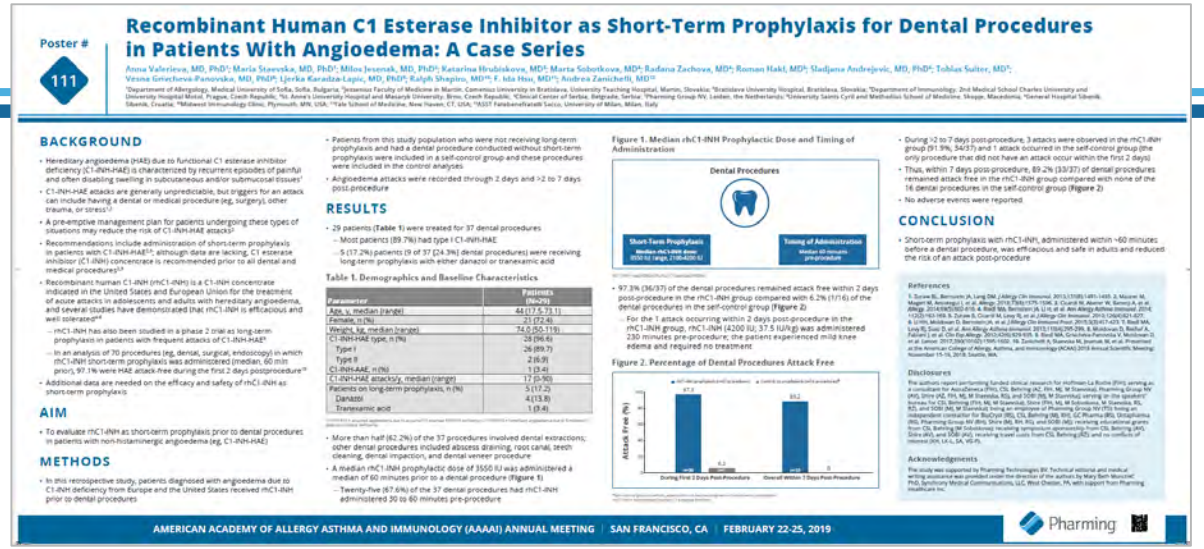
*Self-control group who did not receive long-term or short-term prophylaxis preprocedure.
LTP = long-term prophylaxis; rhC1-INH = recombinant human C1 esterase inhibitor.
Valerieva A, et al. *J Allergy Clin immunol Pract.* Published online ahead of print August 19, 2019.

rhC1-INH as Short-Term Prophylaxis for Dental Procedures in Patients With Angioedema: A Case Series

Valerieva A, Staevska M, Jesenak M, et al.

Presented at AAAAI Annual Meeting.

February 22-25, 2019; San Francisco, CA



Poster # 111

Recombinant Human C1 Esterase Inhibitor as Short-Term Prophylaxis for Dental Procedures in Patients With Angioedema: A Case Series

BACKGROUND

AIM

METHODS

RESULTS

CONCLUSION

AMERICAN ACADEMY OF ALLERGY ASTHMA AND IMMUNOLOGY (AAAAI) ANNUAL MEETING | SAN FRANCISCO, CA | FEBRUARY 22-25, 2019

Pharming

AAAAI = American Academy of Allergy Asthma & Immunology; rhC1-INH = recombinant human C1 esterase inhibitor.

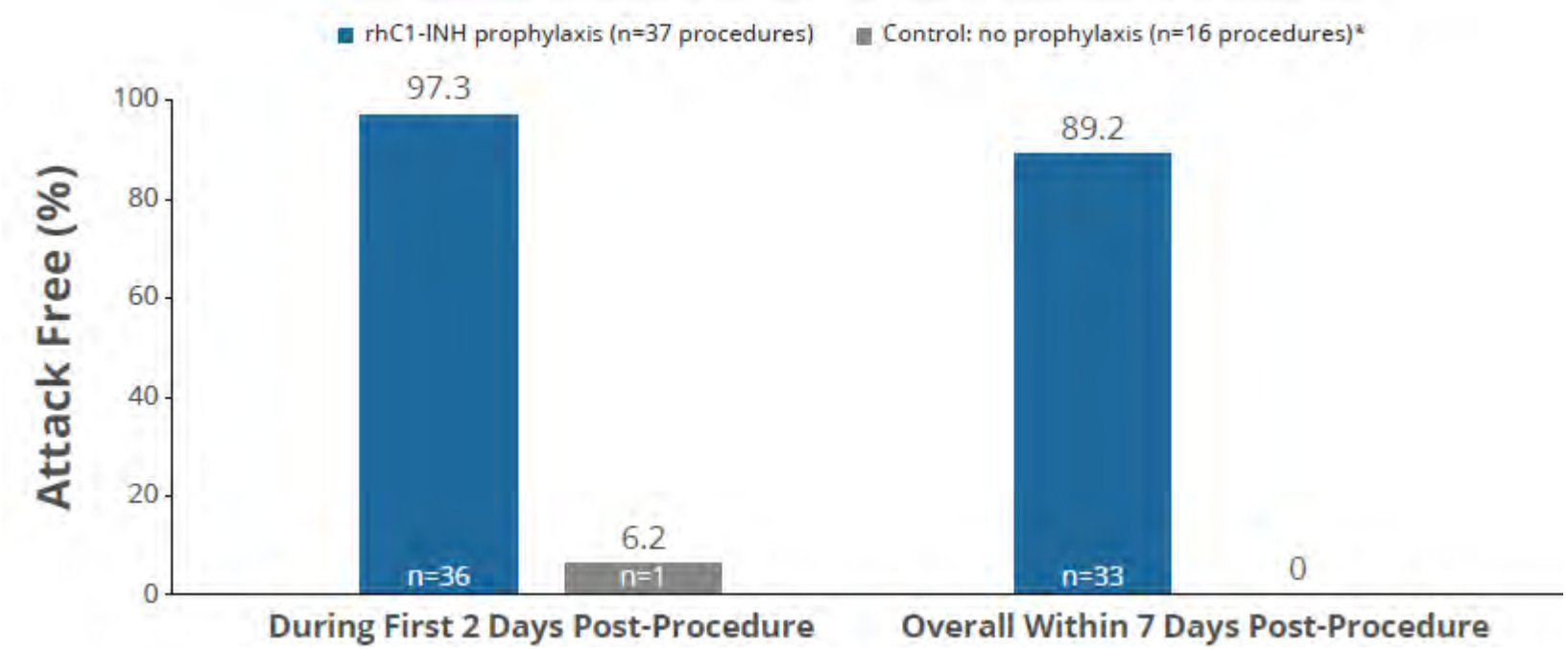
Patient Population

- Retrospective analysis of rhC1-INH administration before dental procedures in patients with C1-INH-HAE
- Control cases included patients who weren't receiving long-term prophylaxis and did not receive short-term prophylaxis for a dental procedure
- HAE attacks were recorded through 7 days postprocedure/event
- 37 procedures with rhC1-INH prophylaxis
  - 62.2% involved dental extractions
  - Other dental procedures included abscess draining, root canal, teeth cleaning, dental impaction, and dental veneer procedure
- 16 control procedures

Parameter	Patients (N=29)
Age, y, median (range)	44 (17.5-73.1)
Female, n (%)	21 (72.4)
Weight, kg, median (range)	74.0 (50-119)
HAE type, n (%) Type I Type II C1-INH-AAE	 26 (89.7) 2 (6.9) 1 (3.4)
HAE attacks/y, median (range)	17 (0-90)
Patients on long-term prophylaxis, n (%) Danazol Tranexamic acid	5 (17.2) 4 (13.8) 1 (3.4)

C1-INH-AAE = acquired angioedema due to acquired C1 esterase inhibitor deficiency; HAE = hereditary angioedema; rhC1-INH = recombinant human C1 esterase inhibitor.
Valerieva A, et al. Presented at: American Academy of Allergy Asthma & Immunology Annual Meeting. February 22-25, 2019; San Francisco, CA.

Efficacy Outcomes



- For 1 attack within 2 days post-procedure in rhC1-INH group
  - rhC1-INH (4200 IU; 37.5 IU/kg) was administered 230 minutes pre-procedure
  - Patient had mild knee edema and required no treatment

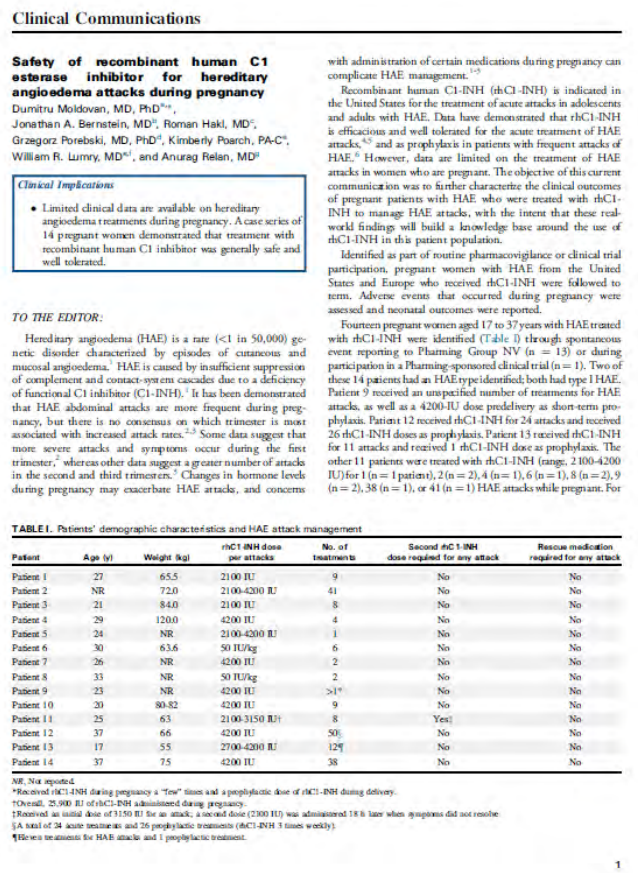
*Self-control group in which patients did not receive long-term or short-term prophylaxis.
rhC1-INH = recombinant human C1 esterase inhibitor.
Valerieva A, et al. Presented at: American Academy of Allergy Asthma & Immunology Annual Meeting. February 22-25, 2019; San Francisco, CA.

Experience With rhC1-INH for HAE Attacks During Pregnancy*

Bernstein JA, Moldovan D, Hakl R, et al.

ACAAI 2018 Annual Scientific Meeting.

November 15-19, 2018; Seattle, WA



Clinical Communications

Safety of recombinant human C1 esterase inhibitor for hereditary angioedema attacks during pregnancy

Dumitru Moldovan, MD, PhD[a,*], Jonathan A. Bernstein, MD[b], Roman Hakl, MD[c], Grzegorz Porebski, MD, PhD[d], Kimberly Poarch, PA-C[e], William R. Lumry, MD[e,f], and Anurag Relan, MD[g]

Clinical Implications

- Limited clinical data are available on hereditary angioedema treatments during pregnancy. A case series of 14 pregnant women demonstrated that treatment with recombinant human C1 inhibitor was generally safe and well tolerated.

TO THE EDITOR:

Hereditary angioedema (HAE) is a rare (<1 in 50,000) genetic disorder characterized by episodes of cutaneous and mucosal angioedema.[1] HAE is caused by insufficient suppression of complement and contact-system cascades due to a deficiency of functional C1 inhibitor (C1-INH).[1] It has been demonstrated that HAE abdominal attacks are more frequent during pregnancy, but there is no consensus on which trimester is most associated with increased attack rates.[2,3] Some data suggest that more severe attacks and symptoms occur during the first trimester,[2] whereas other data suggest a greater number of attacks in the second and third trimesters.[3] Changes in hormone levels during pregnancy may exacerbate HAE attacks, and concerns with administration of certain medications during pregnancy can complicate HAE management.[1-3]

Recombinant human C1-INH (rhC1-INH) is indicated in the United States for the treatment of acute attacks in adolescents and adults with HAE. Data have demonstrated that rhC1-INH is efficacious and well tolerated for the acute treatment of HAE attacks,[4,5] and as prophylaxis in patients with frequent attacks of HAE.[6] However, data are limited on the treatment of HAE attacks in women who are pregnant. The objective of this current communication was to further characterize the clinical outcomes of pregnant patients with HAE who were treated with rhC1-INH to manage HAE attacks, with the intent that these real-world findings will build a knowledge base around the use of rhC1-INH in this patient population.

Identified as part of routine pharmacovigilance or clinical trial participation, pregnant women with HAE from the United States and Europe who received rhC1-INH were followed to term. Adverse events that occurred during pregnancy were assessed and neonatal outcomes were reported.

Fourteen pregnant women aged 17 to 37 years with HAE treated with rhC1-INH were identified (Table I) through spontaneous event reporting to Pharming Group NV (n = 13) or during participation in a Pharming-sponsored clinical trial (n = 1). Two of these 14 patients had an HAE type identified; both had type I HAE. Patient 9 received an unspecified number of treatments for HAE attacks, as well as a 4200-IU dose predelivery as short-term prophylaxis. Patient 12 received rhC1-INH for 24 attacks and received 26 rhC1-INH doses as prophylaxis. Patient 13 received rhC1-INH for 11 attacks and received 1 rhC1-INH dose as prophylaxis. The other 11 patients were treated with rhC1-INH (range, 2100-4200 IU) for 1 (n = 1 patient), 2 (n = 2), 4 (n = 1), 6 (n = 1), 8 (n = 2), 9 (n = 2), 38 (n = 1), or 41 (n = 1) HAE attacks while pregnant. For

TABLE I. Patients' demographic characteristics and HAE attack management

Patient	Age (y)	Weight (kg)	rhC1-INH dose per attacks	No. of treatments	Second rhC1-INH dose required for any attack	Rescue medication required for any attack
Patient 1	27	65.5	2100 IU	9	No	No
Patient 2	NR	72.0	2100-4200 IU	41	No	No
Patient 3	21	84.0	2100 IU	8	No	No
Patient 4	29	120.0	4200 IU	4	No	No
Patient 5	24	NR	2100-4200 IU	1	No	No
Patient 6	30	63.6	50 IU/kg	6	No	No
Patient 7	26	NR	4200 IU	2	No	No
Patient 8	33	NR	50 IU/kg	2	No	No
Patient 9	23	NR	4200 IU	>1*	No	No
Patient 10	20	80-82	4200 IU	9	No	No
Patient 11	25	63	2100-3150 IU†	8	Yes‡	No
Patient 12	37	66	4200 IU	50§	No	No
Patient 13	17	55	2700-4200 IU	12¶	No	No
Patient 14	37	75	4200 IU	38	No	No

NR, Not reported.
*Received rhC1-INH during pregnancy a "few" times and a prophylactic dose of rhC1-INH during delivery.
†Overall, 25,900 IU of rhC1-INH administered during pregnancy.
‡Received an initial dose of 3150 IU for an attack; a second dose (2300 IU) was administered 18 h later when symptoms did not resolve.
§A total of 24 acute treatments and 26 prophylactic treatments (rhC1-INH 3 times weekly).
¶Eleven treatments for HAE attacks and 1 prophylactic treatment.

1

*Moldovan D, et al. *J Allergy Clin Immunol Pract*. Published online ahead of print June 3, 2019. doi: https://doi.org/10.1016/j.jaip.2019.05.042.
ACAAI = American College of Allergy, Asthma, & Immunology; HAE = hereditary angioedema; rhC1-INH = recombinant human C1 esterase inhibitor.

Results

- Pregnant women with HAE who received rhC1-INH were followed to full term

Patient	Age, y	Weight, kg	rhC1-INH Dose Per Attacks	Number of Treatments	Second rhC1-INH Dose Required for Any Attack	Rescue Medication Required for Any Attack
Case 1	27	65.5	2100 IU	9	No	No
Case 2	NR	72.0	2100-4200 IU	41	No	No
Case 3	21	84.0	2100 IU	8	No	No
Case 4	29	120.0	4200 IU	4	No	No
Case 5	24	NR	2100-4200 IU	1	No	No
Case 6	30	63.6	50 IU/kg	6	No	No
Case 7	26	NR	4200 IU	2	No	No
Case 8	33	NR	50 IU/kg	2	No	No
Case 9	23	NR	4200 IU	>1*	No	No
Case 10	20	80-82	4200 IU	9	No	No
Case 11	25	63	2100-3150 IU†	8	Yes‡	No
Case 12	37	66	4200 IU	50§	No	No
Case 13	17	55	2700-4200 IU	12¶	No	No
Case 14	37	75	4200 IU	38	No	No

*Received rhC1-INH during pregnancy a “few” times and a prophylactic dose of rhC1-INH during delivery. †Overall, 25,900 IU of rhC1-INH administered during pregnancy. ‡Received an initial dose of 3150 IU for an attack; second dose (2100 IU) was administered 18 h later when symptoms did not resolve. §Total of 24 acute treatments and 26 prophylactic treatments (rhC1-INH 3 times weekly). ¶Eleven treatments for HAE attacks and 1 prophylactic treatment. HAE = hereditary angioedema; NR = not reported; rhC1-INH = recombinant human C1 esterase inhibitor.

Moldovan D, et al. *J Allergy Clin Immunol Pract*. Published online ahead of print June 3, 2019. doi: https://doi.org/10.1016/j.jaip.2019.05.042.

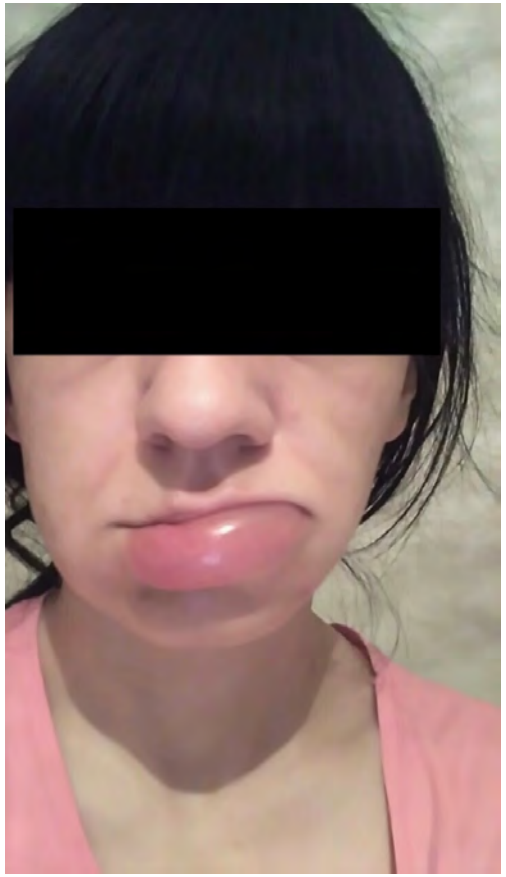
Results (Cont'd)

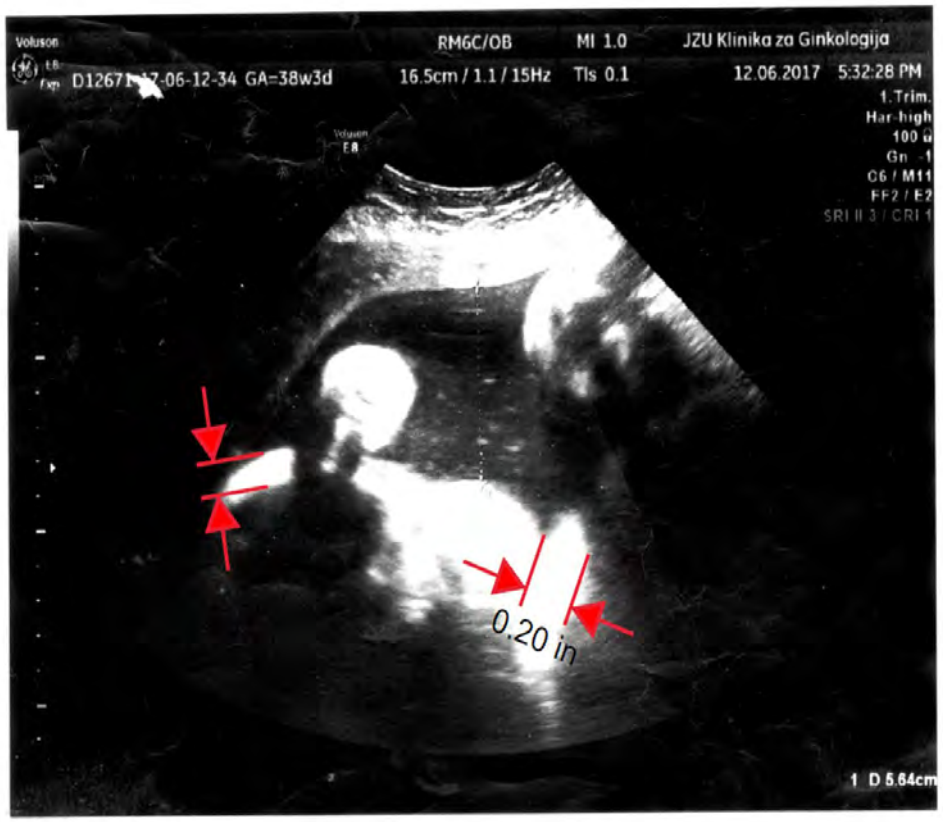
- There were no AEs considered related to rhC1-INH treatment during pregnancy period
  - One patient (case 6) experienced an episode of nausea, vomiting, and diarrhea, considered related to a "stomach bug"
- All pregnancies resulted in live births with no fetal distress, birth defects, or congenital abnormalities

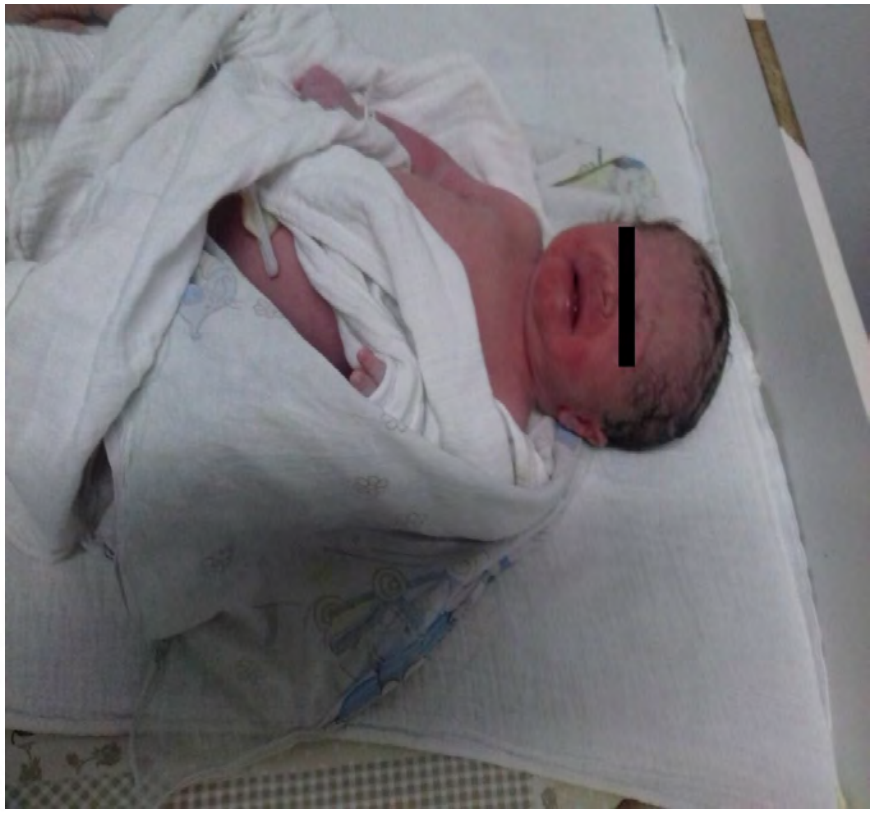
AEs = adverse events ; rhC1-INH = recombinant human C1 esterase inhibitor.

Moldovan D, et al. *J Allergy Clin Immunol Pract*. Published online ahead of print June 3, 2019. doi: https://doi.org/10.1016/j.jaip.2019.05.042.

Hereditary Angioedema Attack In Utero and Treatment of Mother and Fetus







Vesna Grivcheva-Panovska, M.D., Ph.D., and Bruno Giannetti, M.D., Ph.D., Poster accepted for presentation, ACAAI, 2019 Annual Scientific Meeting (November 7-11, 2019; Houston, Texas).

Leveraging our “End to End” Infrastructure

Research and Development: Meeting the Unmet Need

Prof. Bruno Giannetti MD PhD

rhC1-INH in Pre-Eclampsia

Overview of Pre-eclampsia (NL: zwangerschapsvergiftiging)

The Complement Cascade

PE - Definition, Prevalence

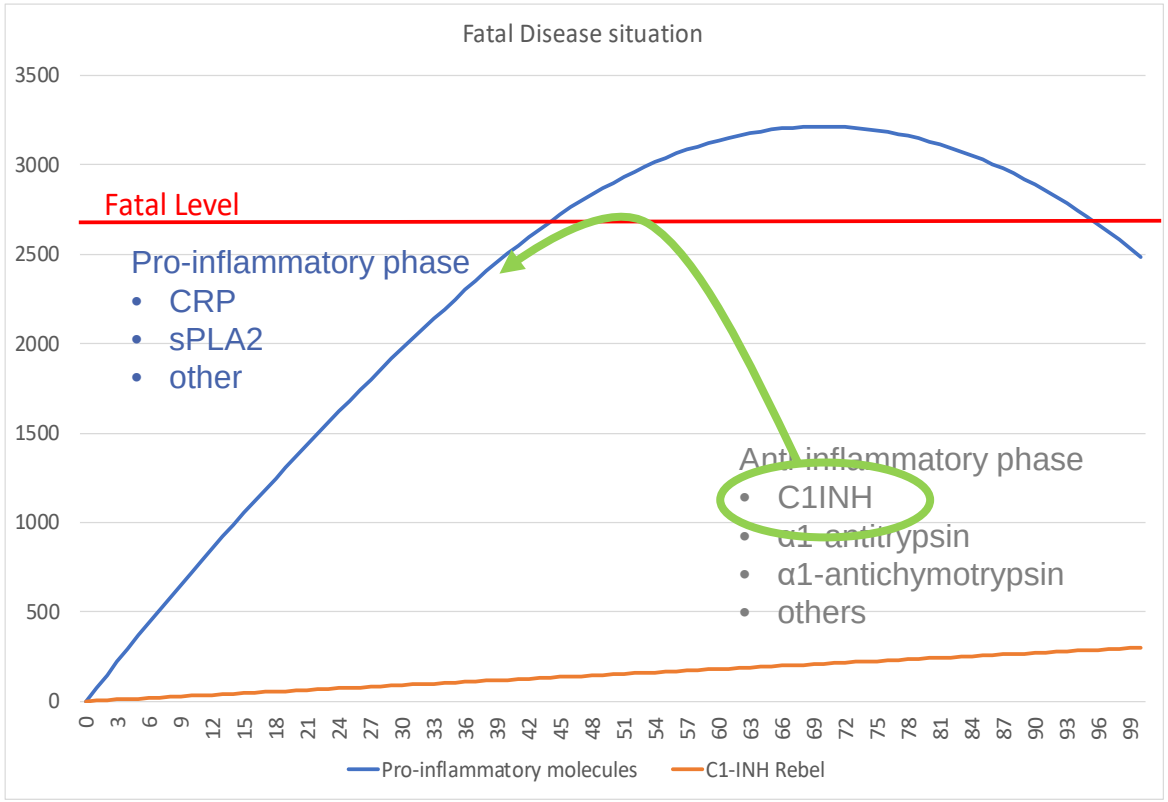
PE - Clinical Manifestation

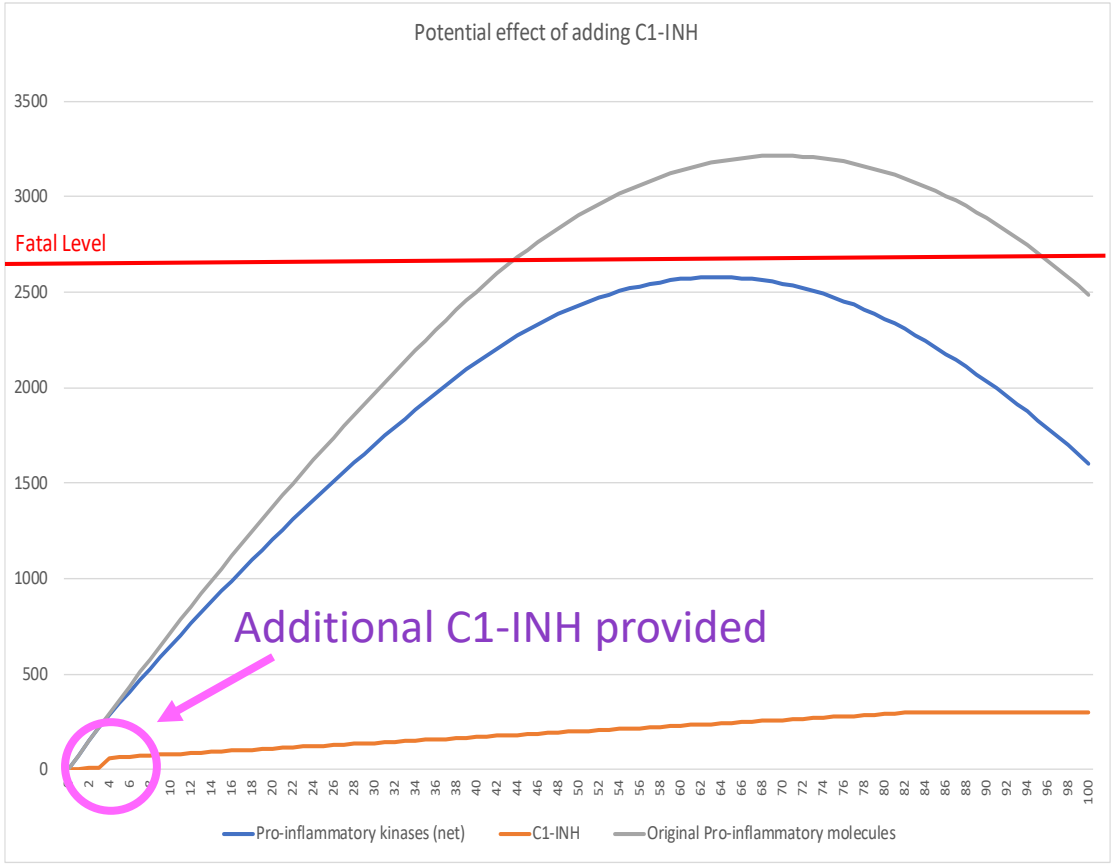
Pathophysiological Hypotheses

Clinical Plan

Therapeutic potential for rhC1INH

- C1INH appears to slow inflammatory response and thus limit tissue damage – potentially applicable in a number of clinical conditions

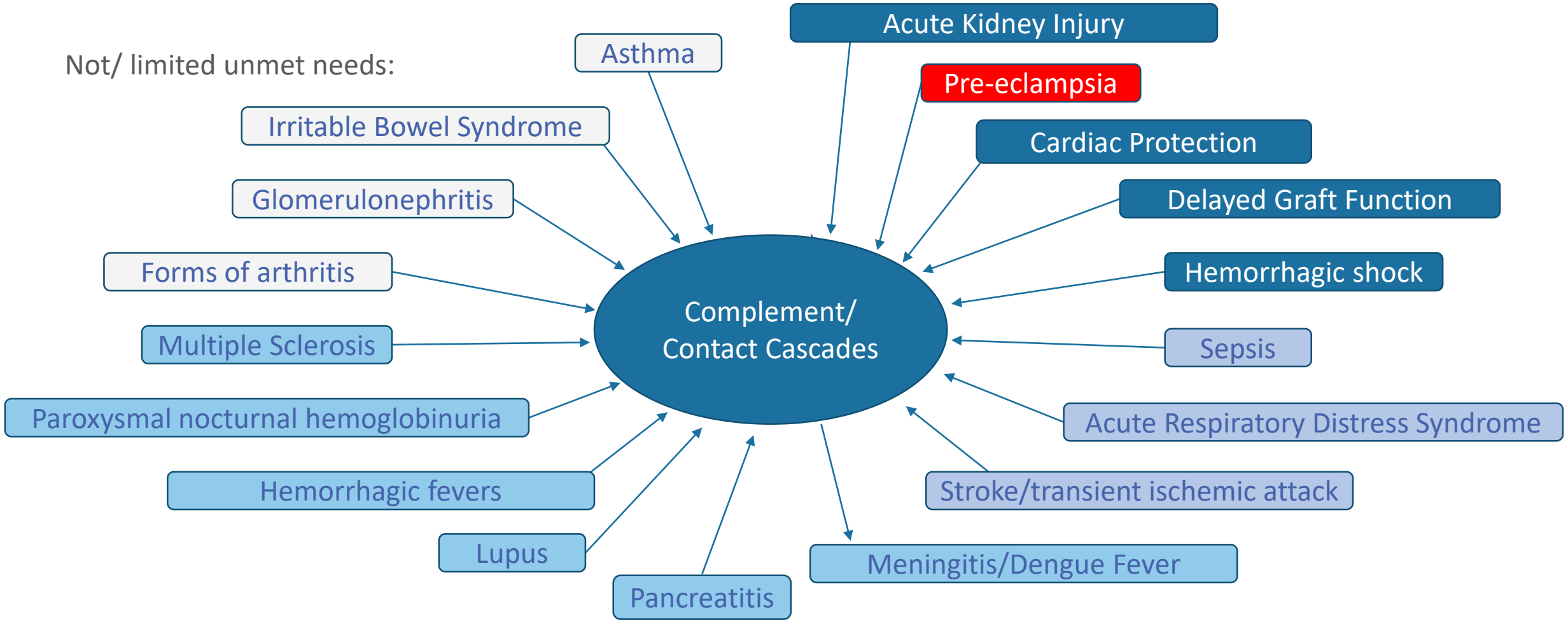




Note: for illustration only

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:



Pre-eclampsia: Diagnosis

- 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

Criteria: 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

Pre-eclampsia (PE), Prevalence, Complications

- Pre-eclampsia (PE) has a prevalence of 1-17% throughout the world. Estimated yearly cases of PE in the US alone: 120.000+.

  (Steegers et al., 2010; Osungbade and Ige, 2011)

- Delivery is presently the only therapy of PE, but this is not an option for early PE (from week 20 of gestation).
- The main goal of symptomatic therapy is to prolong gestation of PE patients as far as possible

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

Maternal complications

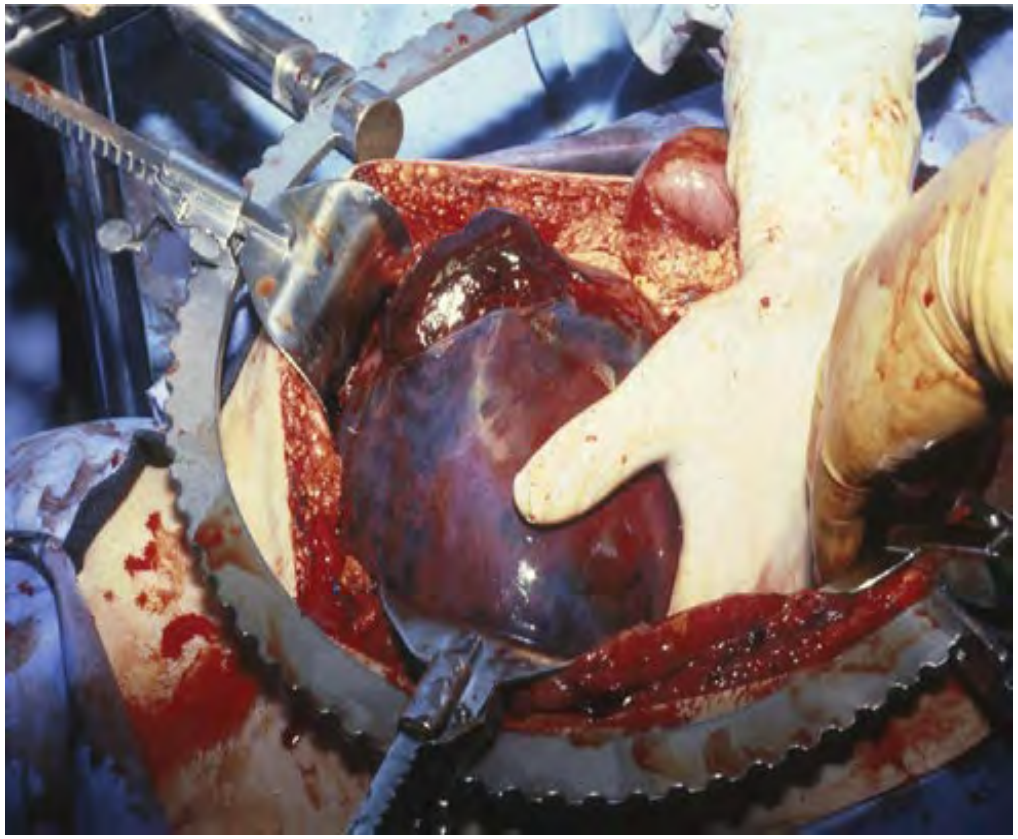
- Abruptio placentae (1–4%)
- Disseminated coagulopathy/HELLP syndrome (10–20%)
- Pulmonary oedema/aspiration (2–5%)
- Acute renal failure (1–5%)
- Eclampsia (<1%)
- Liver failure or haemorrhage (<1%)
- Stroke (rare)
- Death (rare)
- Long-term cardiovascular morbidity

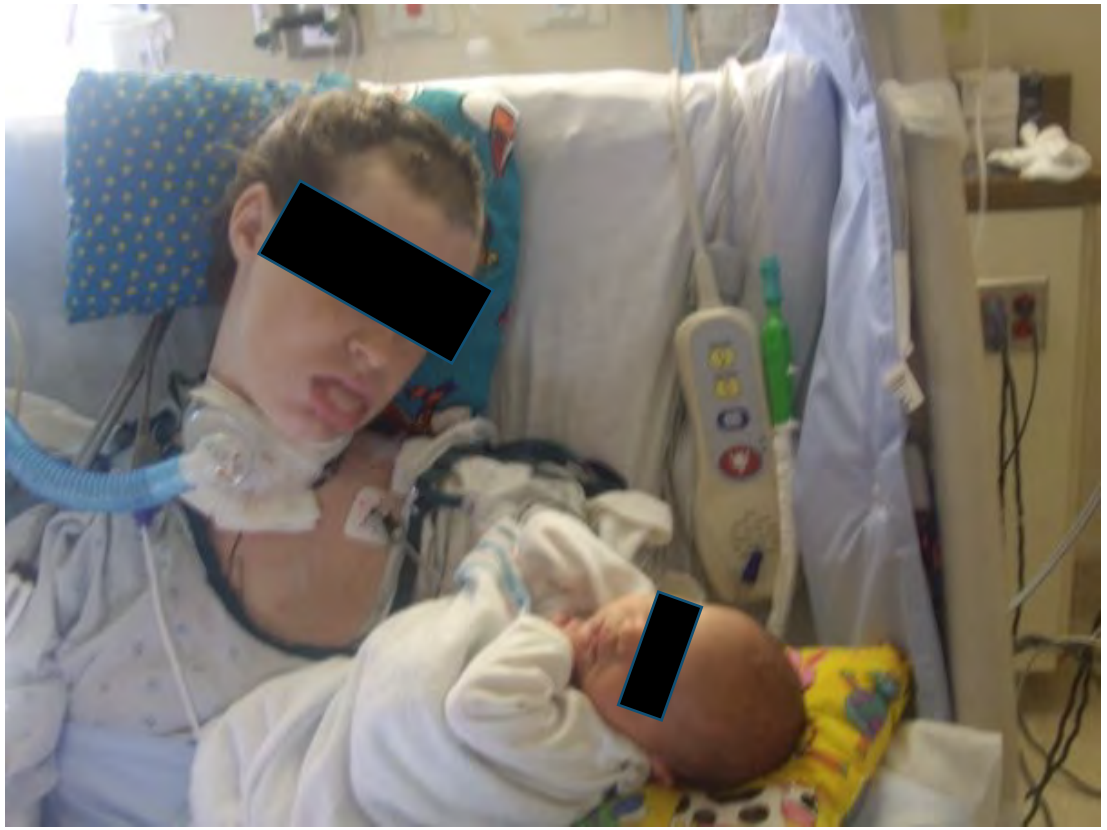
Neonatal complications

- 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)

G.Dekker, Presentation, NY, June 21, 2018

Pre-eclampsia (PE) Complications





G.Dekker, Presentation, NY, June 21, 2018

Pre-eclampsia (PE), Pathophysiological Hypotheses

- Pregnant women and pre-eclamptic women have reduced circulating C1INH levels. Severely affected patients have significantly reduced C1INH levels

  (W M Halbmeyer et al., 1991)

- Postulated mechanisms to the aetiology of PE (immunological, infectious, toxic) point to a chronic endothelial inflammation reaction with complement activation and therefore a related C1INH consumption

  (G Girardi, 2018; Y Ma et al, 2018)

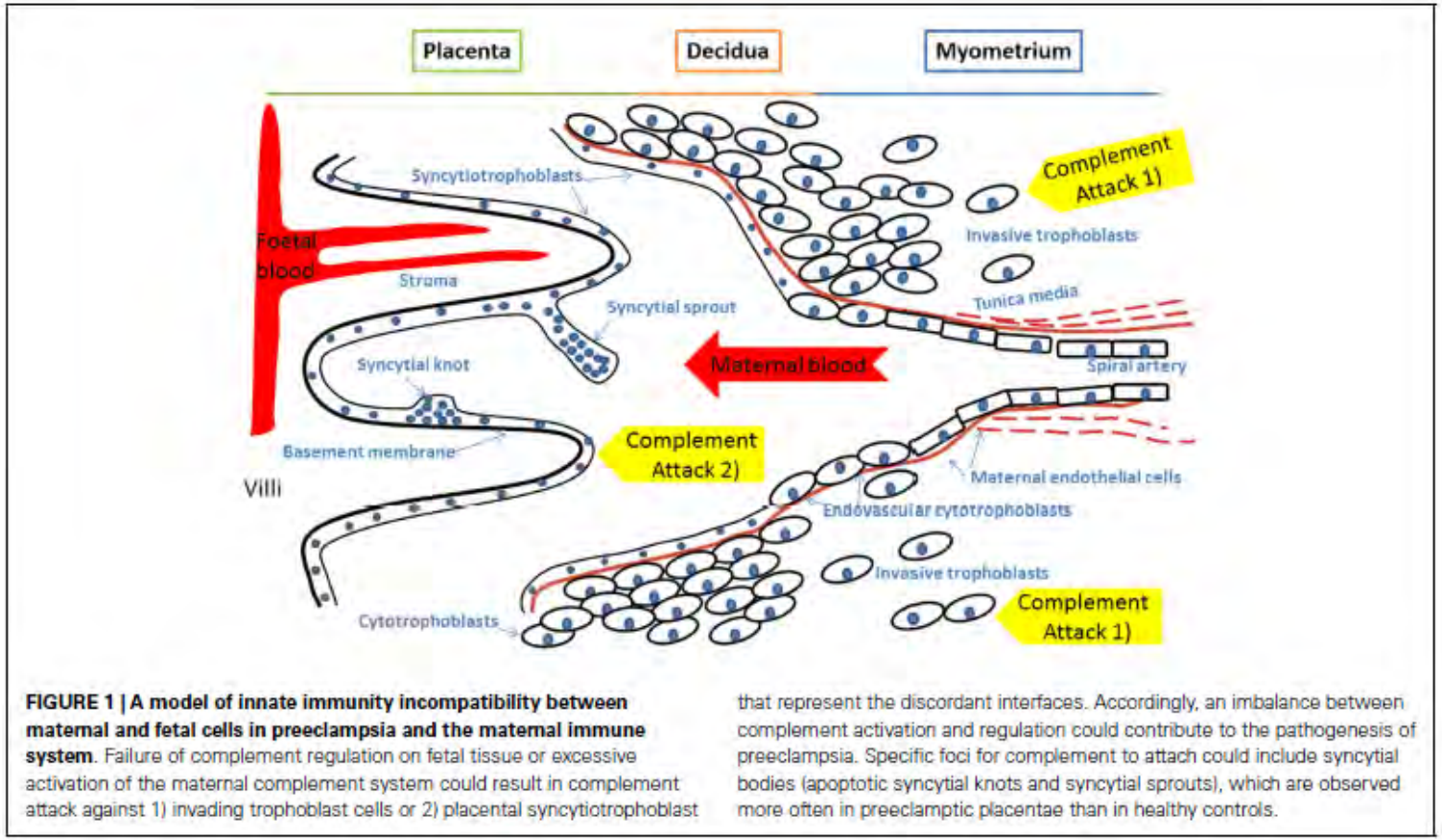
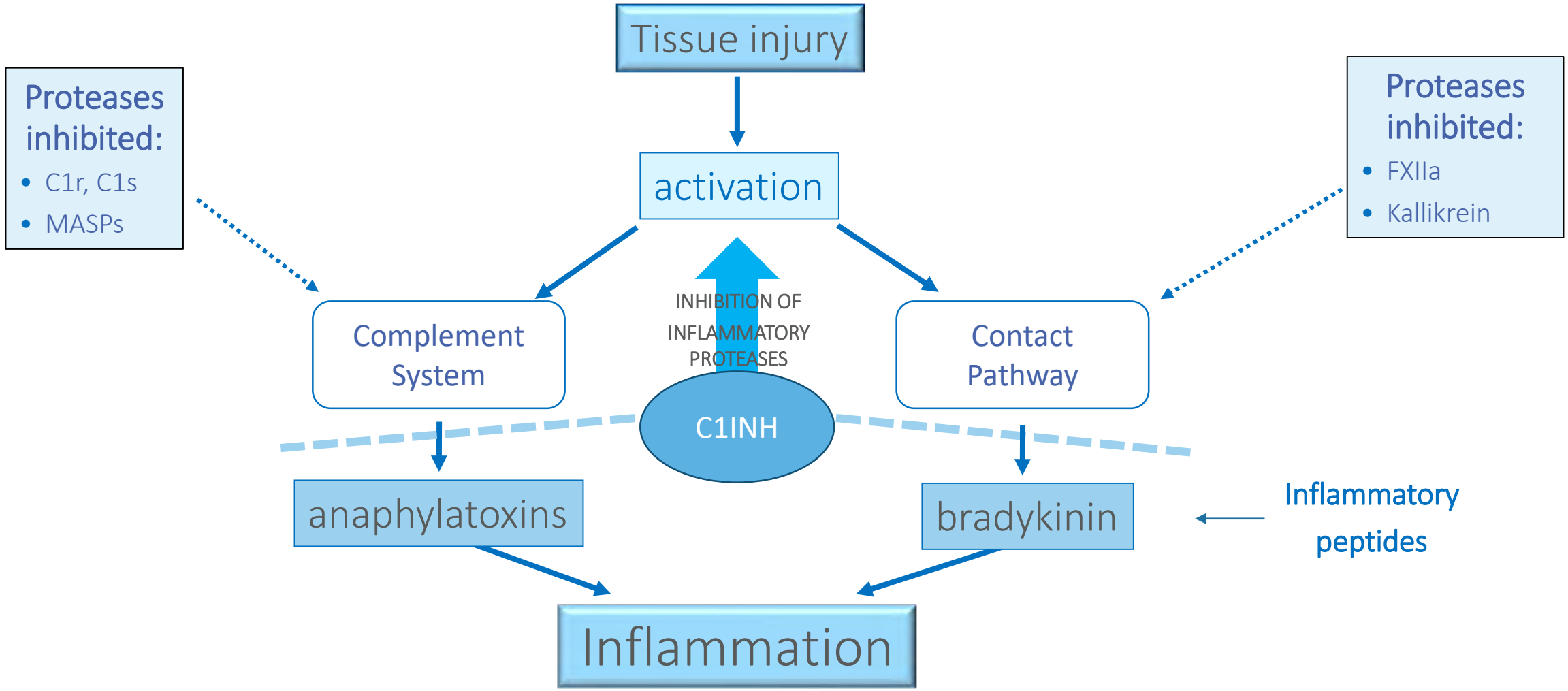
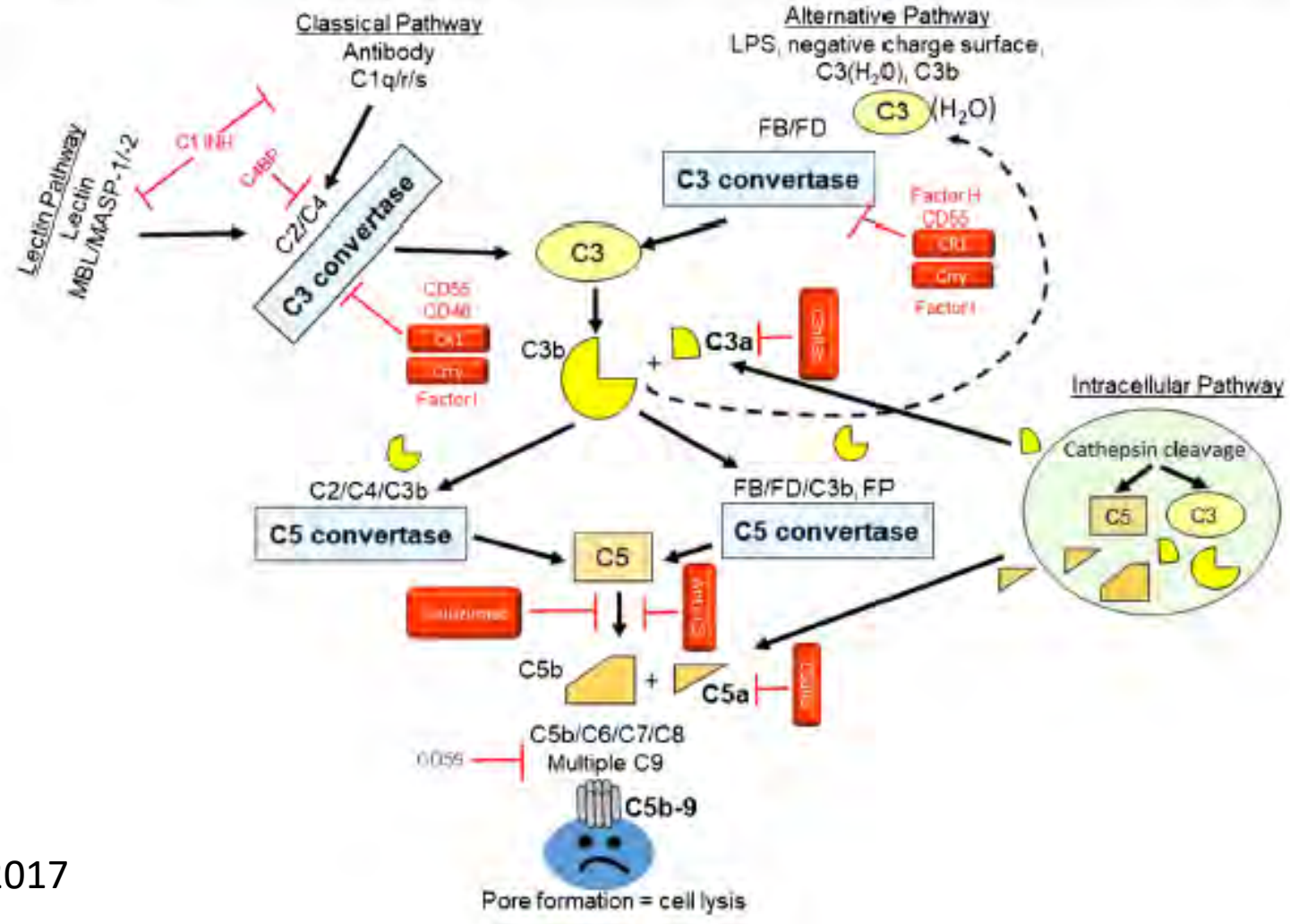


FIGURE 1 | A model of innate immunity incompatibility between maternal and fetal cells in preeclampsia and the maternal immune system. Failure of complement regulation on fetal tissue or excessive activation of the maternal complement system could result in complement attack against 1) invading trophoblast 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.

The Complement Cascade - Overview



Complement cascade involvement in Pre-eclampsia



JF Regal, S Fleming 2017

Pre-eclampsia (PE) Clinical Plan

- There is no animal model mimicking appropriately the human pre-eclampsia situation.
- Ruconest® has been given to > 50 pregnant HAE patients to treat or to prevent HAE attacks (up to 40 times during a single pregnancy) – no safety issue detected

  (Pharming, PSUR 2018)

- Ruconest® has been given to a pregnant HAE patient during delivery. Ultrasound monitoring of the baby revealed a peripheral HAE attack *in utero*. Ruconest® administration resulted in efficacious therapy of both mother and the newborn child (subsequently tested HAE positive)

  (V Grischeva, B Giannetti, ACAAI, 2019 poster publication accepted)

- Phase II clinical trial protocol to explore safety and efficacy of Ruconest® in the treatment of PE has been filed and accepted in the Netherlands and filed in Australia
- Trial has been initiated in The Netherlands. Awaiting final signature by EC in Australia

Research and Development: Activated PI3K-δ Syndrome (APDS)

Dr. Anurag Relan

Primary Immunodeficiency and APDS Background

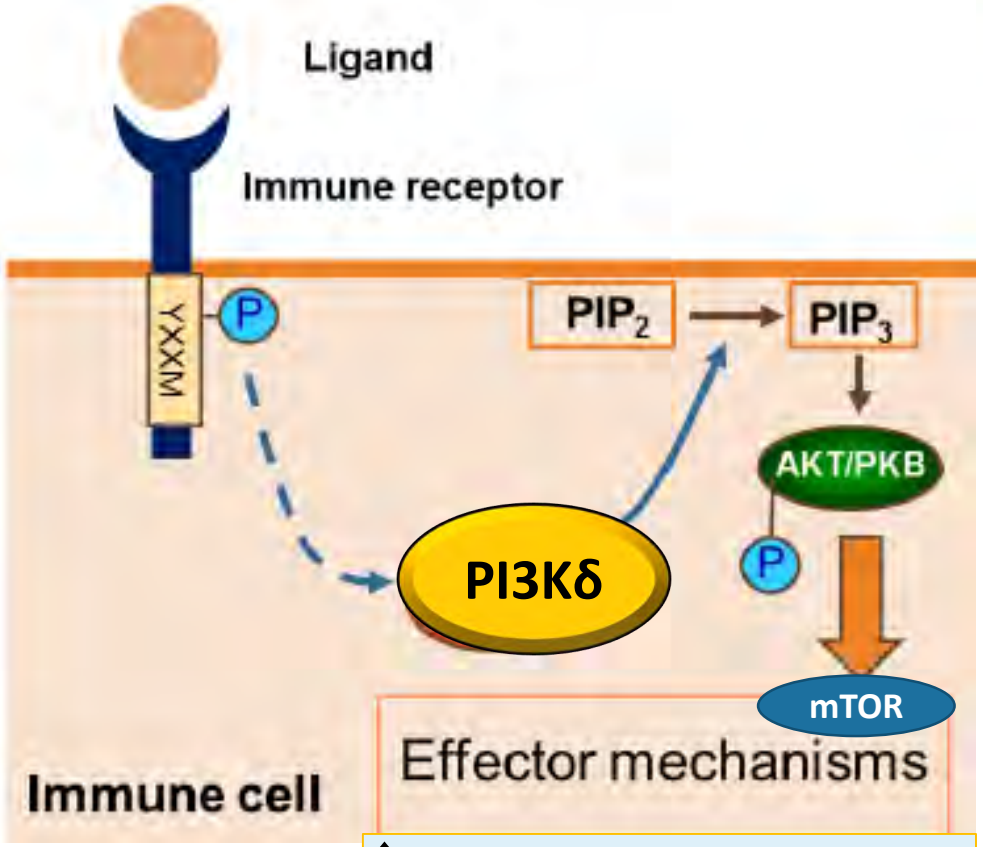
- Primary immunodeficiencies (PID) lead to immune system dysregulation with numerous resulting complications
  - Prevalence 1 in 1200
  - More than 300 genes known to cause different PIDs
  - Highly variable clinical presentation, but increased susceptibility to infection is common to most PIDs

- Activated PI3 kinase delta syndrome (APDS) is a PID
  - Caused by autosomal dominant mutations
  - Increased activity of phosphoinositide-3-kinase δ (PI3Kδ)
  - Estimated prevalence 1-2/million
  - More than 240 reported in literature
  - Screening in subset of PID patients has found rates: 5/669 (1%) and 17/184 (9%)
  - Commercially available genetic test

Angulo I, et al. Science. 15;342. 2013. Lucas CL. Nature Immunology. 15, 88-97, 2014.
Michalovich D, et al. Frontiers Immuno. 2018. Jamee M, et al. Clin Rev Allergy Immunology. 2019.

PI3Kδ and APDS Pathophysiology

- Phosphoinositide 3–kinase PI3K is a signaling pathway involved in a broad variety of cellular functions
- The PI3K delta isoform is primarily present in the immune system
- Regulation of PI3KD activity is required to ensure normal function and differentiation of immune cells.
- Since 2013, more than 200 patients have been found with mutations leading to hyperactivation of the PI3KD pathway
- As a result of this over activity, the B and T cells involved in immune response can fail to properly differentiate



↑ Effector cell differentiation
↑ Lymphoproliferation burst
↑ CD8+ T cell senescence

↓ Memory T cell function
↓ Control of EBV and CMV

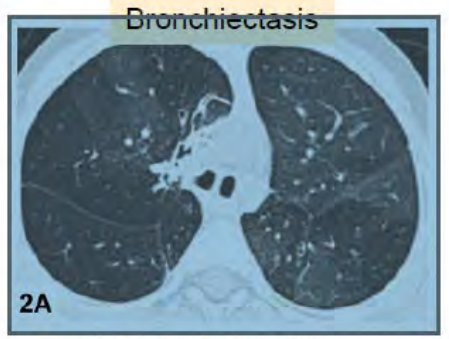
Lucas CL. Nature Immunology. 15, 88-97, 2014.

APDS Clinical Spectrum

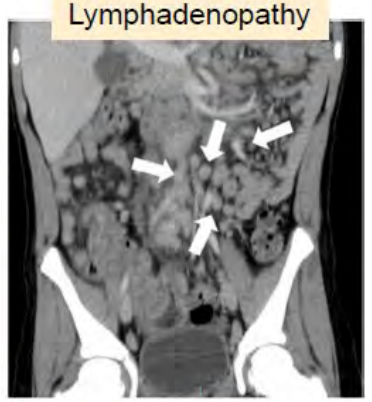
Pharming

Varying clinical manifestations of symptoms and signs

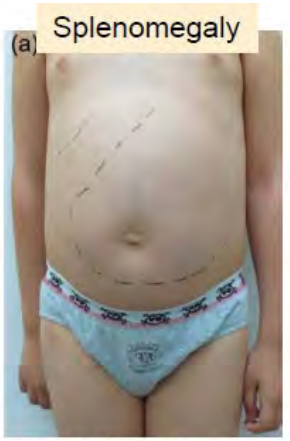
- Recurrent infections
- Organomegaly
- Malignancy
- Autoimmunity



Coulter et al, J.Allerg.Clin. Immunol. 2016



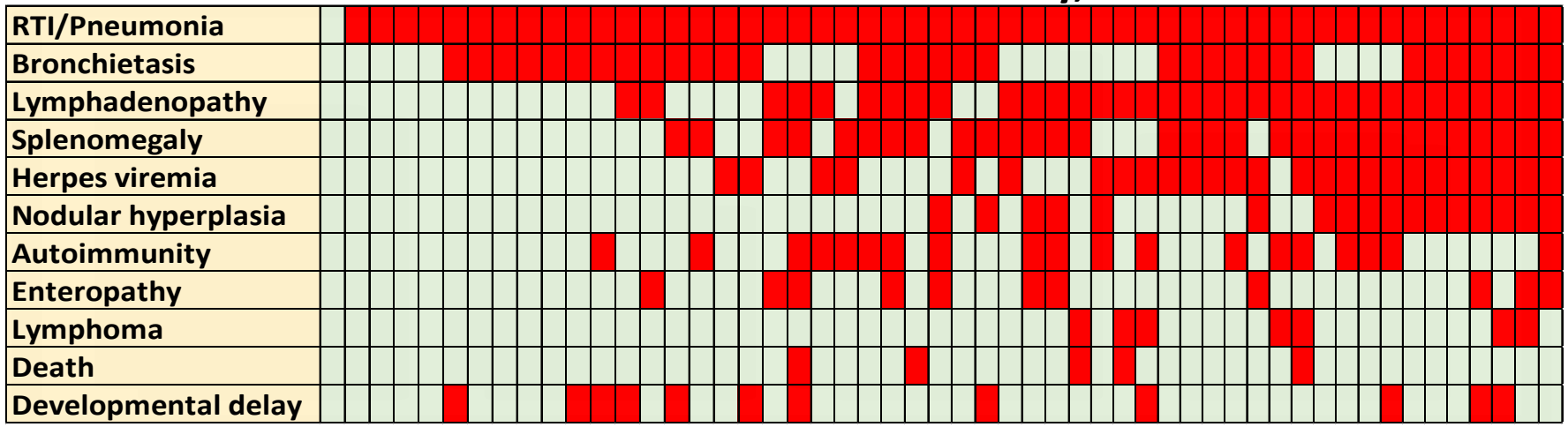
Lucas et al, Nature Immunol, 2014



Elgizouli et al Clin.Exp.Immunol. 2015

Jamee M, et al. Clin Rev Allergy Immunology. 2019.

ADPS Patient Cohort Study, n=53

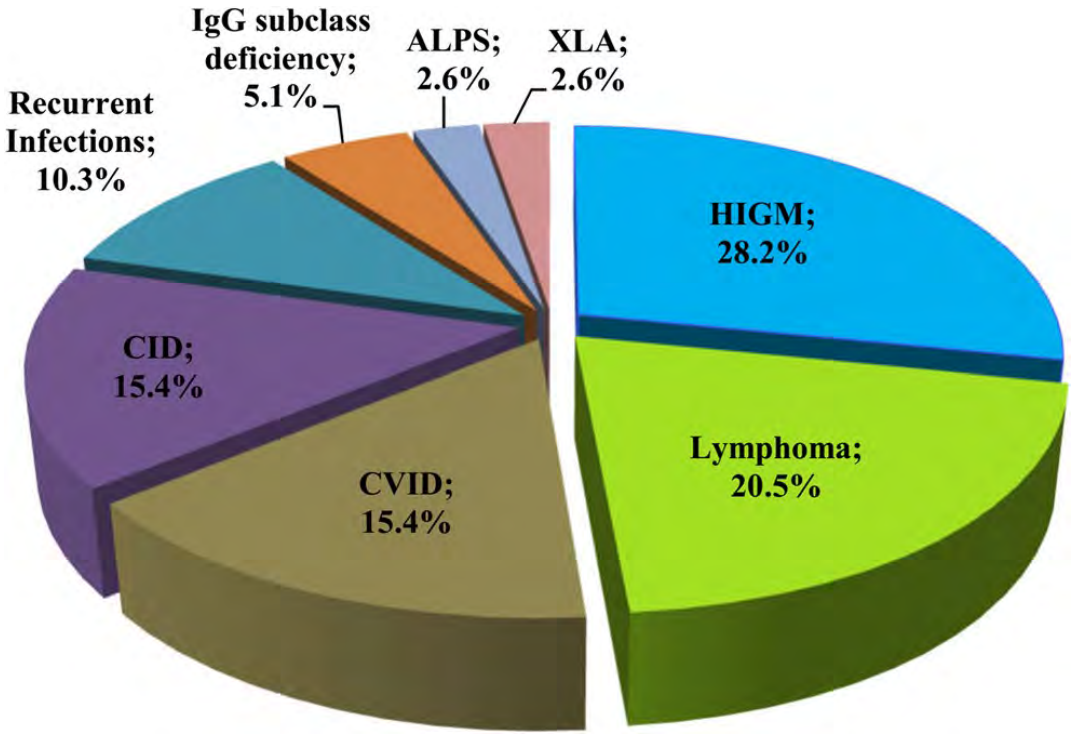


Modified from: Coulter TI, et al. JACI. Vol 139:2, 2017.

= Presence of a complication

APDS Misdiagnosis

Distribution of primary clinical diagnosis of APDS patients



Review of 243 published APDS patients

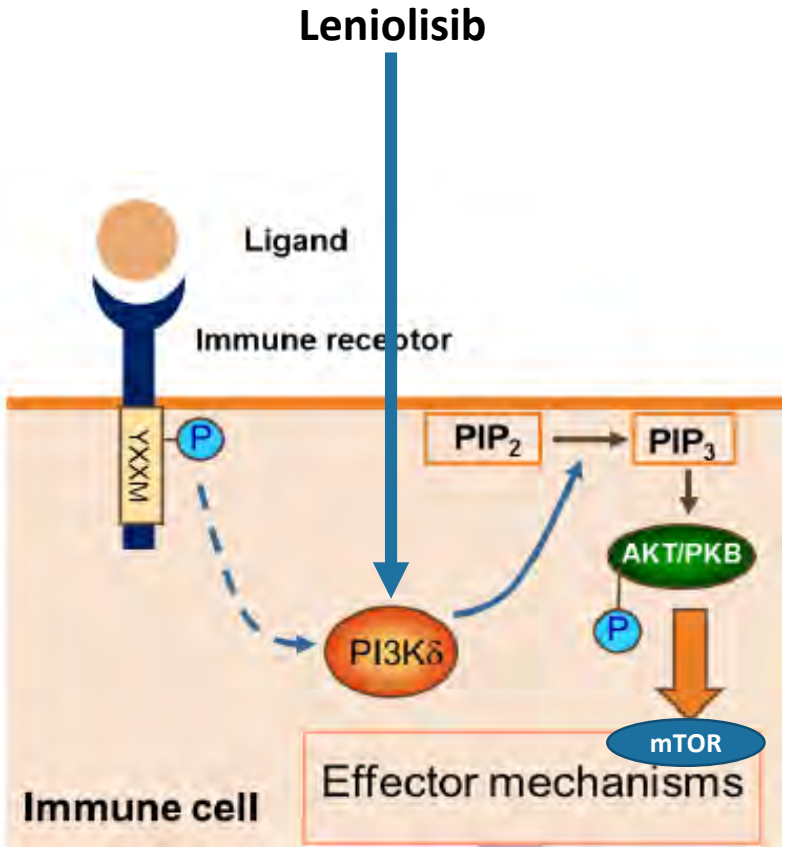
- Symptoms occurred early 1-2 years of age
- Median age diagnosis: 12 years
- Positive family history of PID: 39%

Jamee M, et al. Clin Rev Allergy Immunology. 2019.

APDS Treatment Options

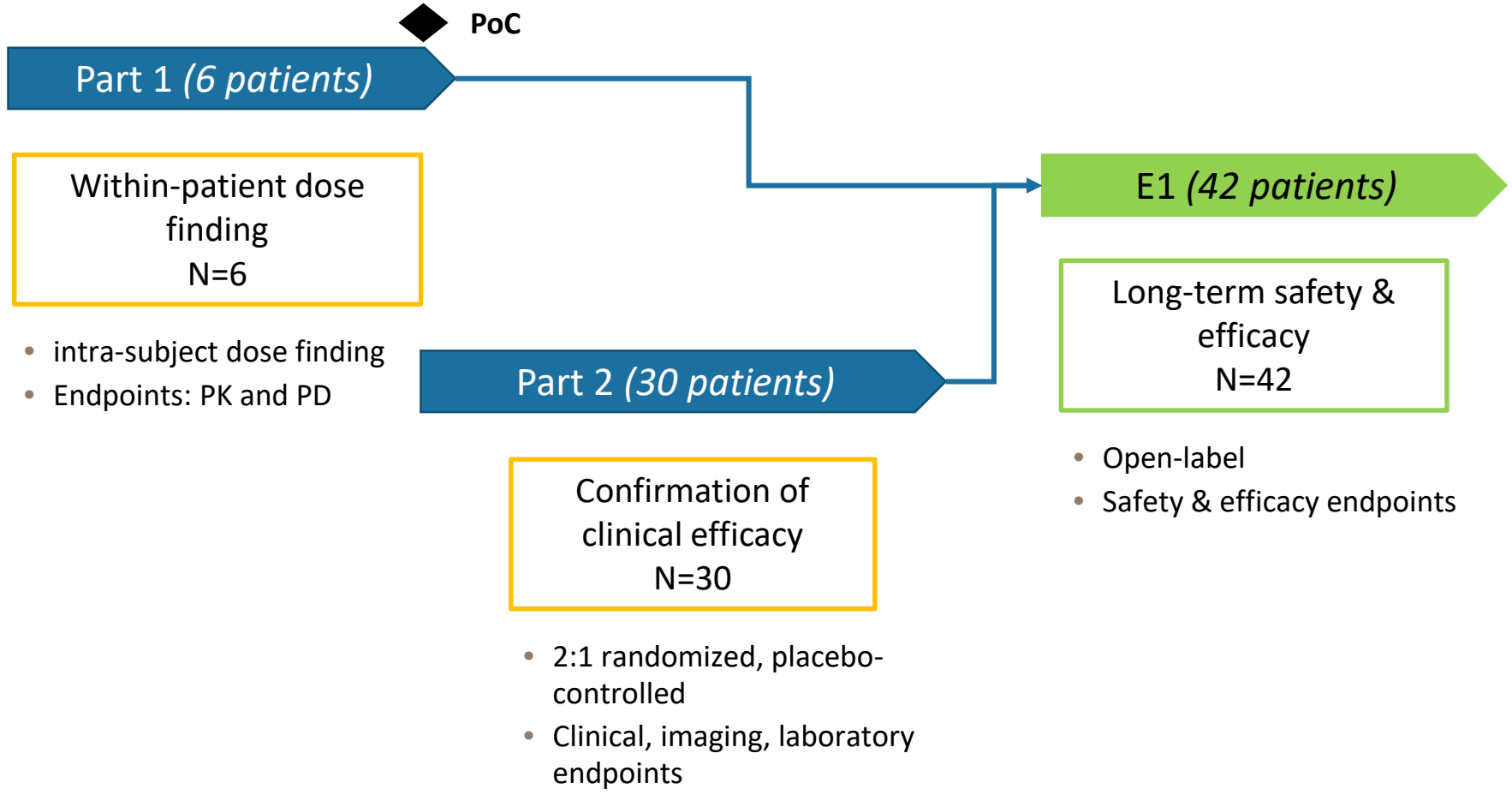
- Current treatment options for APDS:
  - Symptomatic treatment e.g., antibiotics
  - Immune globulin replacement therapy (IVIG/SCIG)
  - Stem cell transplantation
  - Case reports of mTOR inhibitor rapamycin

- Leniolisib
  - Potent, selective PI3Kδ inhibitor
  - Treats the root cause of APDS
  - Orally bioavailable – tablet/capsule
  - Direct PK/PD relationship observed
  - Currently in registration-enabling pivotal study
  - If approved, the drug is expected to reach the market in 1H 2022



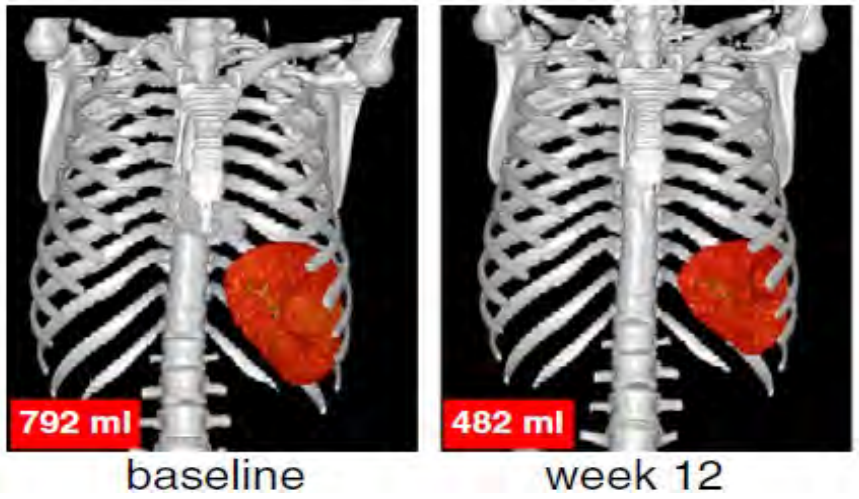
Clinical: Leniolisib - Pivotal Study Program

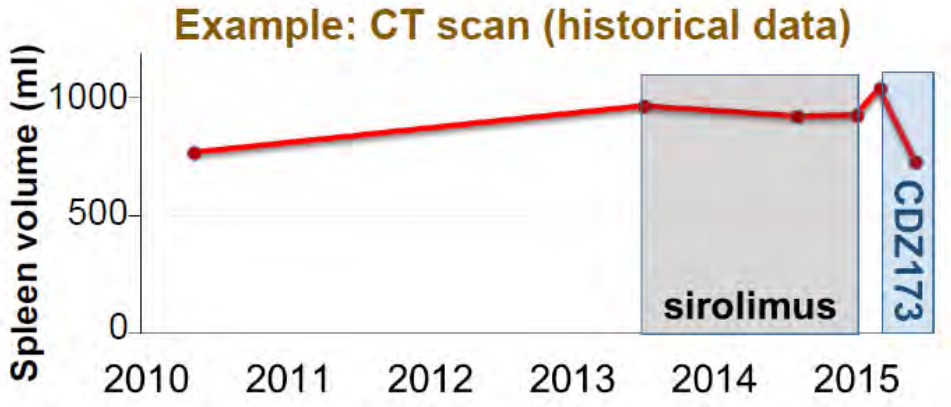
Two part **core study** and **extension study**



Leniolisib - Key Results from Part 1 of Core Study

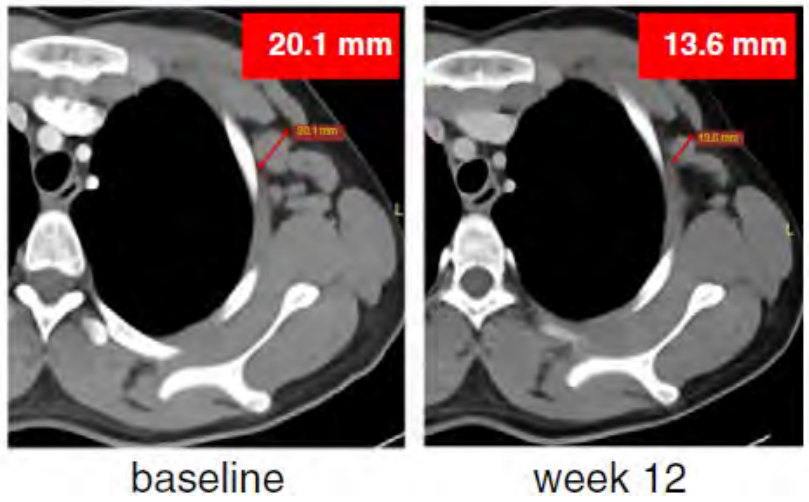
Reduction in spleen size





Patient	Spleen volume Δbaseline	Lymph node Δbaseline
1	-26%	-51%
2	-39%	-13%
3	-57%	-65%
4	-36%	-33%
5	-39%	-48%
6	-37%	-31%
Mean	**-39%**	**-40%**

Lymph node size



Rao VK, et al. Blood. 2017.

Financial Performance & 2019 Outlook

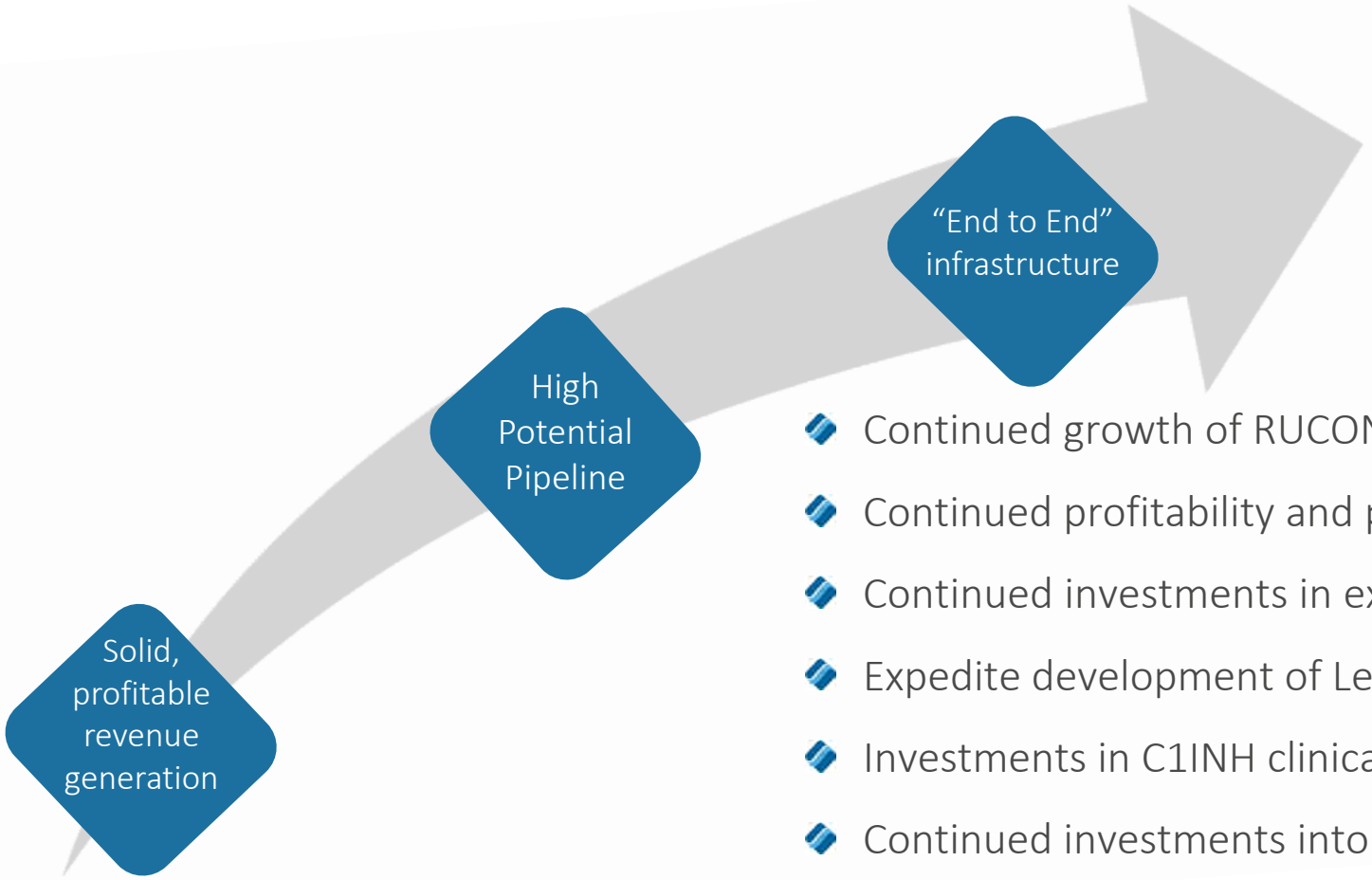
Third Quarter 2019: Financial Results

9 months to 30 September

Amounts in €m except per share data	*2019 3rd Quarter*	*2019 1st 9 months*	*2018 1st 9 months*	*% Change*
Income Statement				
Revenue from product sales	45.3	122.8	97.7	*26%*
Other revenue	0.2	0.6	0.6	
Total revenue	45.5	123.4	98.3	*26%*
Gross profit	40.1	107.1	82.4	*30%*
Operating result	18.1	42.7	31.0	*38%*
Net result	10.5	24.1	13.9	*73%*
Balance Sheet				
Cash & marketable securities	64.4	64.4	72.2	*(11%)*
Share Information				
Earnings per share (€): - Undiluted	0.017	0.038	0.022	*73%*
- Fully diluted	0.015	0.036	0.021	*71%*

* *After restatement on the basis set out above and in Note 4 to the Financial Statements in the Annual Report 2018.*

Summary and Outlook 2019 and beyond



- Continued growth of RUCONEST® sales
- Continued profitability and positive cash flows
- Continued investments in expansion of manufacturing
- Expedite development of Leniolisib to FDA and EMA approval
- Investments in C1INH clinical trials for PE and AKI
- Continued investments into development PRT for Pompe and Fabry
- Re-evaluation of most advantageous route of administration for RUCONEST®

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ENXTAM: PHARM

Bloomberg: PHAR.AS