

# HAE management: What are the new alternatives?

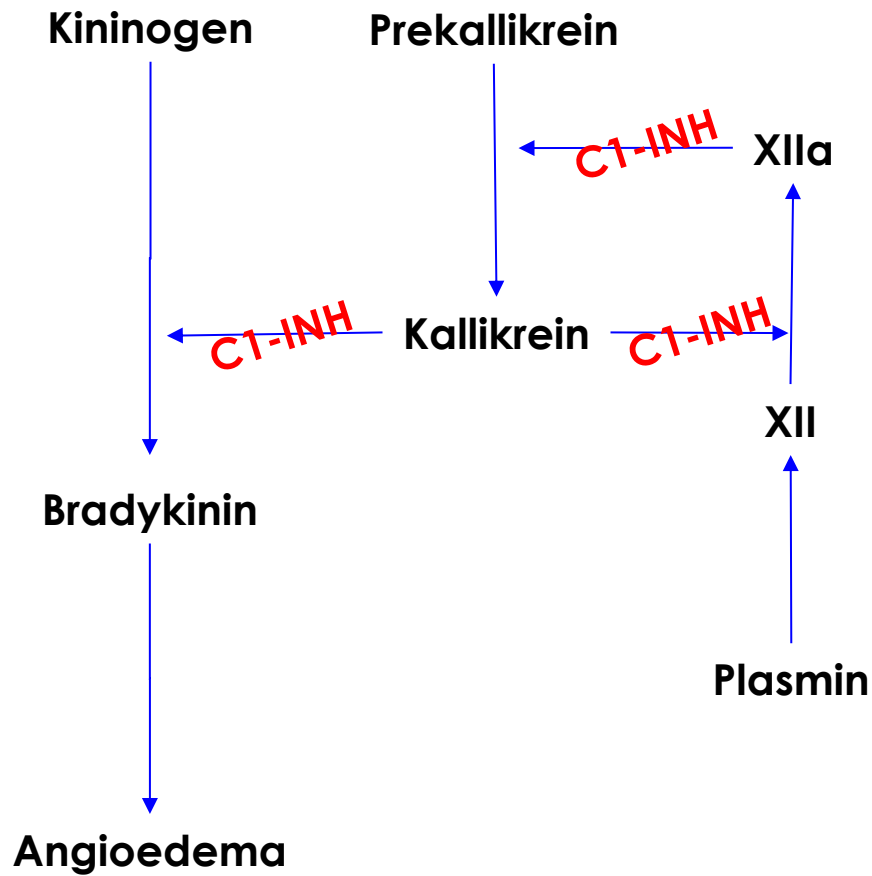
Markus Magerl  
13<sup>th</sup> of December 2018  
Grenoble

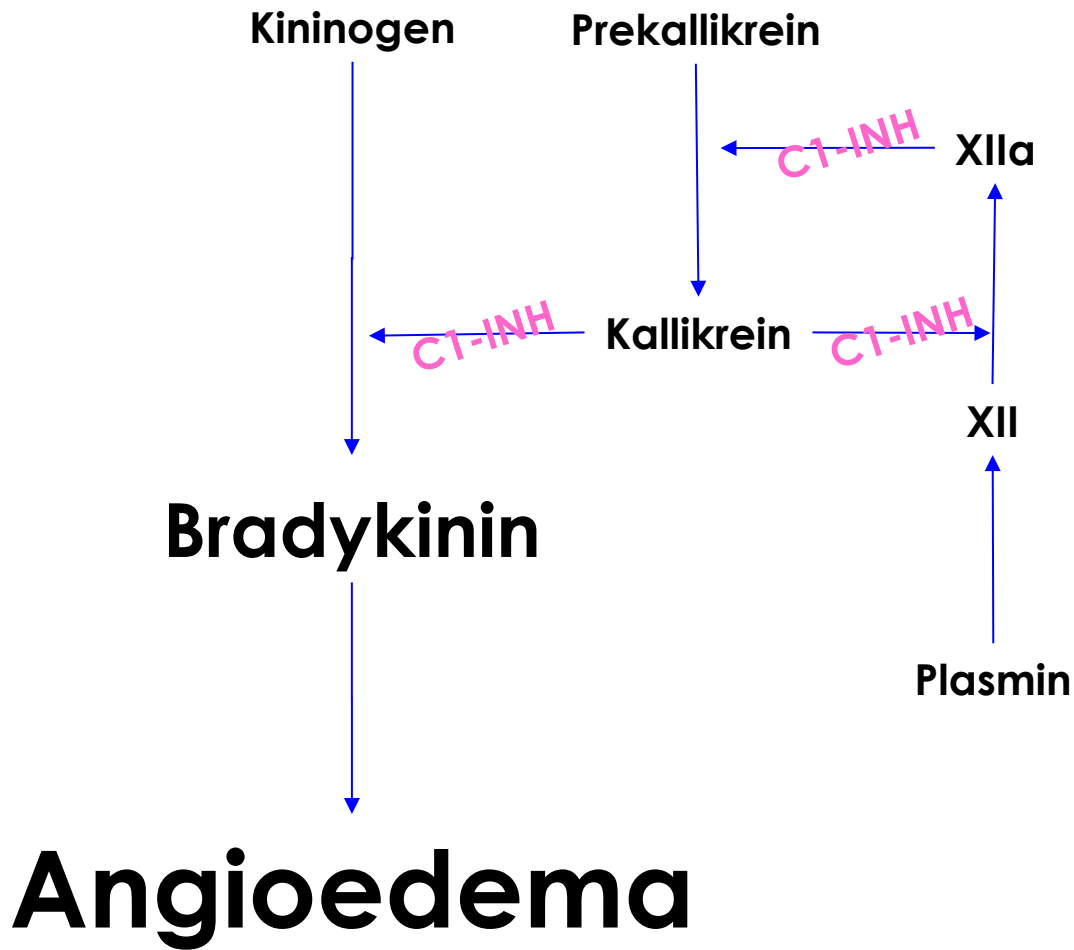


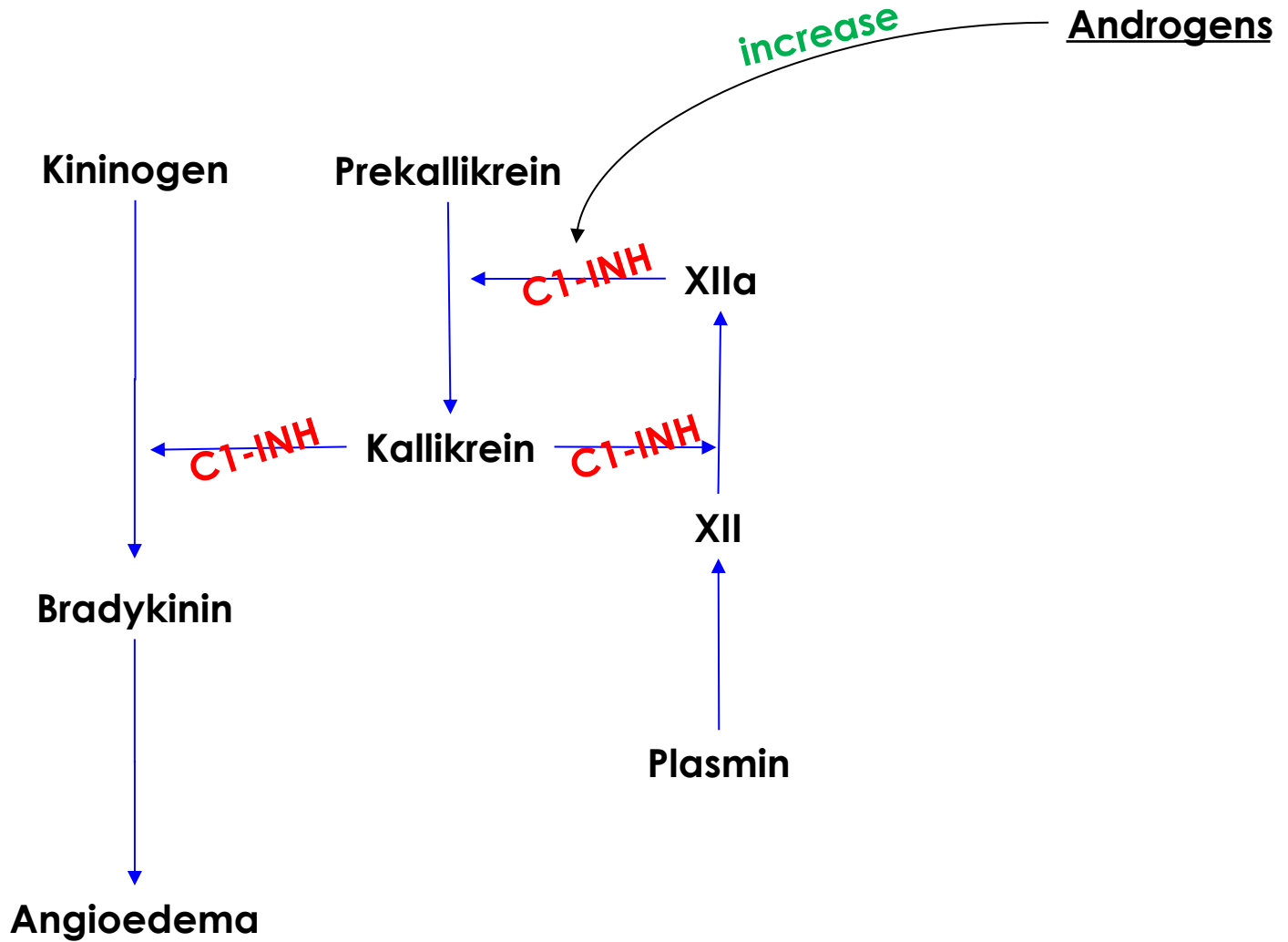
# Disclosures

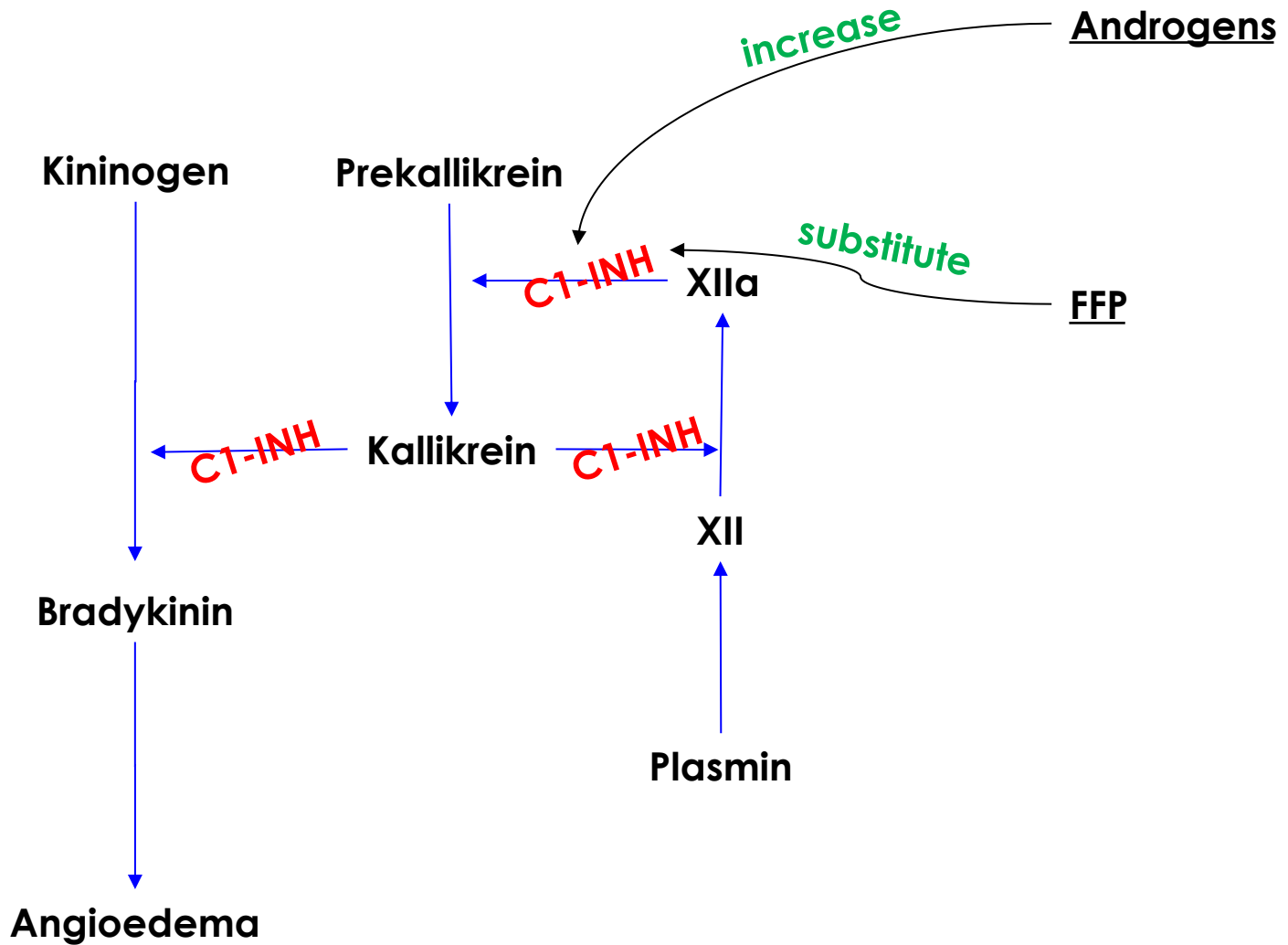
Speaker, Advisor, Researcher for Biocryst, CSL  
Behring, Dyax, Octapharma, Pharming, and/or Shire.

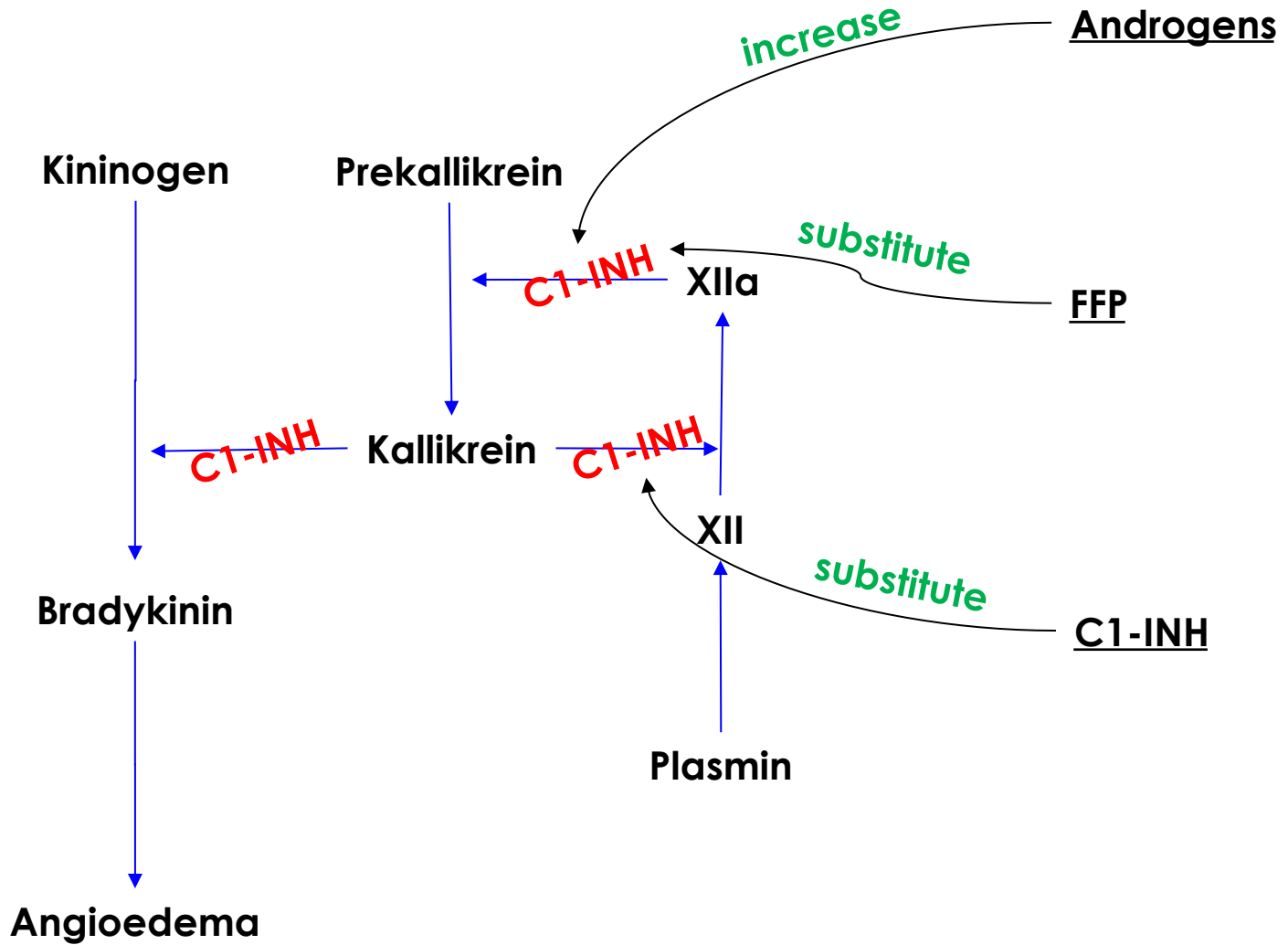


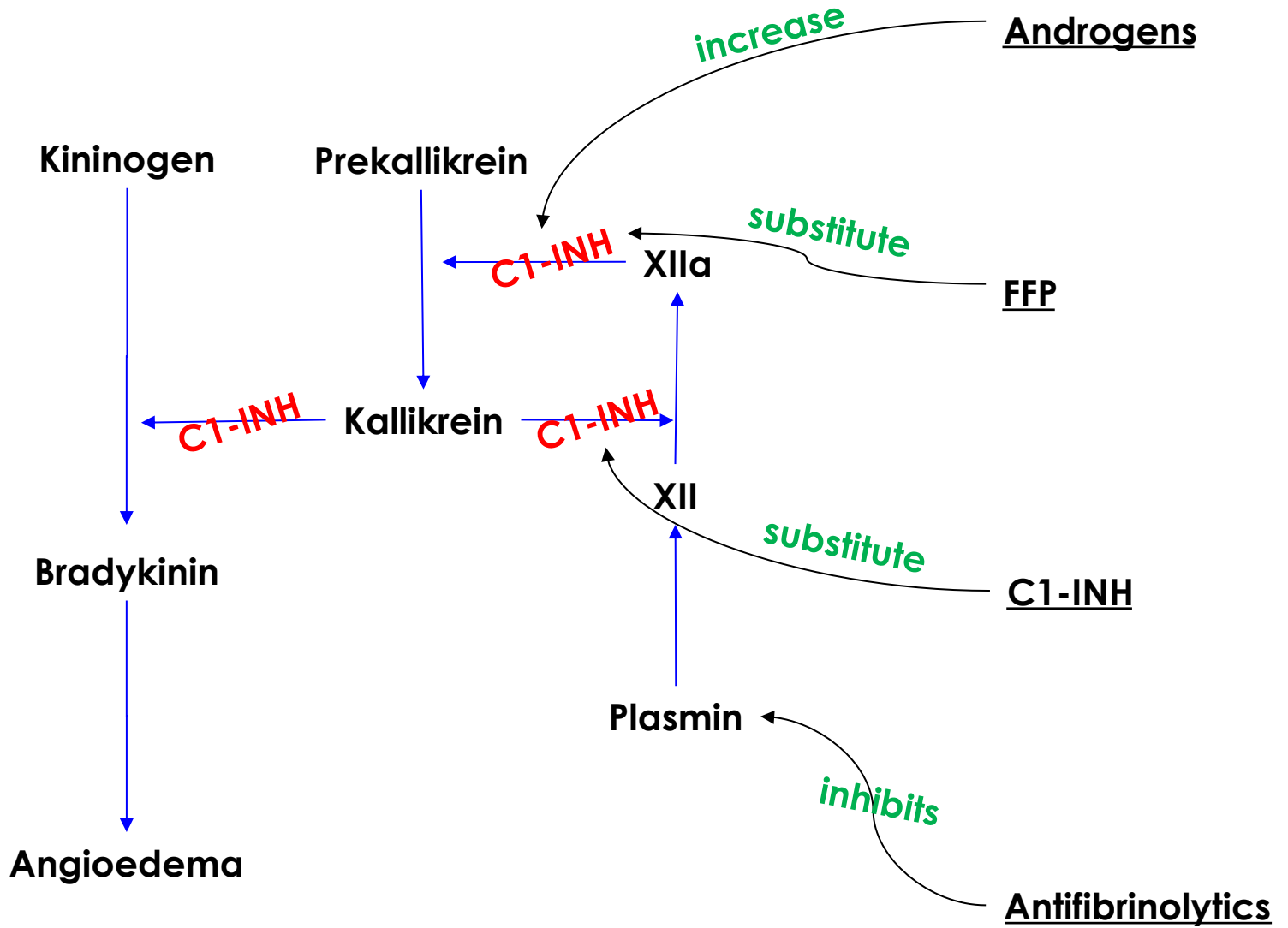




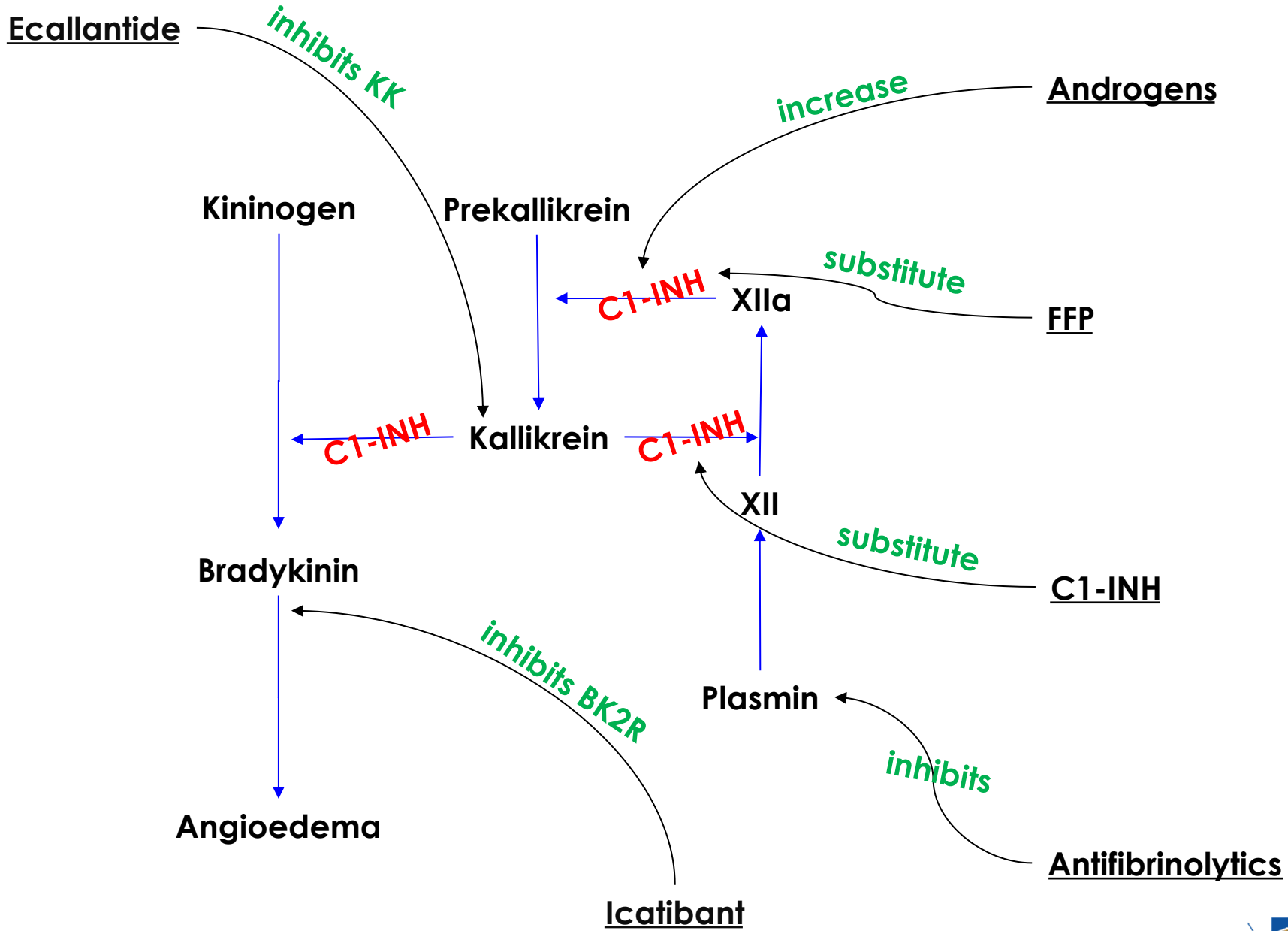












Ecallantide

*inhibits KK*

*increase*

Androgens

Kininogen

Prekallikrein

*substitute*

FFP

2018

*C1-INH*

*C1-INH*

Kallikrein

*C1-INH*

XIIa

*substitute*

C1-INH

XII

Plasmin

*inhibits BK2R*

*inhibits*

Angioedema

Antifibrinolytics

Icatibant

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# why more?

*C1-INH*

Kallikrein

*C1-INH*

XII

*substitute*

C1-INH

Bradykinin

*inhibits BK2R*

Plasmin

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C1-INH

Bradykinin

*inhibits BK2R*

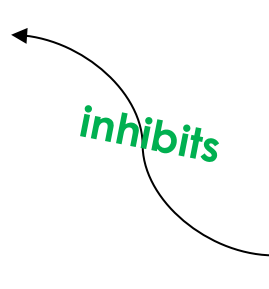
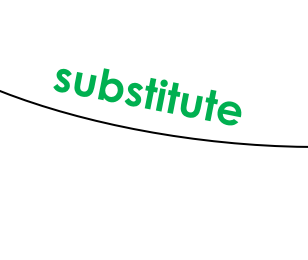
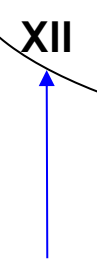
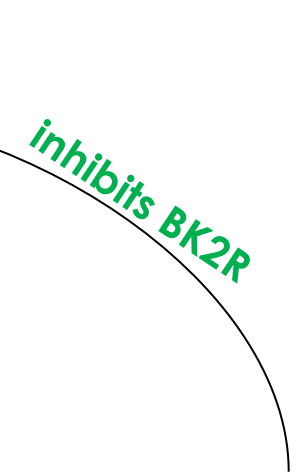
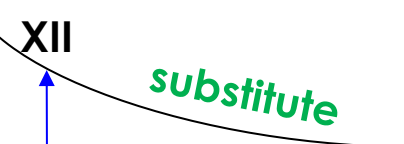
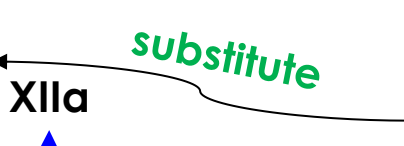
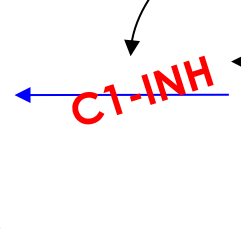
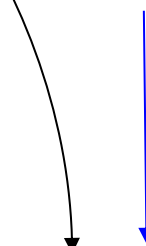
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# 2018

Kallikrein

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**C1-INH**

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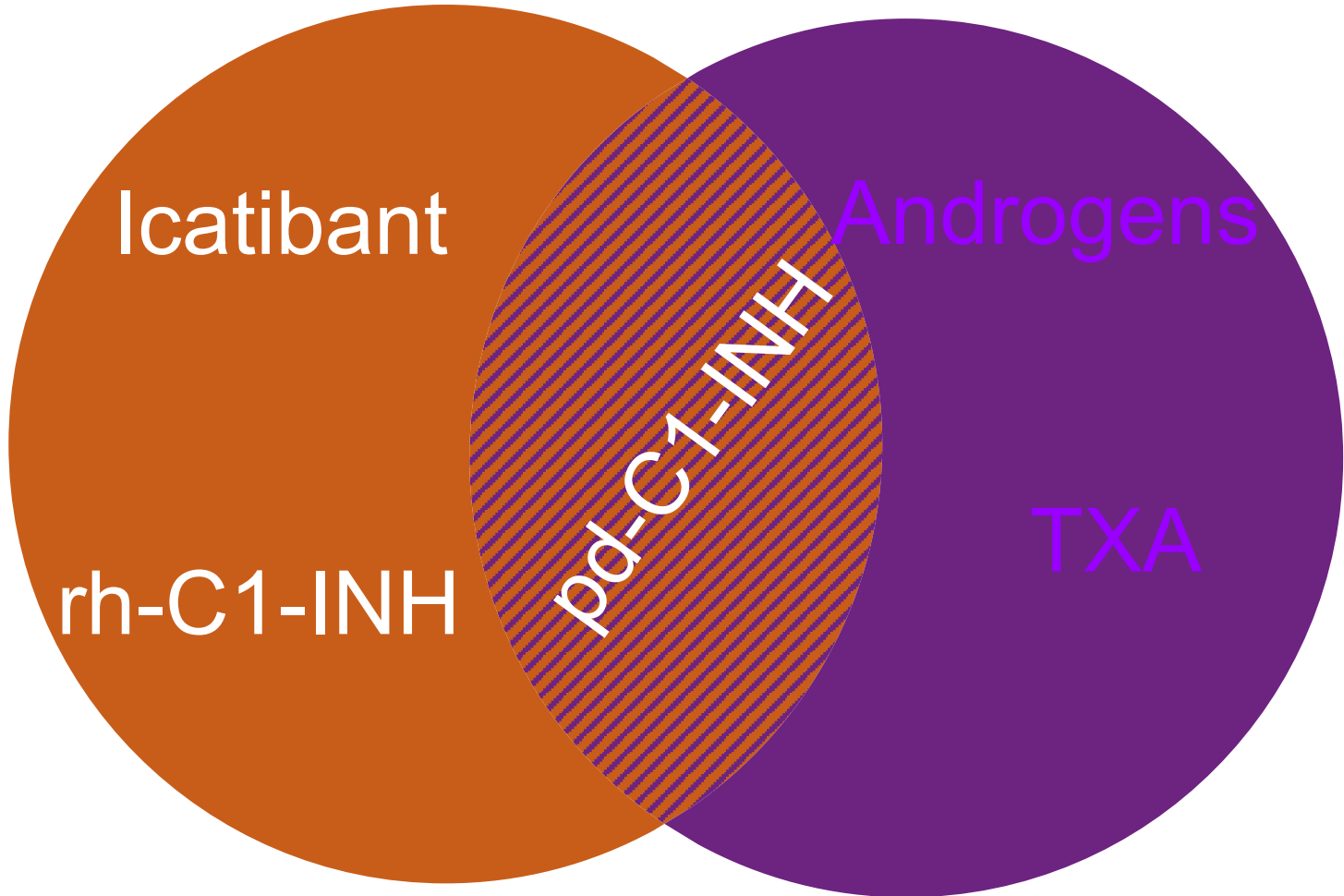
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Angioedema

**Icatibant**

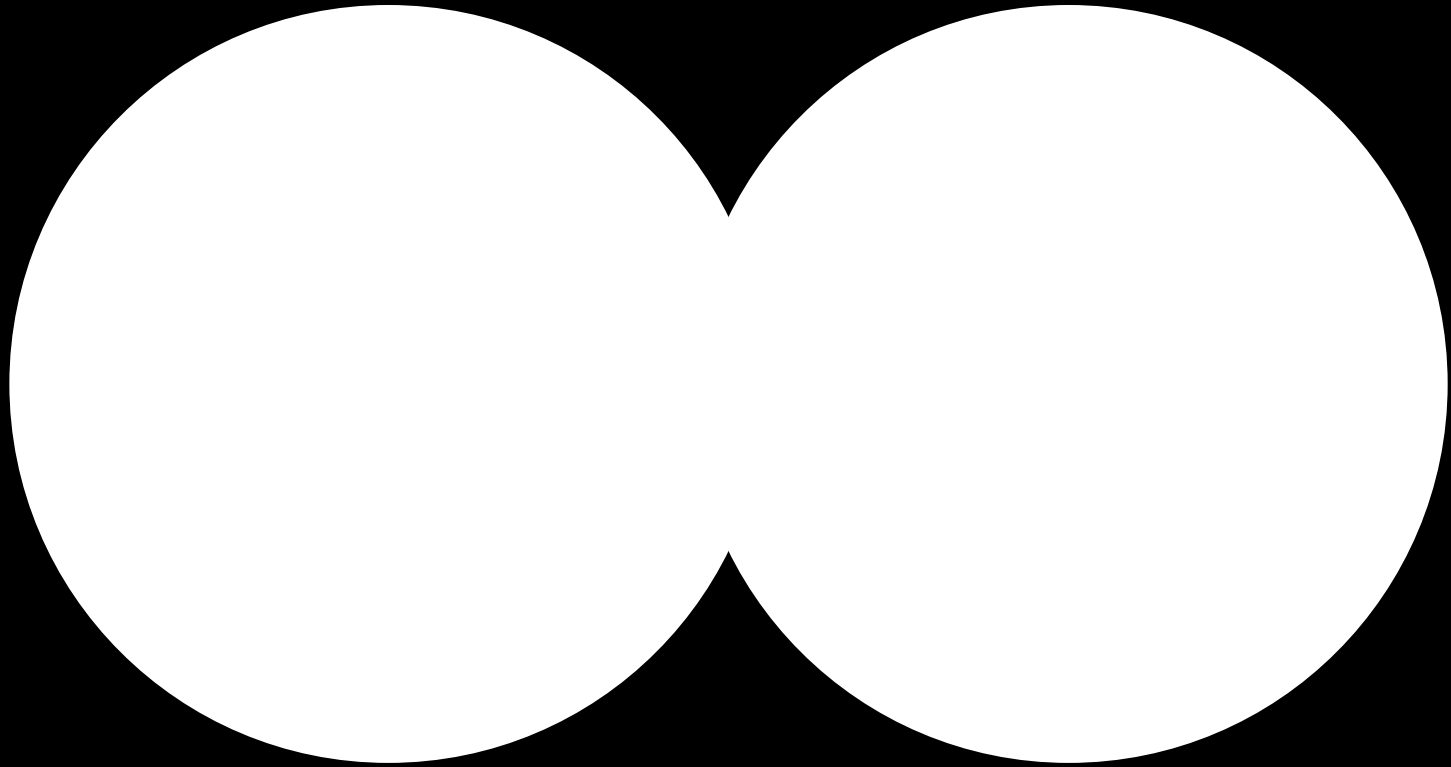
On Demand

Prophylaxis





# Minor doubts about future treatment strategy



# Minor doubts about future treatment strategy



Prophylaxis



# Lanadelumab (DX-2930)

human monoclonal antibody

directed against plasma kallikrein

Chinese Hamster Ovary Cells (standard meth.)

subcutaneous, half-life 2 weeks

# HELP Study

phase 3

multicenter

double-blind

placebo-controlled

4 arms



Banerji A, et al. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018 Nov 27;320(20):2108-2121



# Study Design

**150mg every 4W**



**Placebo**

**300mg every 4W**

**300mg every 2W**



**Lana 150mg**

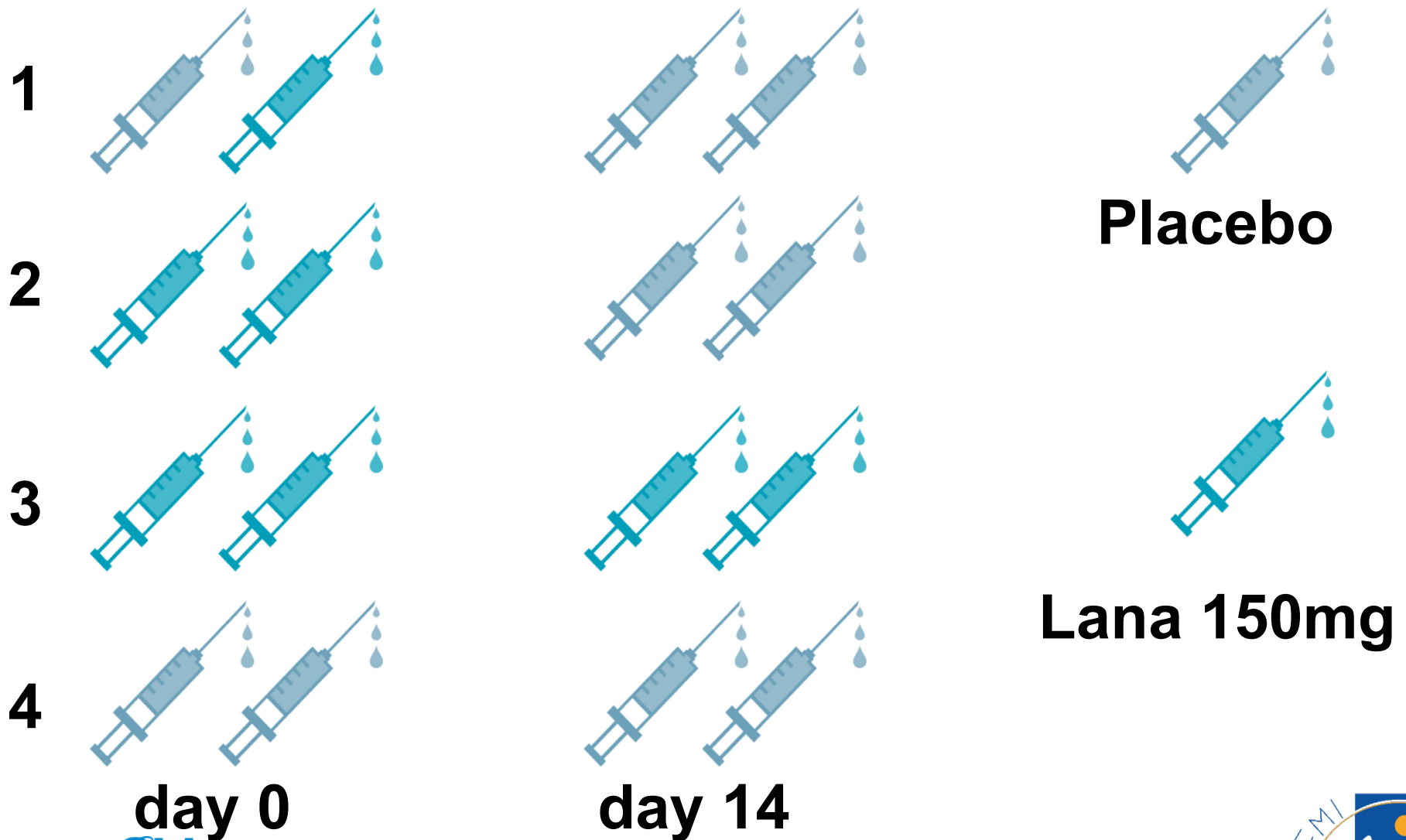
**PLC every 2W**



Banerji A, et al. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018 Nov 27;320(20):2108-2121



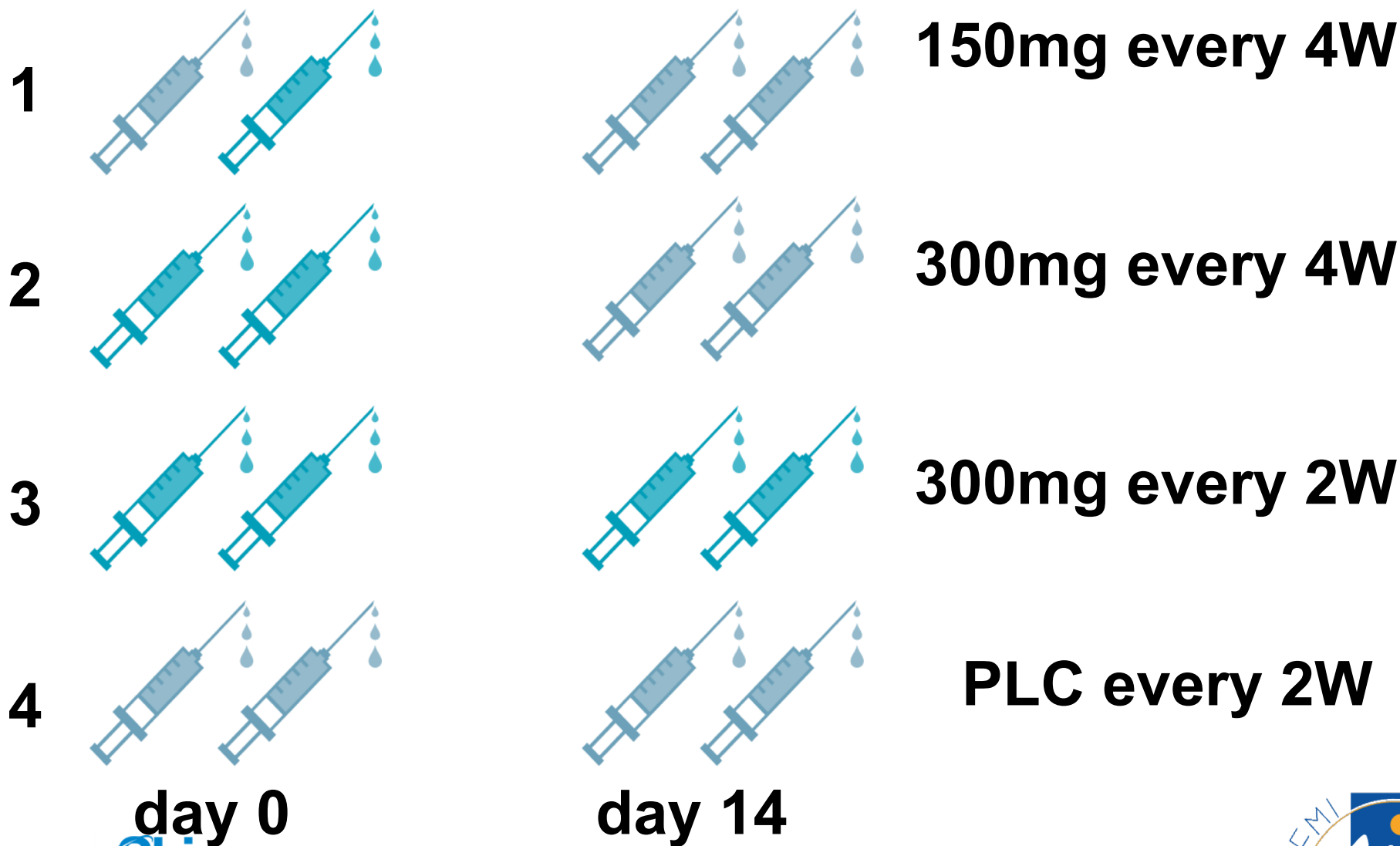
# Study Design



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# Study Design

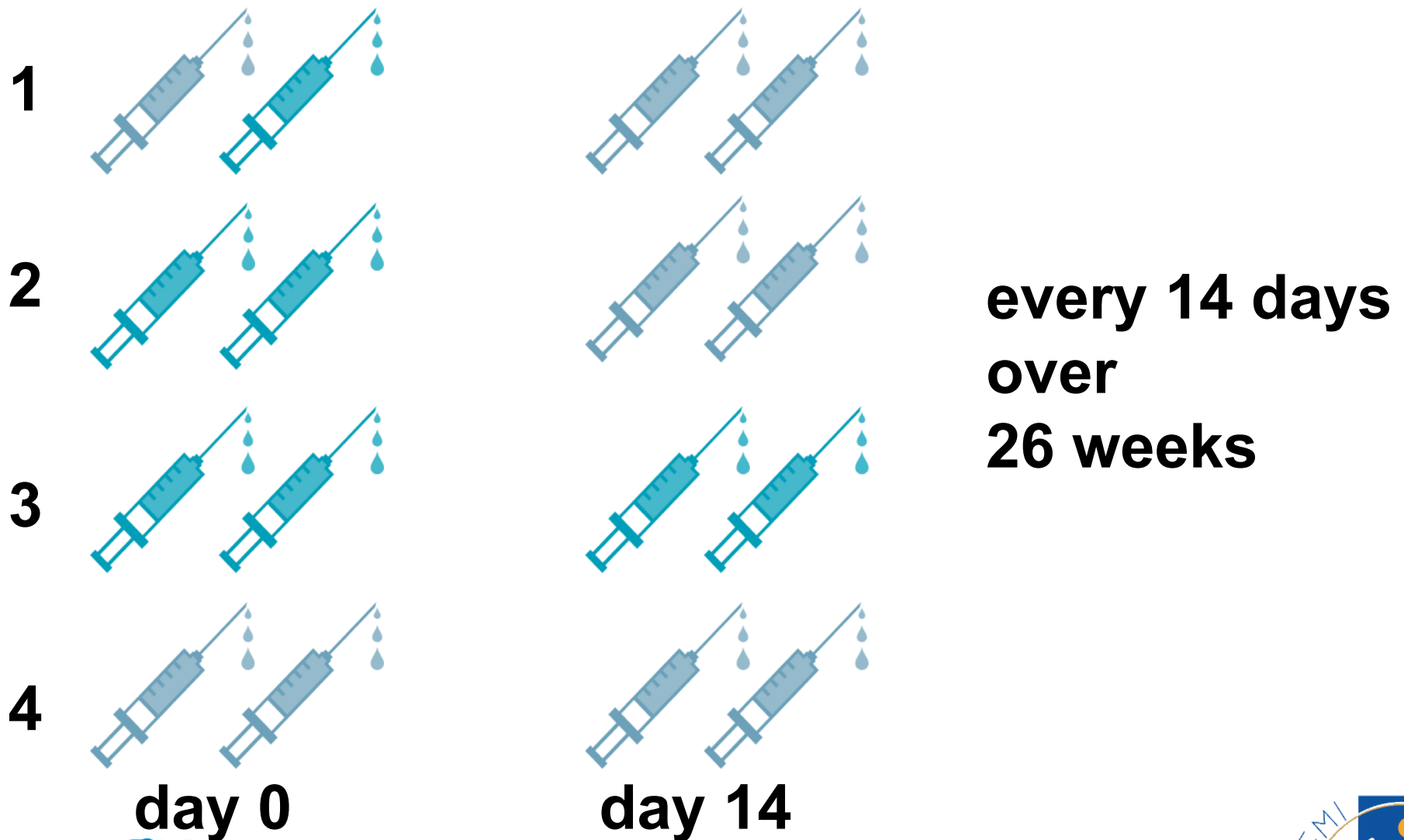


Shire

Banerji A, et al. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018 Nov 27;320(20):2108-2121



# Study Design



Shire

Banerji A, et al. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018 Nov 27;320(20):2108-2121

# Patients

HAE 1 or 2

≥ 12 years (D ≥ 18)

125 patients

Baseline: 3,5 attacks/M (Inclusion: ≥ 1Att/M)

52% ≥ 3 attacks/M

64% history laryngeal edema

54% LTP



# Study Endpoints

## Primary

- Number of HAE attacks from Days 0–182 (26 weeks)

## Secondary

- Number of HAE attacks requiring acute treatment from Days 0–182
- Number of moderate or severe HAE attacks from Days 0–182
- Number of HAE attacks from Days 14–182

## Safety

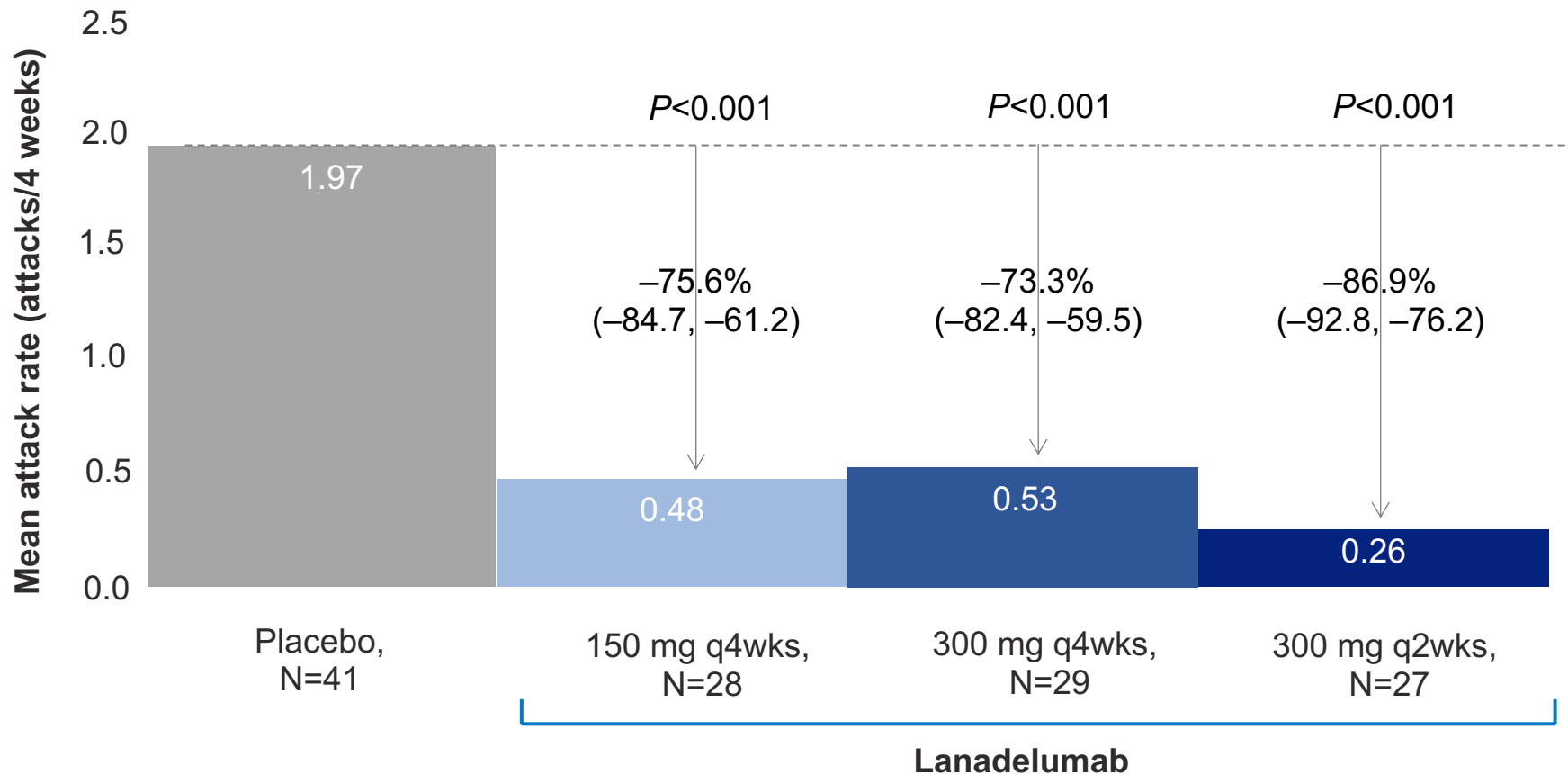
- Adverse events
- Clinical laboratory
- ECG
- Immunogenicity

## Exploratory

- Maximum attack severity
- Percentage of patients attack-free
- Reduction from run-in period in attack rate (i.e., responder analysis)
- Efficacy at steady state
- HR-QoL with AE-QoL and EQ-5D-5L
- Incidence of high-morbidity attacks
- Subgroup analyses\*



# Results (primary endpoint)



Banerji A, et al. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018 Nov 27;320(20):2108-2121

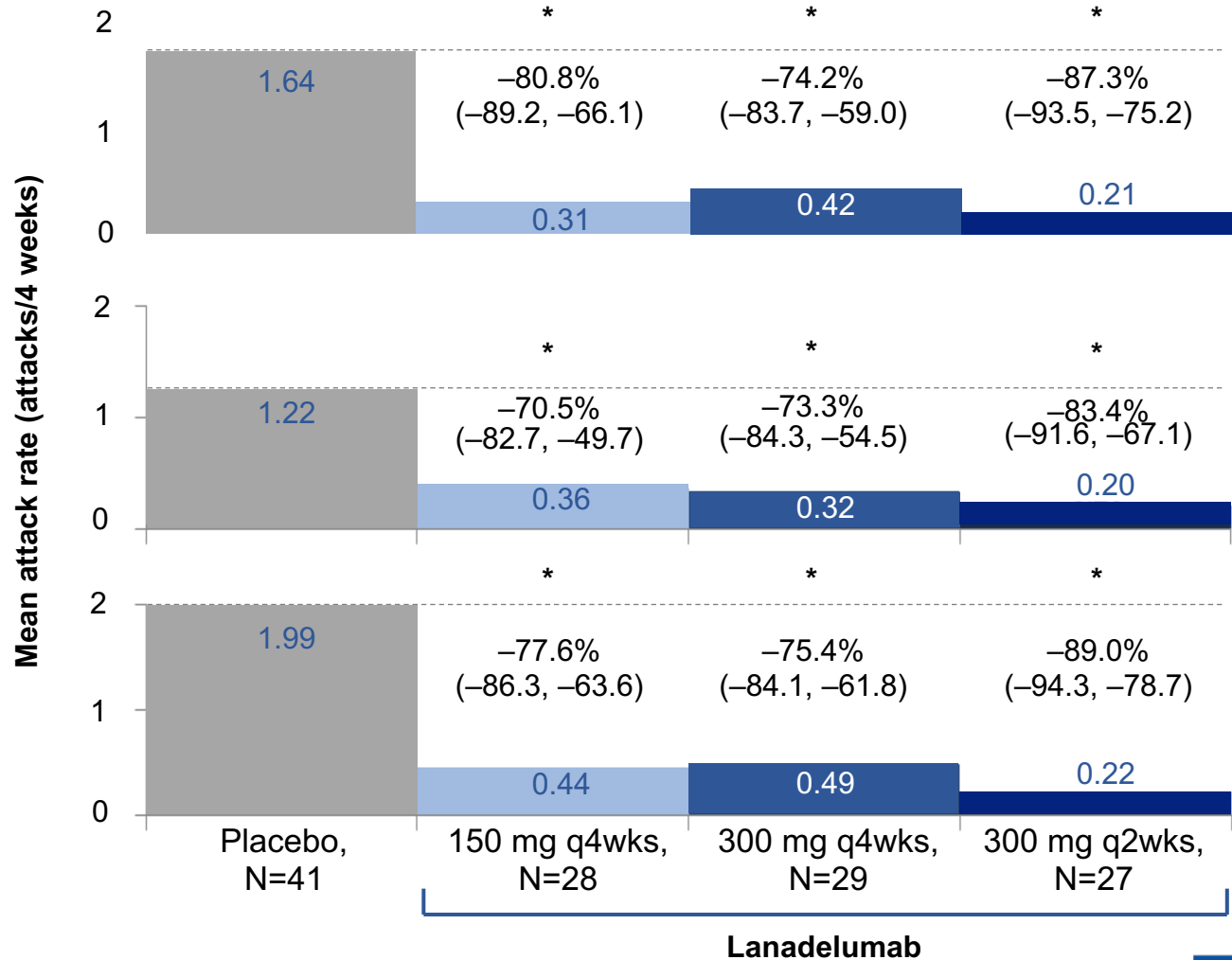


# Results (secondary endpoints)

**Attacks Requiring Acute Treatment**

**Moderate or Severe Attacks**

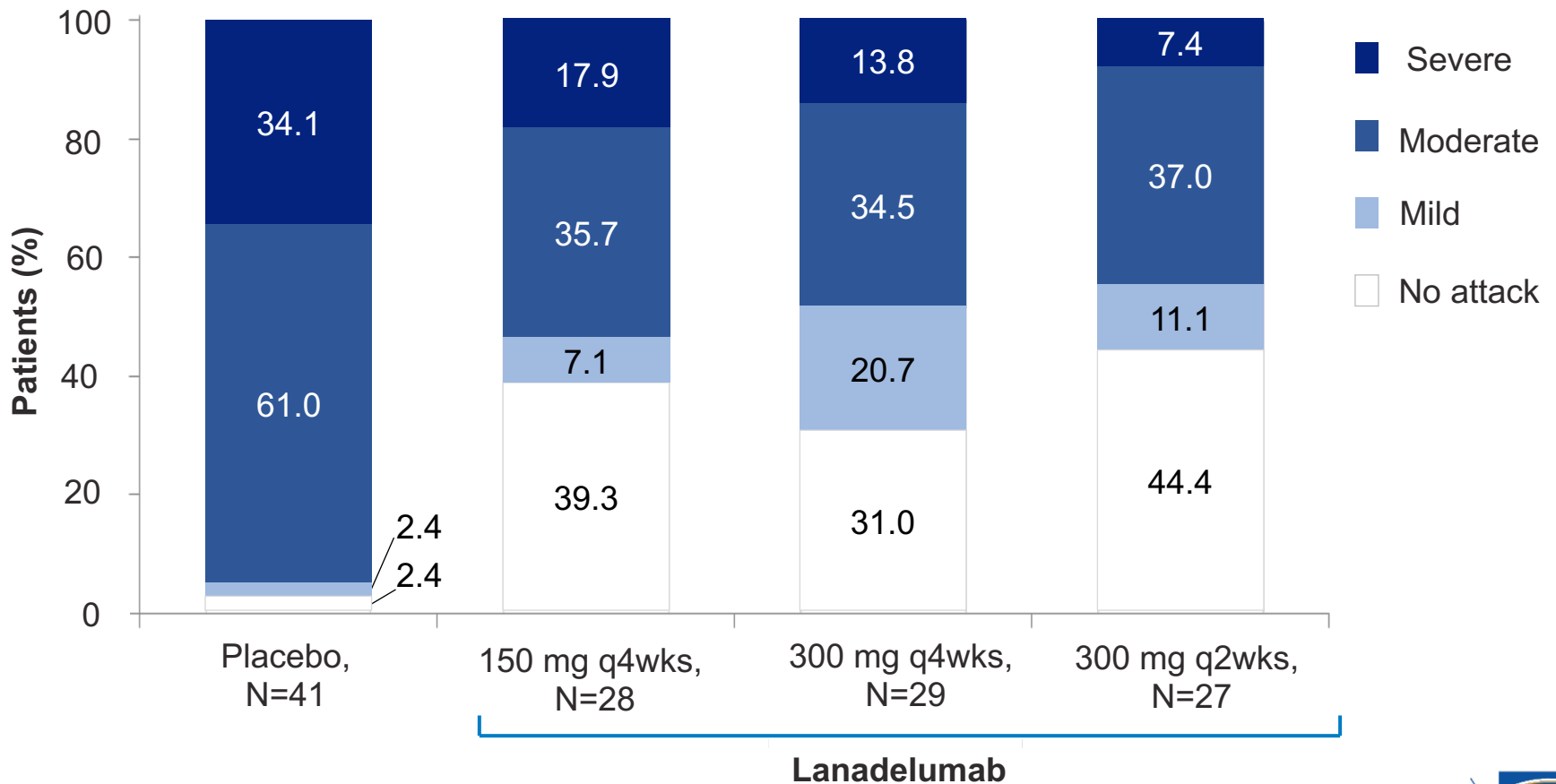
**Attacks After Day 14**



\* Adjusted P<0.001 vs placebo



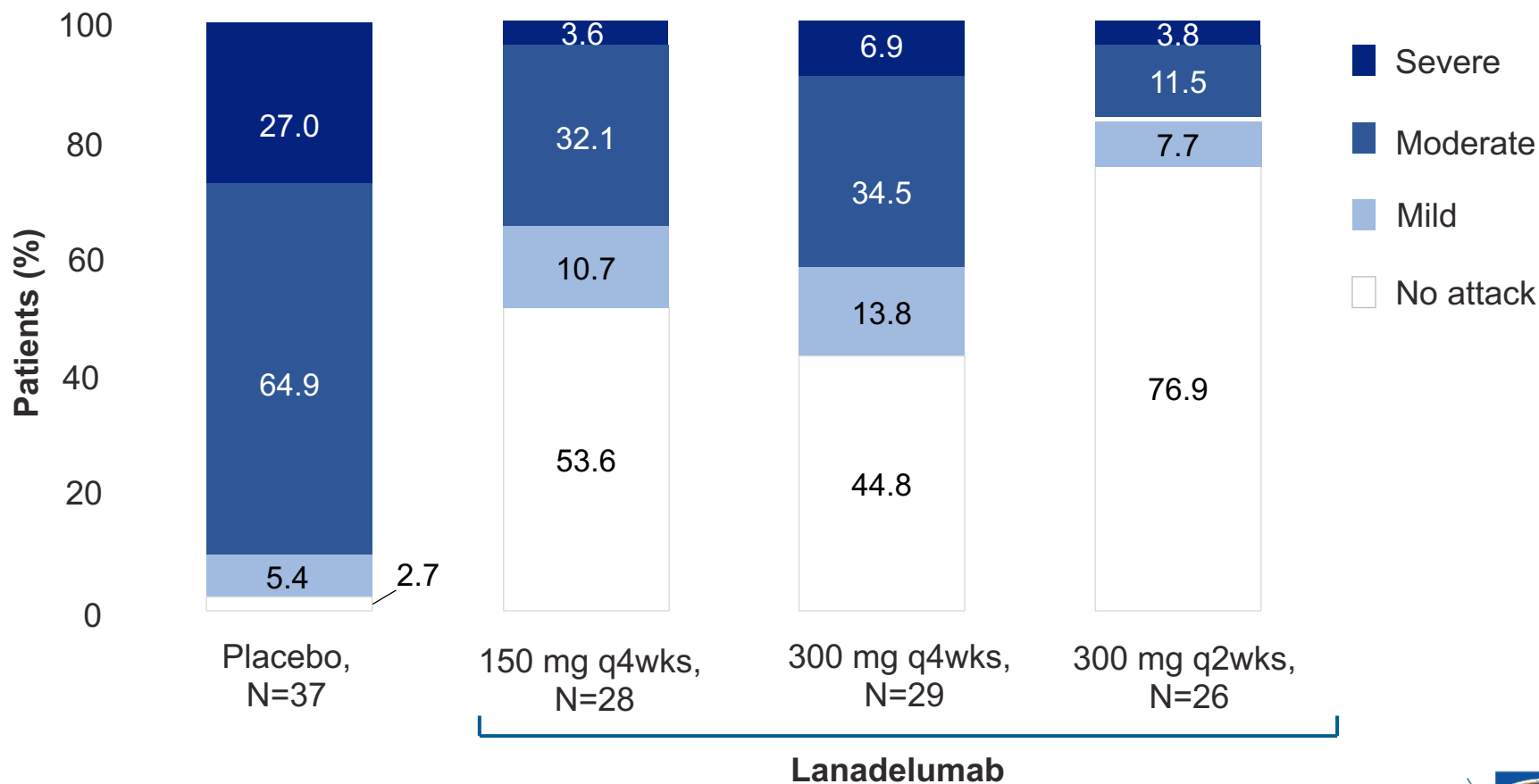
# Severity of attacks (explorative endpoint)



Banerji A, et al. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018 Nov 27;320(20):2108-2121



# At Steady State (day 70-182)



Banerji A, et al. Effect of Lanadelumab Compared With Placebo on Prevention of Hereditary Angioedema Attacks: A Randomized Clinical Trial. JAMA. 2018 Nov 27;320(20):2108-2121



# Quality of life (AE-QoL)

Treatment Period (Day 0–182)	Placebo, N=38	Lanadelumab		
		150 mg q4wks, N=26	300 mg q4wks, N=27	300 mg q2wks, N=26
<b>% of patients achieving MCID <math>\geq</math>6 points</b>	37%	65%	63%	81%
<b>Odds ratio vs. placebo (P-value)*</b>	N/A	3.2 (P=0.03)	2.9 (P=0.04)	7.2 (P<0.01)

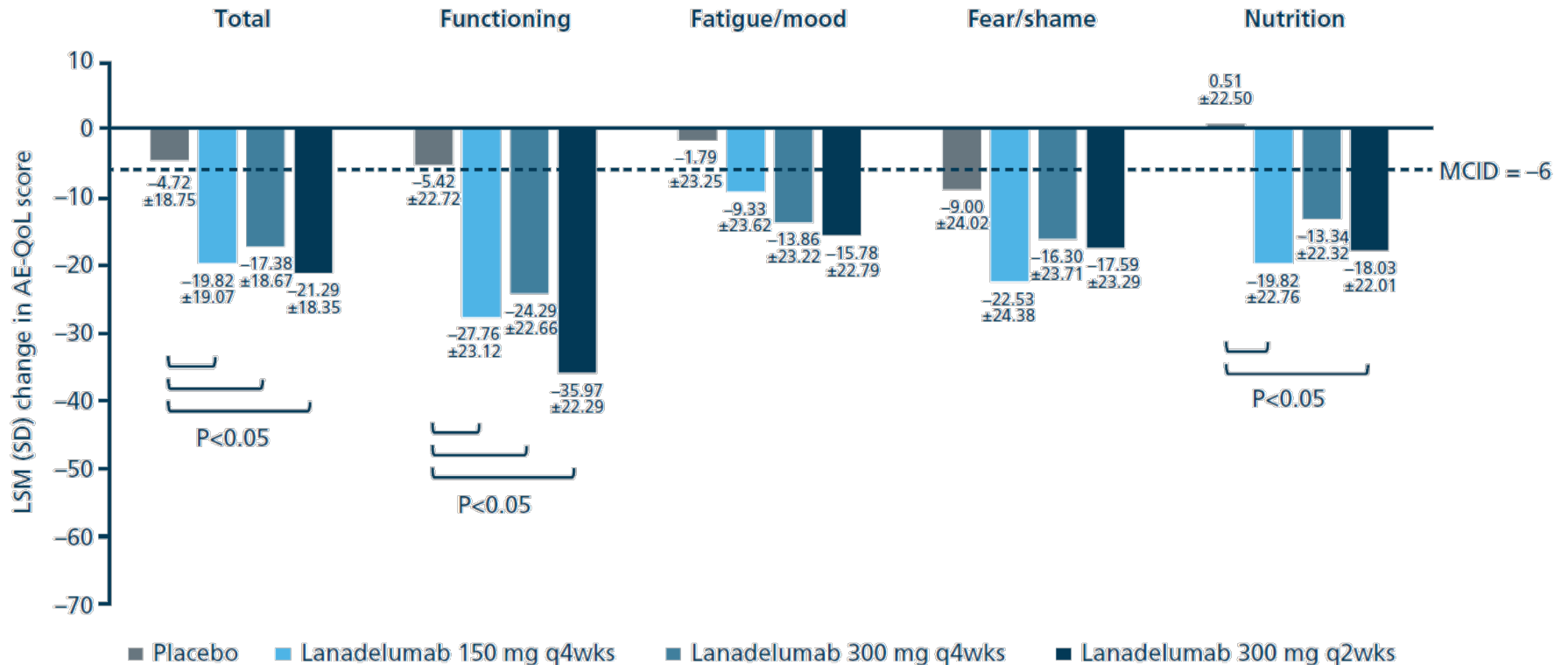


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# Quality of life (AE-QoL)



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# Safety

no therapy related SAE

Most frequent AE: mild moderate pain to injection site (29% PLC vs. 43% verum)



# Safety

	Lanadelumab Total (n = 84)	Placebo (n = 41)
<b>Adverse Events<sup>a</sup></b>		
Any adverse event	76 (90.5)	31 (75.6)
Injection site pain	36 (42.9)	12 (29.3)
Viral upper respiratory tract infection	20 (23.8)	11 (26.8)
Headache	17 (20.2)	8 (19.5)
Injection site erythema	8 (9.5)	1 (2.4)
Injection site bruising	6 (7.1)	0
Dizziness	5 (6.0)	0
Any treatment-related adverse event <sup>b</sup>	50 (59.5)	14 (34.1)
Injection site pain	35 (41.7)	11 (26.8)
Injection site erythema	8 (9.5)	1 (2.4)
Injection site bruising	5 (6.0)	0
Headache	6 (7.1)	1 (2.4)
Any serious adverse event <sup>c</sup>	4 (4.8)	0
Any related serious adverse event	0	0
Any adverse event leading to discontinuation	1 (1.2)	1 (2.4) <sup>d</sup>



# Future

## CSL Behring

C1-Inhibitor (HAEGARDA) subcutaneous

Volume reduced formulation 500U/ml

60 U / kg BW every 3 or 4 days

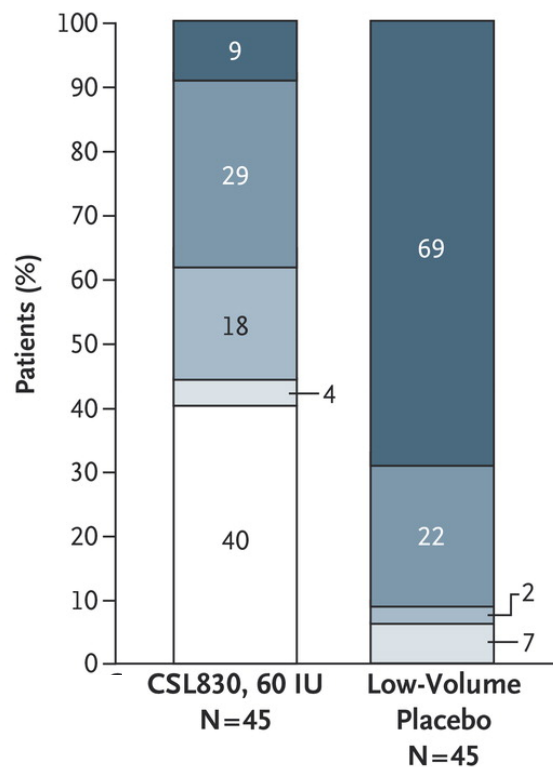
16-week treatment period



# Future

## 60 U/kg BW subcutaneous 2x/week

■ Severe ■ Moderate ■ Mild ■ Unknown severity ■ No attack



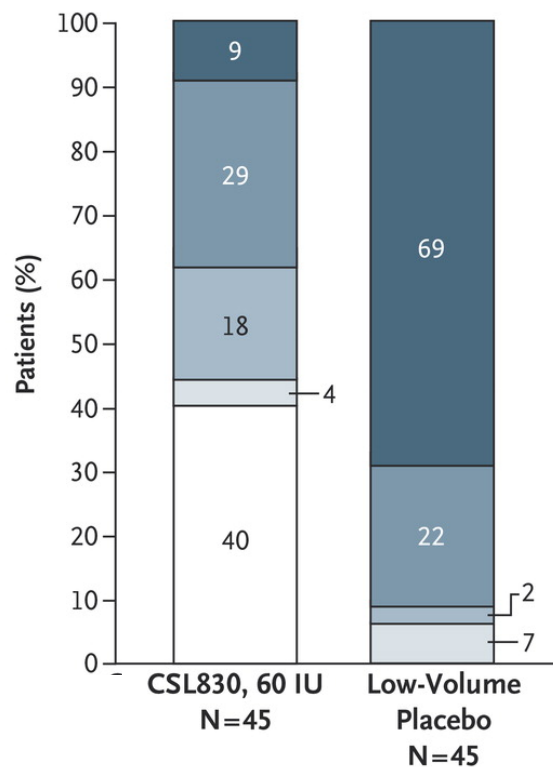
Prevention of Hereditary Angioedema Attacks with a Subcutaneous C1 Inhibitor.  
Longhurst H, et al. N Engl J Med. 2017 Mar 23;376(12):1131-1140



# Future

## 60 U/kg BW subcutaneous 2x/week

■ Severe ■ Moderate ■ Mild ■ Unknown severity ■ No attack



### Reduction in no. of attacks

Median/mean 95%/84%

### Reduction of resc. medication

Median/mean 100%/89%



# Future is today (in the US)

United States    Important Safety Information    Prescribing Information    For Healthcare Providers

Prevent HAE Attacks    HAEGARDA Treats the Cause    How to Take HAEGARDA    Starting HAEGARDA    Resources and Support    Prescription Form

*Be Empowered to*  
**BREAK FREE FROM HAE**

ASK YOUR DOCTOR ABOUT THE



<https://www.haegarda.com/>



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# 2020

*C1-INH*

Kallikrein

*C1-INH*

XII

*substitute*

C1-INH

kinin

*inhibits BK2R*

Plasmin

*inhibits*

Antifibrinolytics

Angioedema

Icatibant





# Future

## Shire

C1-Inhibitor subcutaneous (SHP616)

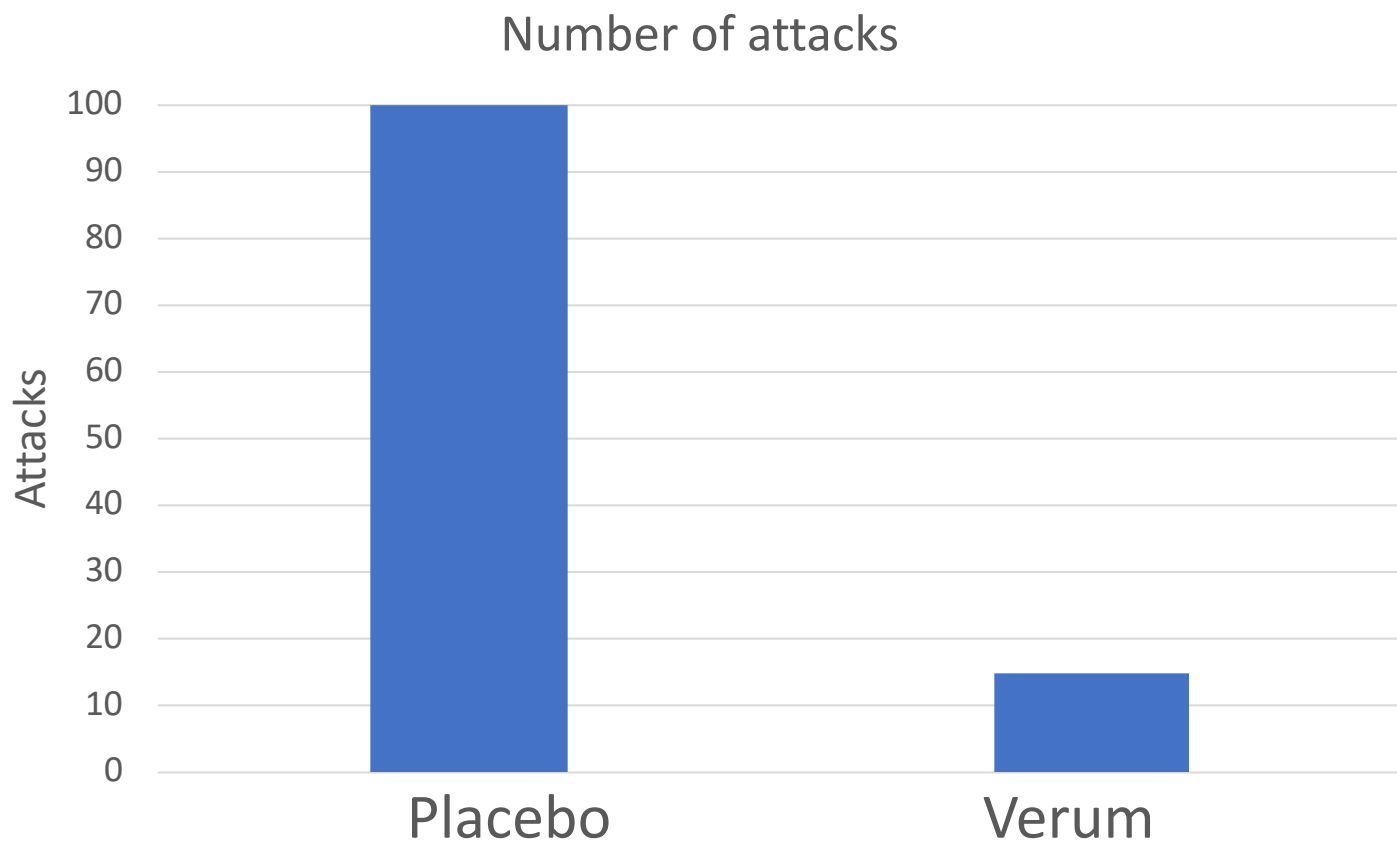
Volume reduced formulation 2000 U in 4ml, 2x / week

14-week treatment period



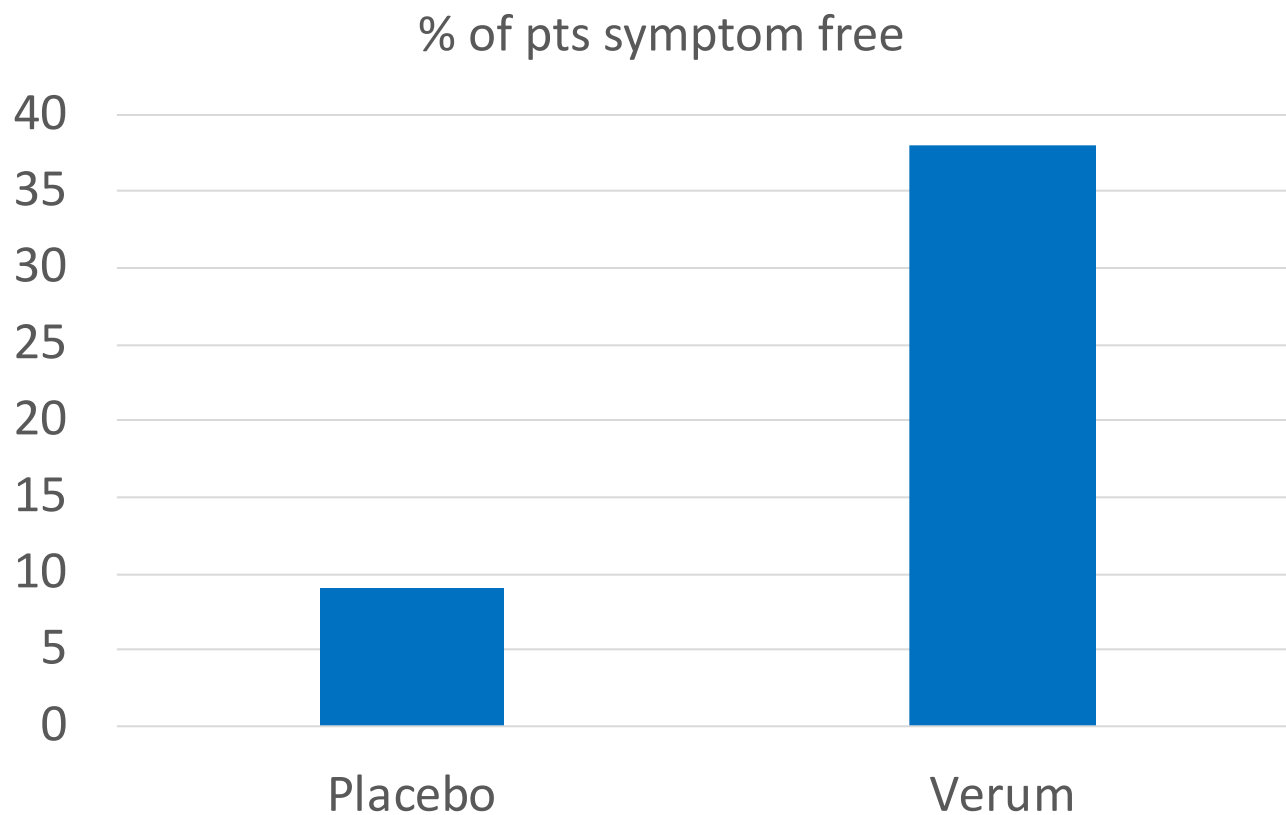
# Future

## 2000 U subcutaneous 2x/week



# Future

## 2000 U subcutaneous 2x/week



# Future

## BioCryst

Oral Kallikrein inhibitor BCX-7353

Phase 2

4-week treatment phase

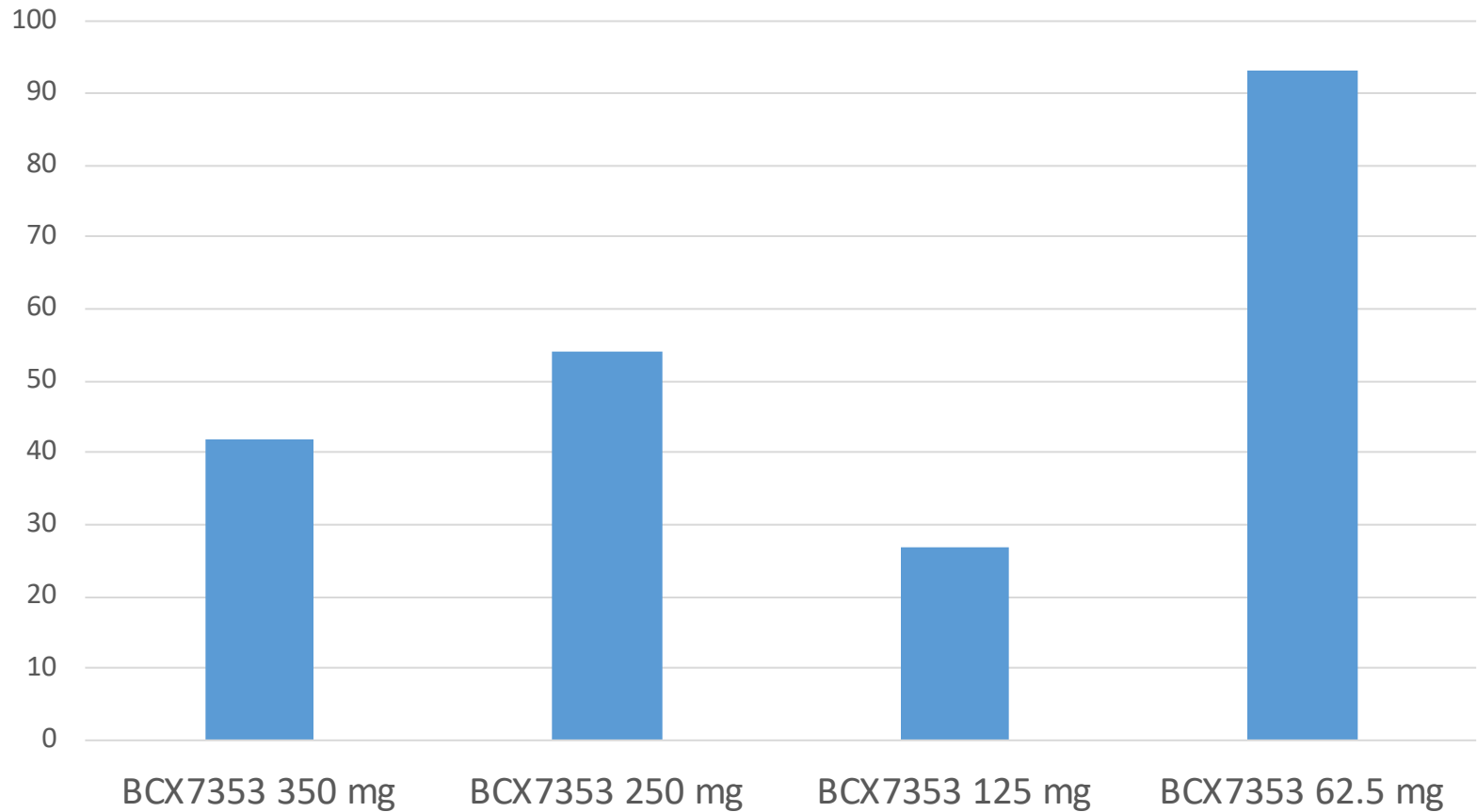


Aygören-Pürsün E et al. Oral Plasma Kallikrein Inhibitor for Prophylaxis in Hereditary Angioedema. *N Engl J Med.* 2018 Jul 26;379(4):352-362



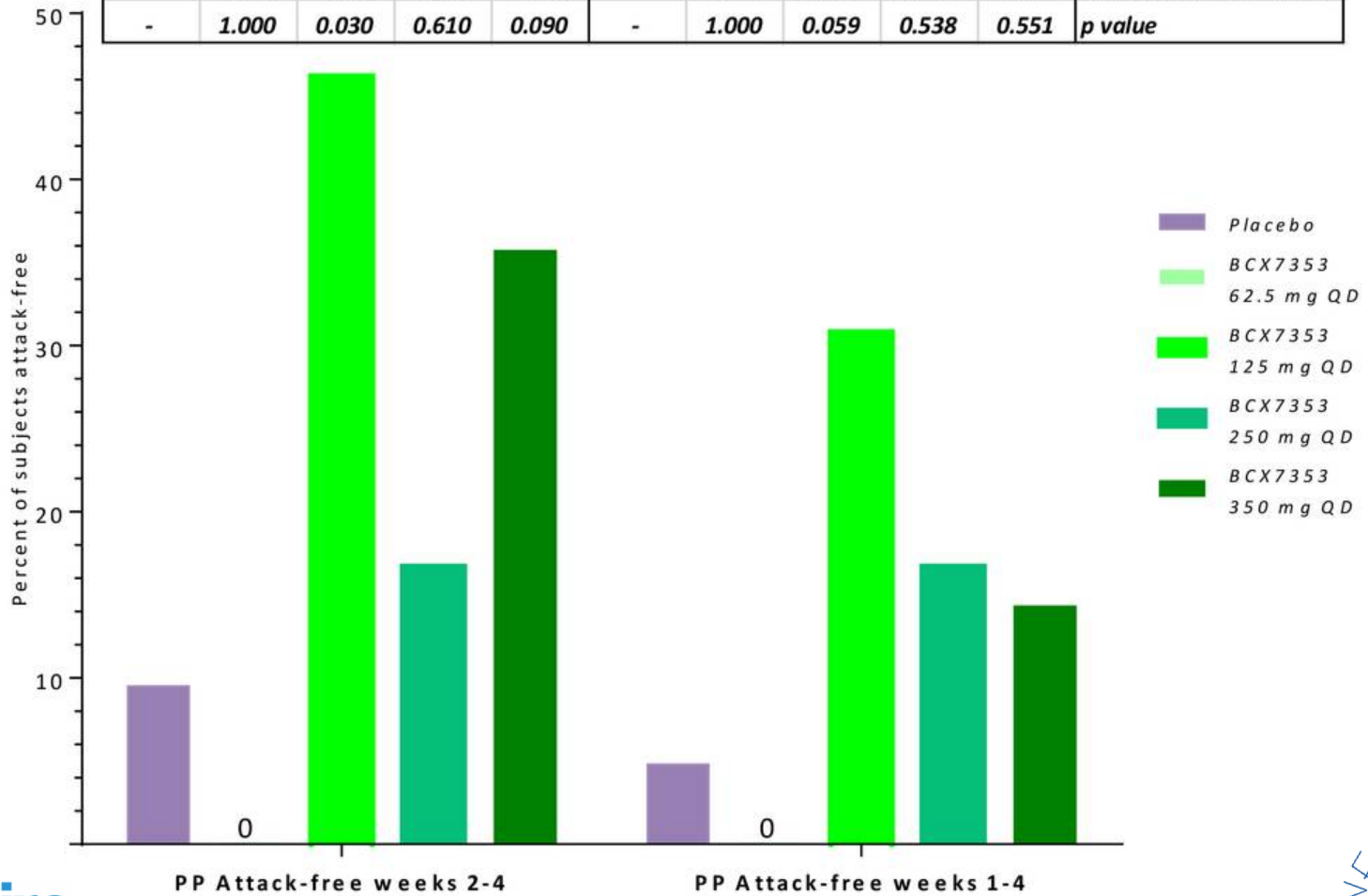
# Future

No. of attacks vs. placebo

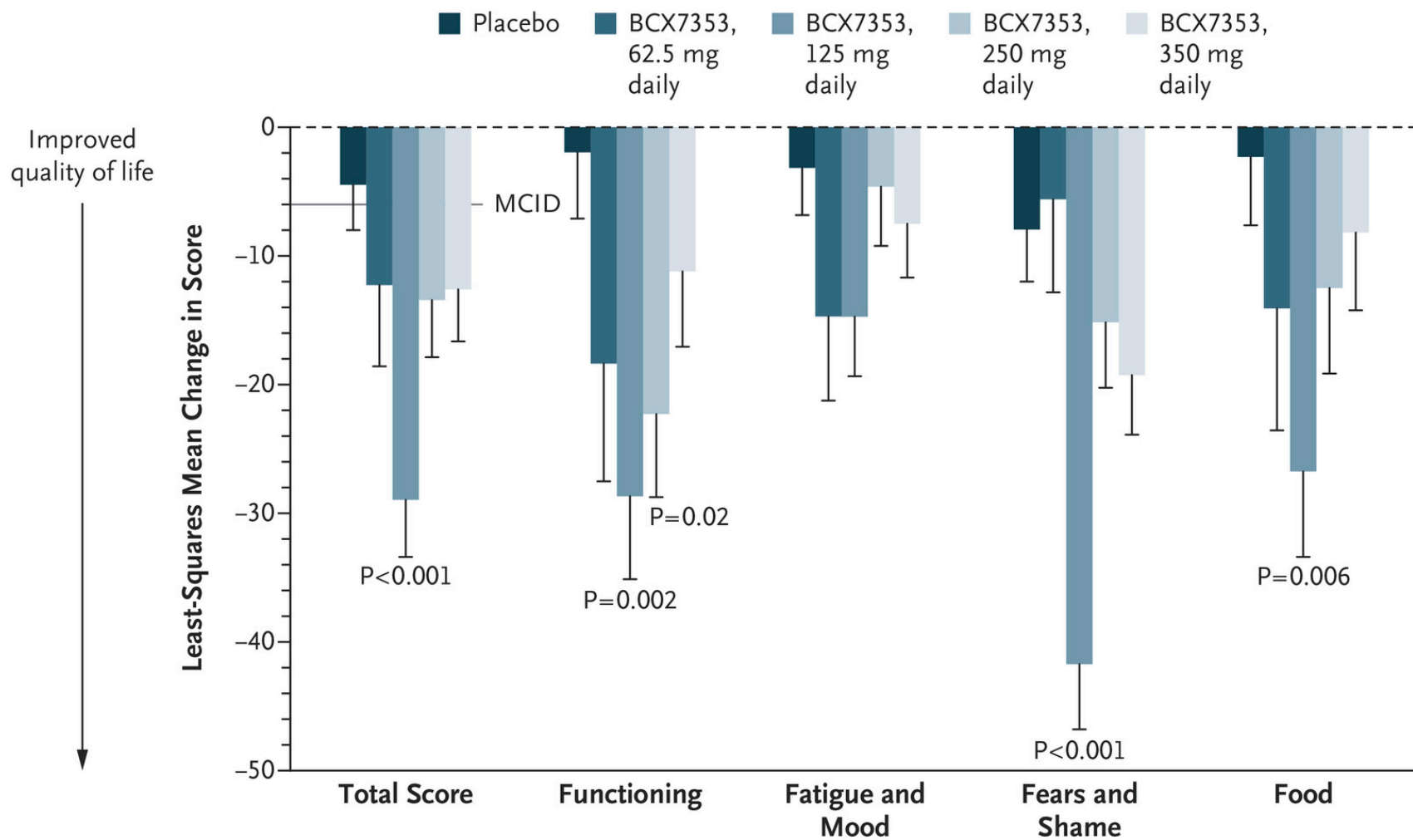


# Percent of subjects attack-free, PP

PBO	62.5 mg	125 mg	250 mg	350 mg	PBO	62.5 mg	125 mg	250 mg	350 mg	
<i>Weeks 2-4</i>					<i>Weeks 1-4</i>					
9.5%	0.0%	46.2%	16.7%	35.7%	4.8%	0.0%	30.8%	16.7%	14.3%	% Attack free
-	-9.5%	36.7%	7.2%	26.2%	-	-4.8%	26.0%	11.9%	9.5%	Difference, Active-PBO
-	1.000	0.030	0.610	0.090	-	1.000	0.059	0.538	0.551	p value



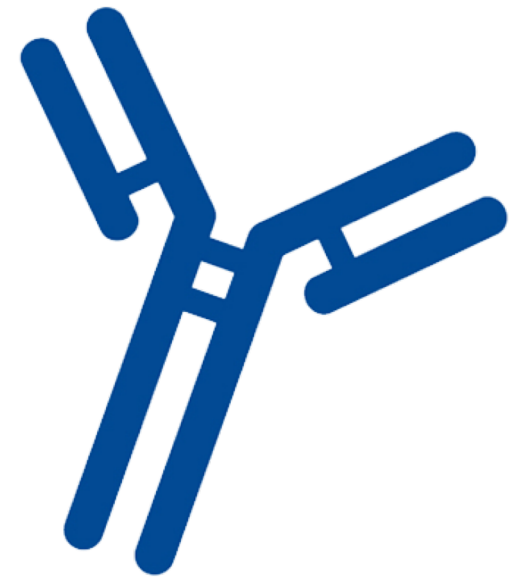
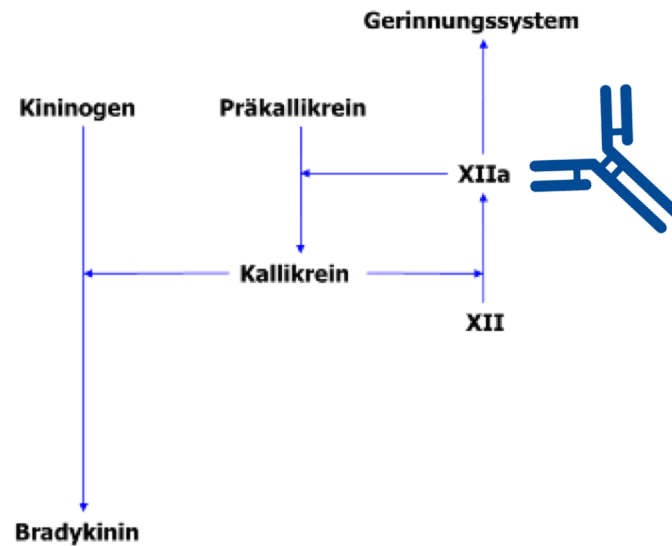
# Future



# Future

## CSL Behring

Subcutaneous, monoclonal AB against FXIIa



Ab, antibody; FXII, factor 12.



# Future

## Kalvista

KVD 900 oral, small-molecule plasma kallikrein inhibitor

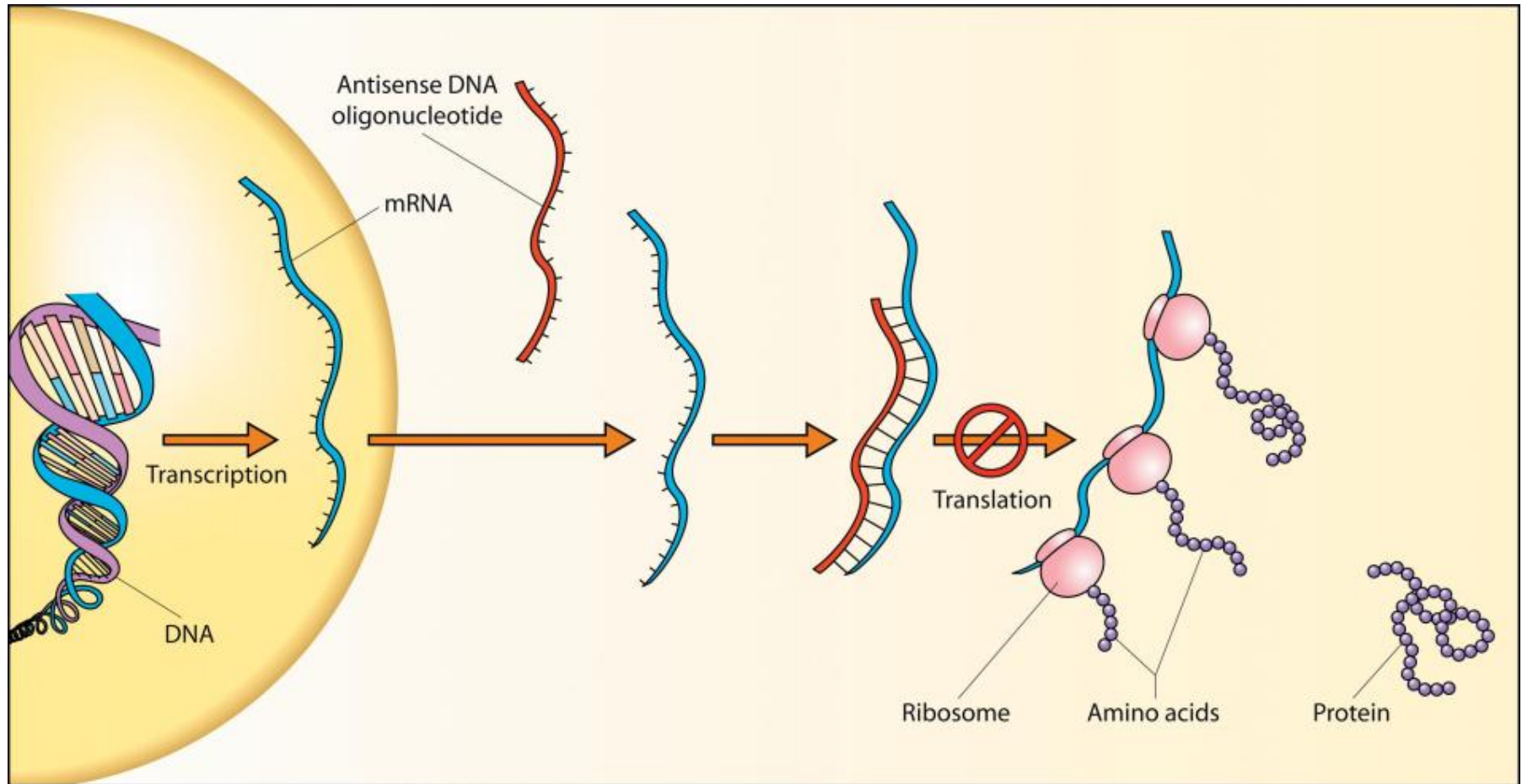
31 Dec 2017: Phase-I clinical trials in hereditary angioedema (volunteers in United Kingdom)

for prophylactic as well as acute treatment

Personal data.



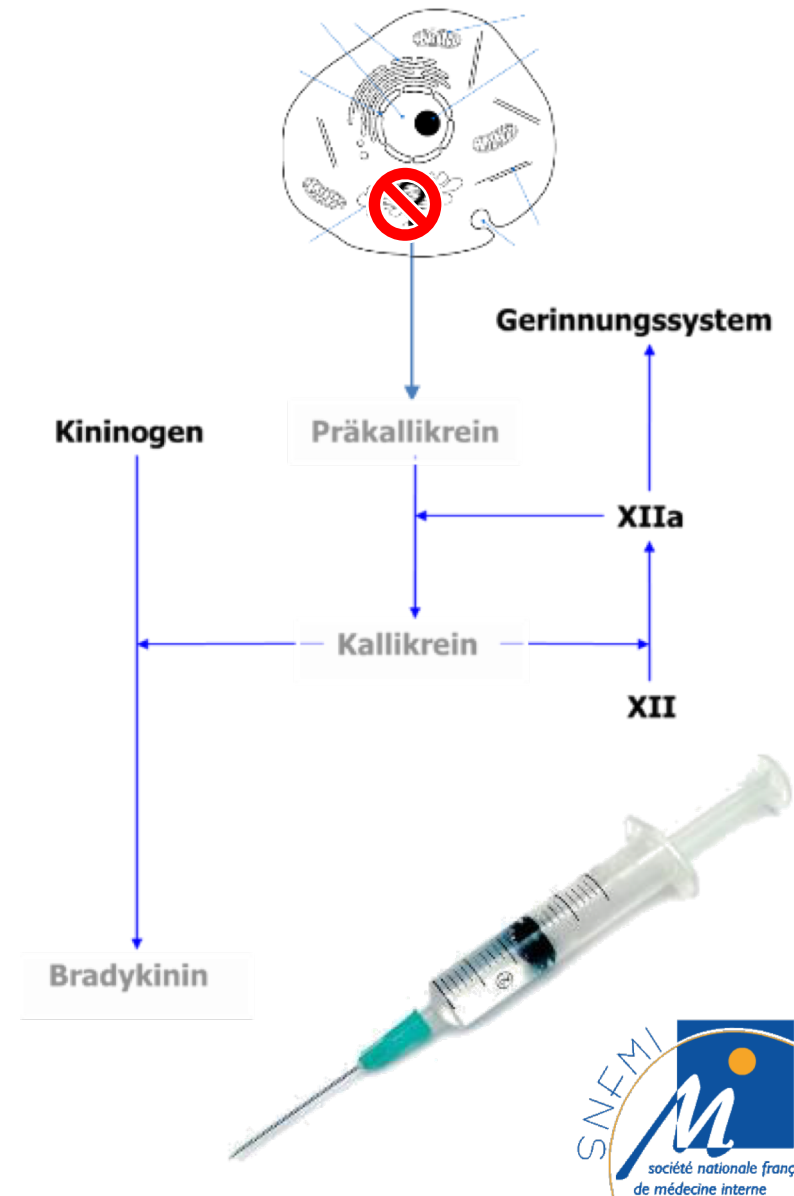
# Future Antisense Drugs



# Future

Safety, Tolerability, Pharmacokinetics,  
and Pharmacodynamics of  
IONIS-PKK-LRx Administered  
Subcutaneously to Healthy Volunteers

Efficacy and Safety of IONIS-PKCRx  
for Preventive Treatment of Chronic  
Migraine



# Coming soon

- C1-INH for subcutaneous prophylaxis
- Kallikrein-antibody prophylaxis
- Kallikrein tablet prophylaxis
- Kallikrein liquid for on-demand
- FXII-antibody for prophylaxis
- Oligonucleotids for prophylaxis
- Future drugs focus on prophylaxis

# Conclusions

- Given, that new drugs are safe & efficient:
- This may change the treatment paradigms
- What is the future of on-demand therapy?      First line?   ← →  
Emergency medication?
- More treatment options,  
more room for individualization