MAYO CLINIC

Anti-C5a antibody Vilobelimab (IFX-1) treatment in patients with ulcerative pyoderma gangrenosum: Phase 2, open-label dose escalation trial

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Speaker Disclosures

- AbbVie [C]
- Infla Rx [C]
- Janssen [C]
- Kymera [C]
- Novartis [C]
- UCB [C]
- Processa [RI]
- Boehringer Ingelheim [C,RI]

C Consultant, **RI** Research Investigator,

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Outline

Anti-C5a antibody vilobelimab in Pyoderma Gangrenosum

Study design and measures

Key safety and efficacy outcomes

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Rationale for Targeting C5a in Pyoderma Gangrenosum

BACKGROUND

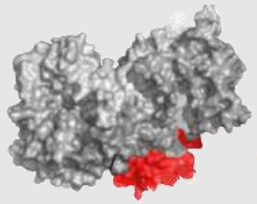
- Neutrophil activation driven by C5a is suggested to be one of the key pathophysiological mechanisms in PG*
- Neutrophils in the peripheral blood of PG patients showed spontaneous NETosis **
- C5a/C5aR interaction is the key driver of neutrophil adherence to the endothelial wall in RA***

  ➔ *Raise the potential for transmigration through endothelial cells*

*Lu et al. Exp Opin Investig Drugs 2020, Skendros et al. J Clin Invest. 2020; Ghias et al J.Invest Derm2021
**Croia et al. Exp Derm 2021, Kanni et al. BJD 2018 ; ***Miyabe et. al. Sci Immunol. 2017

Vilobelimab Mechanism of Action

C5

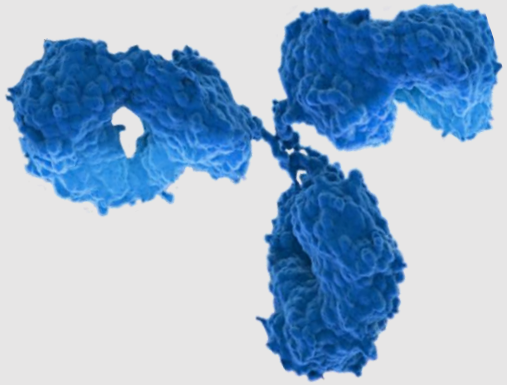


Cleavage and conformational change

C5a

new epitope

Vilobelimab



Cleavage of C5 through:

- Complement pathway activation
- Directly through other enzymes via “extrinsic” pathway

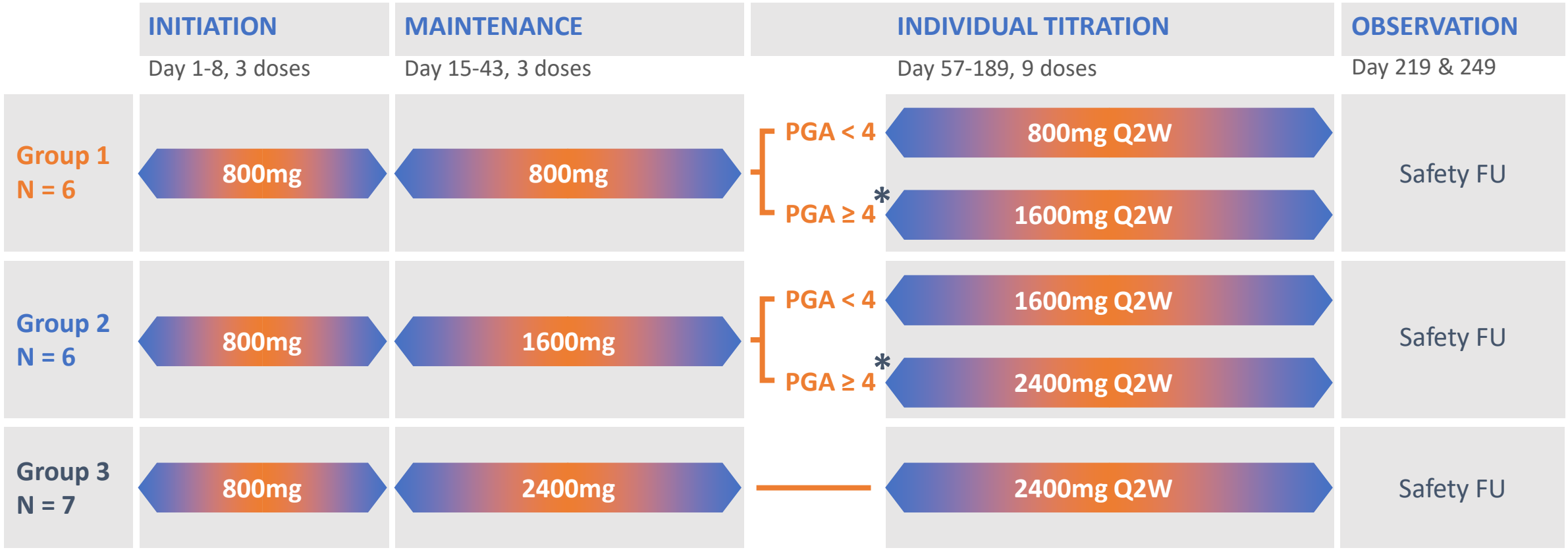
C5a is a key chemo-attractant and a strong activator of neutrophils

Key Features of vilobelimab:

- Blocks C5a biological effects in human blood
- Leaves MAC formation intact
- High affinity to the discovered epitope

Study Design: Sequential Enrollment in Three Dosing Groups

- **Intervention:** IV administration of Vilobelimab
- **Primary endpoint (safety endpoint):** Safety of vilobelimab defined as occurrence, nature and intensity of TEAEs
- **Key secondary endpoints (efficacy endpoint):** Responder rate defined as PGA ≤3; Time to complete closure of target ulcer



*Uptitration to the next dose on day 57 **if** PGA ≥ 4 and at least 5 patients treated with the current dose showed no safety concerns

Assessment of Target Ulcer by PGA Score

PHYSICIAN'S GLOBAL ASSESSMENT (PGA) SCORE

0	Completely clear	except for possible residual hyperpigmentation
1	Almost clear	very significant clearance (about 90%); however, patchy remnants of dusky erythema and/or very small ulceration
2	Marked improvement	significant improvement (about 75%); however, a small amount of disease remaining (i.e., remaining ulcers, although have decreased in size, minimal erythema and/or barely perceptible border elevation)
3	Moderate improvement	intermediate between slight and marked; representing about 50% improvement
4	Slight improvement	some improvement (about 25% up to 50%); however, significant disease remaining (i.e., remaining ulcers with only minor decrease in size, erythema or border elevation)
5	No change from baseline	
6	Worse	

- Physician-assessed target ulcer improvement compared to photography at Day 1
- **PGA score of ≤ 3 is considered clinical response**
- **PGA score of ≤ 1 is considered clinical remission and closure of target ulcer**

Key Eligibility Criteria

Key Inclusion Criteria
Ulcerative form of PG
Minimum of 1 evaluable ulcer ≥ $2cm^2$
3 out of 6 PG diagnostic criteria:
Pathergy
History of IBD or inflammatory arthritis
History of papule, pustule or vesicle progressed rapidly to ulcer
Multiple ulcerations
Erythema, undermined border and tenderness
Cribriform scar

Key Exclusion Criteria
Ulceration due to medical causes other than PG
Target ulcer open > 3 years
Any systemic, intralesional or topical treatment for PG, except for oral ≤ 10 mg prednisone equivalent
Infection requiring supressive anti-infective therapy
Previous use of IFX-1(vilobelimab)

Baseline Demographics and Disease Characteristics

Vilobelimab (IFX-1) N = 19

Demography	
Female, n (%)	10 (52.6)
Age, years, Mean (SD)	53.7 (14.9)
Weight, kg, Mean (SD)	110.0 (36.3)
PG characteristics	
PG duration, years, Mean (SD)	3.6 (6.4)
Target ulcer area, cm^2, Mean (SD)	36.0 (43.2)*
Target ulcer assessment, severe to very severe	
Erythema, n (%)	17 (89)
Border elevation, n (%)	11 (57)

Key Comorbidities	
Obesity, n (%)	8 (42)
Diabetes Mellitus, n (%)	4 (21)
Hypertension, n (%)	9 (47)
Osteoarthritis, n (%)	4 (21)
Psoriasis, n (%)	2 (10)
Ulcerative Colitis, n (%)	1 (5)
Baseline concomitant medication use	
Systemic corticosteroids , n (%)	6 (31)
Biologics, n (%)	1 (5)
Dapsone, n (%)	1 (5)

* Two patients had missing data

Safety Data of Vilobelimab

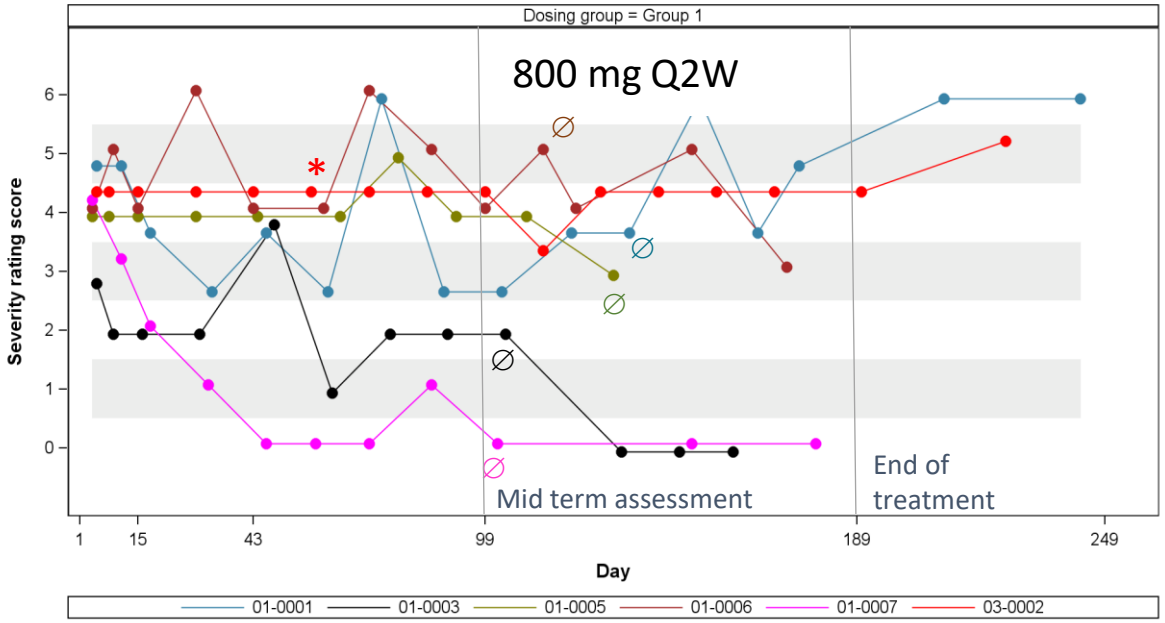
	Total (N=19)			Group 1 (N=6)			Group 2 (N=6)			Group 3 (N=6)		
	Pat. N	(Pat. %)	Events	Pat. N	(Pat. %)	Events	Pat. N	(Pat. %)	Events	Pat. N	(Pat. %)	Events
Any TEAE	15	78.9%	54	6	100.0%	33	4	66.7%	5	5	71.4%	16
Any related TEAE	4	21.1%	6	0	0.0%	0	2	33.3%	2	2	28.6%	4
Any serious TEAE	3	15.8%	7	1	16.7%	5	1	16.7%	1	2	28.6%	2
Any related serious TEAE	1	5.3%	1	0	0.0%	0	1	16.7%	1	1	14.3%	1
Any TEAE leading to drug withdrawal	2	10.5%	2	1	16.7%	1	1	16.7%	1	0	0.0%	0
Any TEAE leading to one dose omission	5	26.3%	7	4	66.7%	6	0	0.0%	0	1	14.3%	1
Any fatal TEAE	0	0.0%	0	0	0.0%	0	0	0.0%	0	0	0.0%	0

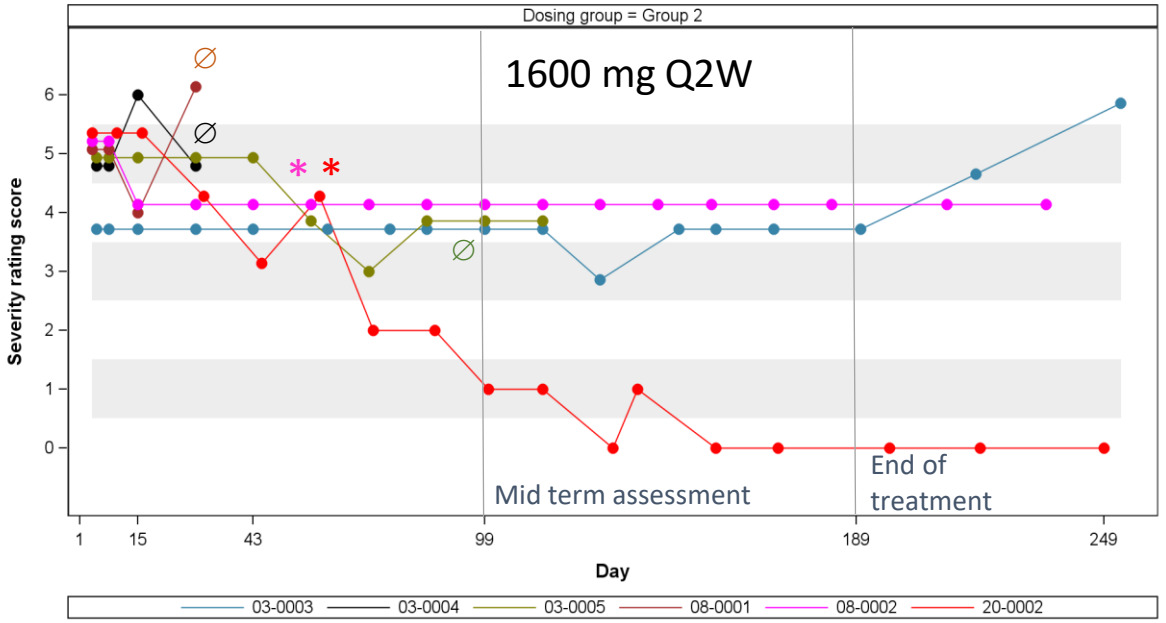
Rash (delayed hypersensitivity)	1	5.3%	1	
Infection requiring use of IV antibiotics*	4	21.1%	8	** Endocarditis, Erisypelas, Intervertebral Discitis, Pneumonia, PG Bacterial Superinfection, Sepsis (2), Wound infection,*

Safety observation:

- No infusion-related reaction within 24 hours -> No acute hypersensitivity
- No dose-dependent adverse events -> Good safety profile of the high dose
- Infections rate in line with underlying conditions -> No impairment of defence mechanism

3 patients achieved closure of target ulcer (PGA ≤ 1) in Group 1 and Group 2

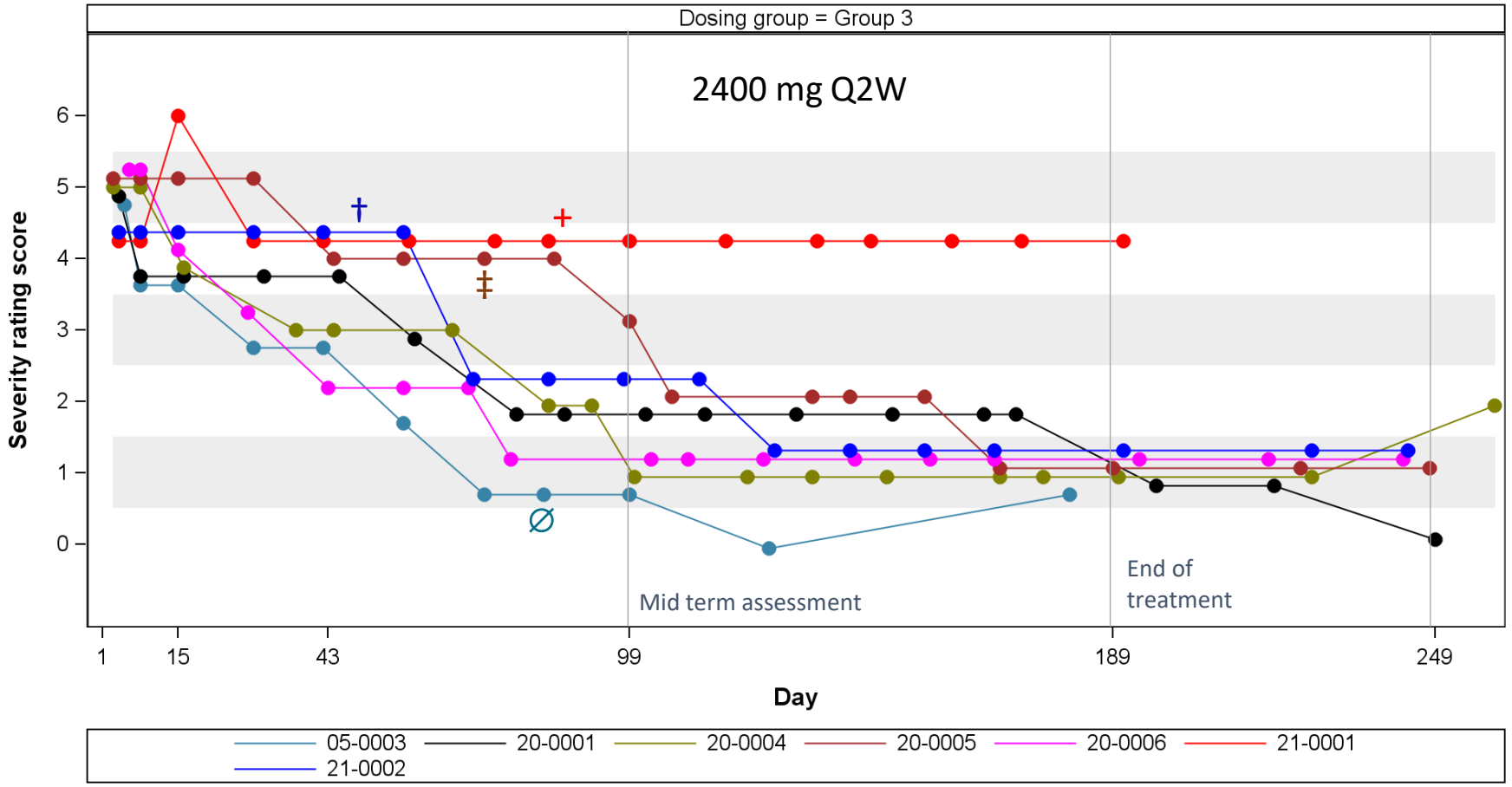




∅ Earlier treatment stop

*Uptitration to 1600 or 2400mg on day 57 if PGA ≥ 4 and no safety concerns

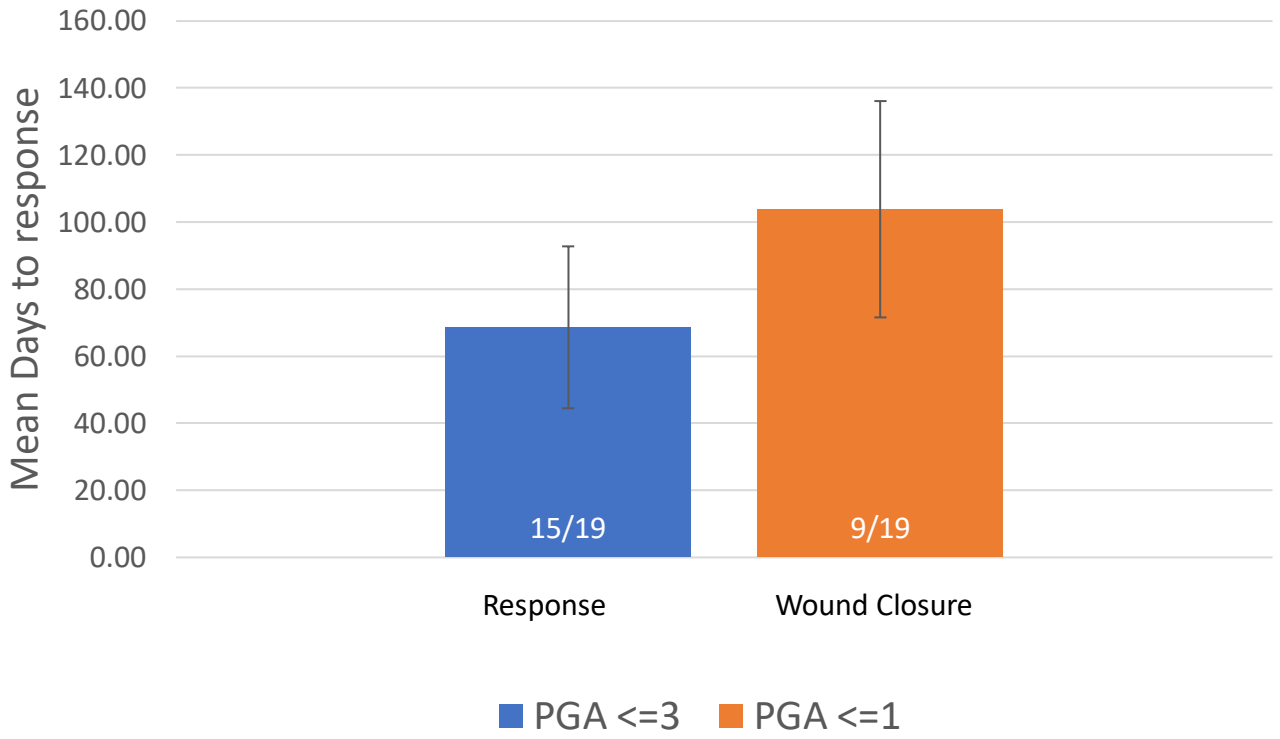
Six Patients Achieved Closure of Target Ulcer (PGA ≤ 1) in Group 3



- 6 patients out of 7 (FAS) achieved target ulcer PGA score of ≤ 1
- 1 Patient had PGA = 4, decrease of target ulcer area > 50%

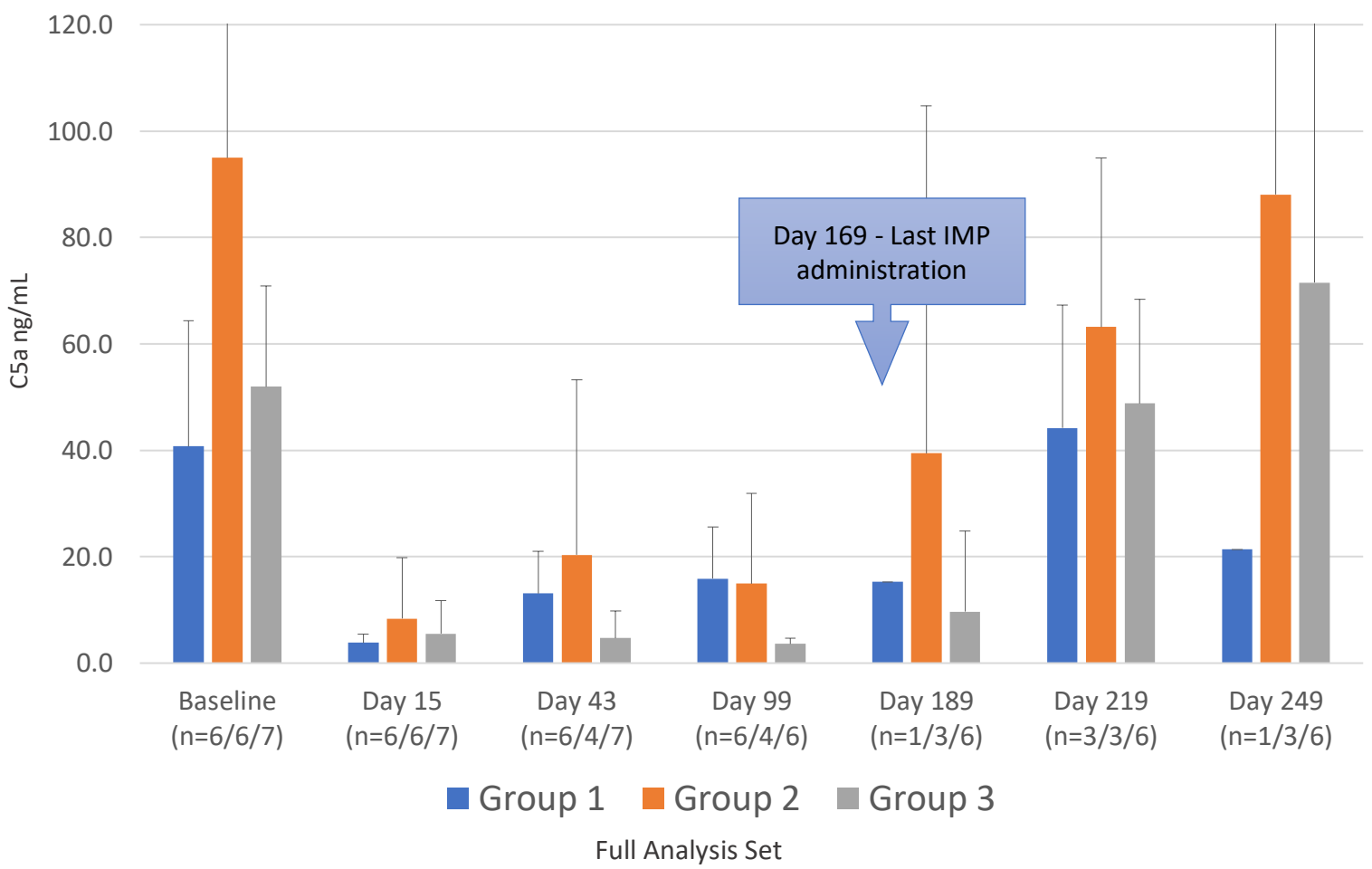
† 100 mg/d ciclosporin since day 50 due to new ulcer, ‡ 10 mg/d prednisone since day 72,
∅ IMP discontinued after 8 doses/ day 71 due to positive TB at screening, No re-activation of TB reported; + new ulcer developed .

Days to Response and to Wound Closure



- 69 days (mean) to target ulcer response (PGA ≤ 3)
- 104 days (mean) to target ulcer closure (PGA ≤ 1)

C5a Plasma Concentration per Dosing Group



- C5a sustained suppression for 189 days in Group 3
- Last infusion of vilobelimab was administered on day 169

Clinical observation

- 6 /7 patients in the high dosing group reached PGA ≤ 1 (clinical remission)

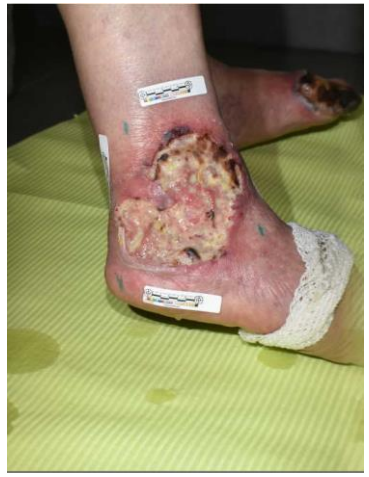
Case Report (20-0002)

Group 2: 3 x 800 mg, 3 x 1600 mg Q2W, individual uptitration to 9 x 2400 mg Q2W

MH: Hypertension since 1998
PG-MH: PG diagnosed in Jun 2019
Previous PG medication: Methylprednisolone Jun 2019 -> Dapsone /Ciclosporin Jun 2019 - Aug 2020 -> re-occurrence after discontinuation of immunosuppressants
Concomitant Medication: Prednisone 10 mg/day since Oct 2020, ongoing at study entry
Study Day 1: Feb 2021

Baseline

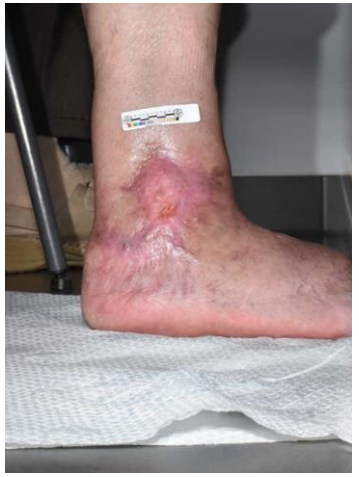
Area: 3695 mm^2



Day 99 (after 9 IMP infusions)

PGA = 1

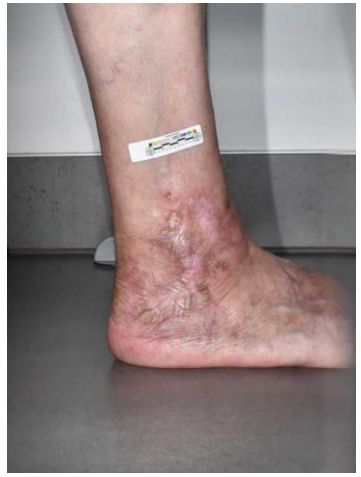
Area: 0.00 mm^2



Day 249 (79 days after last IMP infusion)

PGA = 0

Area: 0.00 mm^2



Conclusion / Take Home Message

- **Vilobelimab Q2W shows good safety and tolerability**
  - No dose-dependent AEs
  - AE profile in line with underlying PG disease, and patients‘ condition

- **Vilobelimab shows dose-dependent response**
  - 2400 mg Q2W results in high rate of target ulcer closure and represents the dose for Phase III exploration
  - Ulcers remain closed 2 months after treatment completion in majority of patients