

# BHV-1450, IgG4 Selective MoDE™ Degradar, Mitigates Anti-Dsg3-Mediated Skin Damage Characteristic of Pemphigus Vulgaris

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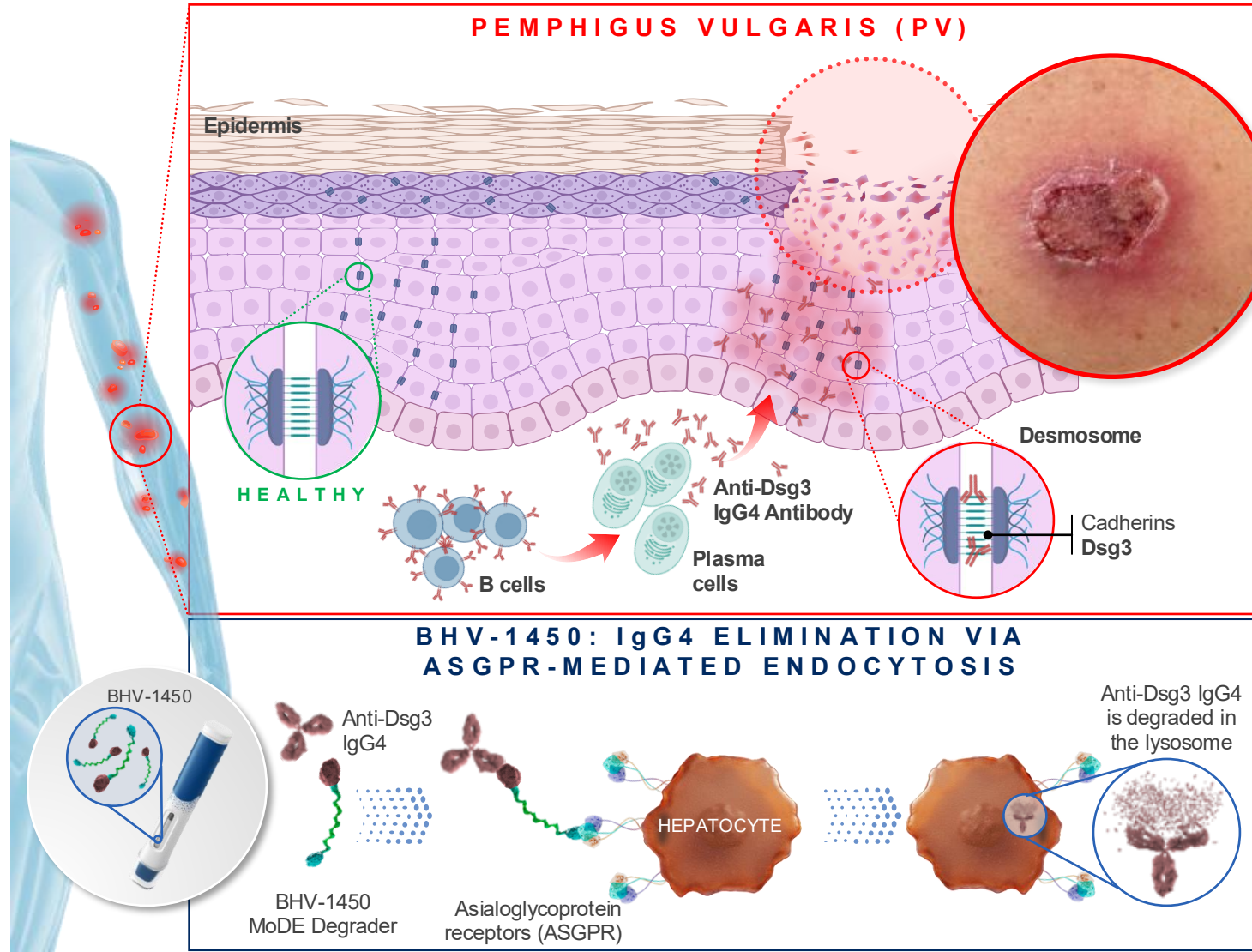


## PEMPHIGUS VULGARIS (PV)

- PV is a life-threatening, chronic autoimmune disorder (incidence 0.1-1 per 100,000 per year worldwide) that causes painful, fragile blisters and erosions on the skin and mucous membranes
- PV is caused by IgG4 autoantibodies that target Desmogleins 1 and 3 (Dsg1, Dsg3), proteins involved in keratinocyte cell-cell adhesion

## HIGH UNMET NEED

- Current care relies on systemic corticosteroids and immunosuppressants
- Long-term use of immunosuppressive therapies is associated with serious adverse effects including increased risk of infection, metabolic complications and bone loss
- Well-tolerated, disease-modifying therapies are urgently needed



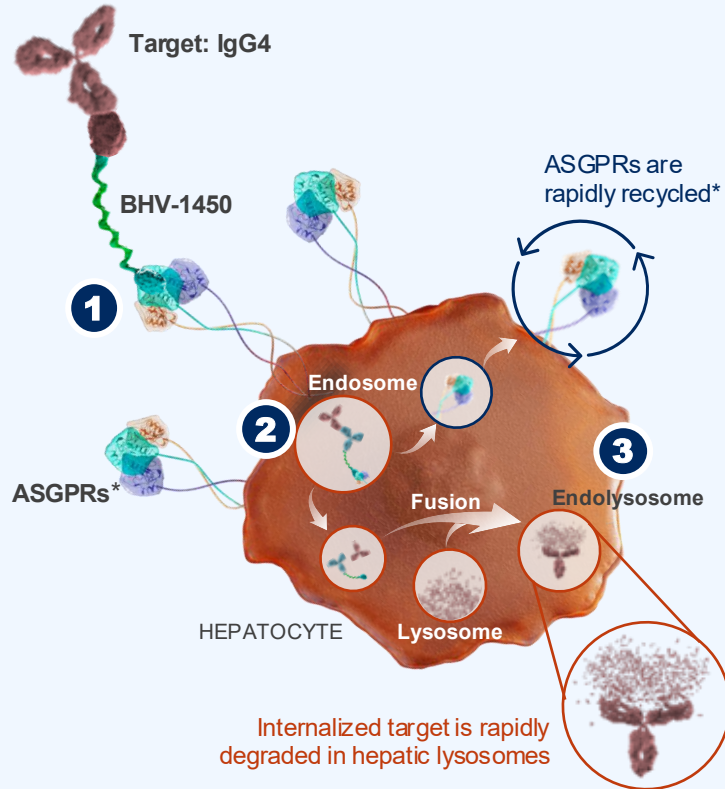
## THERAPEUTIC RATIONALE

- IgG4 Dsg1 and Dsg3-specific autoantibodies are potential therapeutic targets for the treatment of PV
- Targeted removal of IgG4 is a novel approach: BHV-1450 selectively degrades IgG4 without affecting other IgG subclasses or immunoglobulin isotypes

## CLINICAL CANDIDATE: BHV-1450

- BHV-1450 MoDE is a novel, selective extracellular protein degrader of IgG4 with potential to target the pathogenic subclass driving PV without broad immunosuppression
- BHV-1450 engages IgG4 and the asialoglycoprotein receptor (ASGPR) to selectively degrade IgG4 antibodies via endolysosomal pathway
- The mechanism of action of BHV-1450 makes it an ideal candidate for treating PV by directly addressing its root cause and minimizing common adverse effects

## BHV-1450 Mechanism of action



BHV-1450 is a bifunctional molecule that engages IgG4 and ASGPR to selectively degrade IgG4 subclass antibodies via the ASGPR-mediated endolysosomal pathway.



**1**  
Ternary complex formation

**2**  
Endocytosis

**3**  
IgG4 degradation

\*Stylistic representation  
ASGPR, asialoglycoprotein receptor

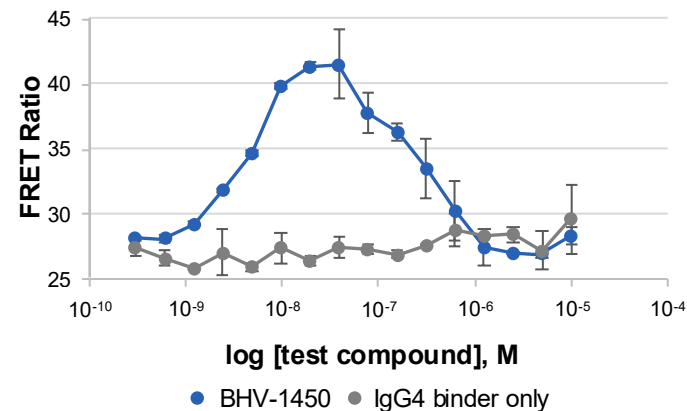
## BHV-1450 selectively binds to human IgG4

Protein	$K_D$ (nM)
Human IgG1	> 1000
Human IgG2	> 1000
Human IgG3	> 1000
Human IgG4	$26 \pm 0.22$

Surface Plasmon Resonance (SPR) analysis of BHV-1450 against human IgG subclasses 1-4.

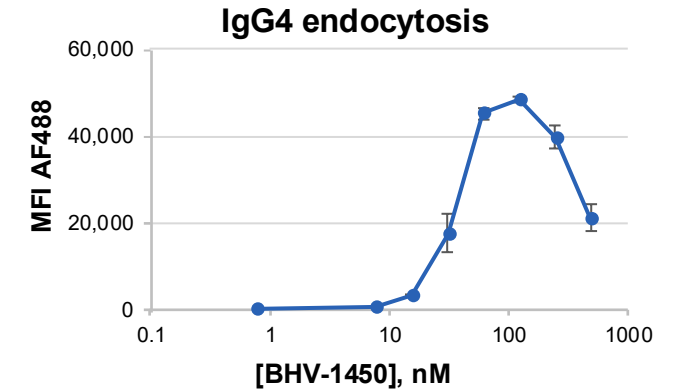
## BHV-1450 mediates induced proximity of ASGPR and human IgG4, resulting in formation of a stable ternary complex

### Ternary complex formation



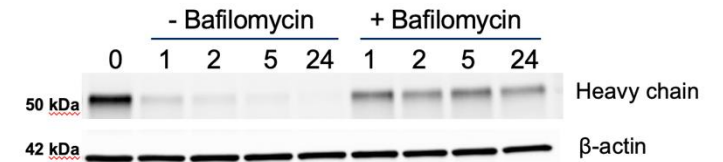
A TR-FRET assay was employed to assess ternary complex formation between IgG4, BHV-1450 and ASGPR. This ternary complex will lead to the endosomal degradation of IgG4 via hepatic ASGPR.

## BHV-1450 mediates effective uptake and lysosomal degradation of IgG4 in *in vitro* cell based-assays



Uptake of fluorescently labeled IgG4 in ASGPR-HEK293 cells occurs in a BHV-1450 dose-dependent manner after 24 hours of incubation.

### IgG4 degradation



Time after wash (h)	% Degradation	
	- Bafilomycin	+ Bafilomycin
1	83	47
2	92	59
5	96	48
24	98	59

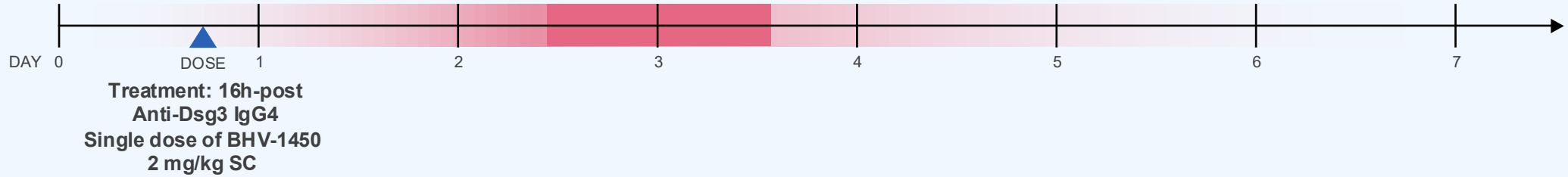
Endocytosed hIgG4 was degraded in cells treated with BHV-1450 as measured by Western blot. The presence of bafilomycin, an inhibitor of lysosomal acidification, attenuated IgG4 degradation, indicating a functional lysosome is required for degradation.

# Mouse model of pemphigus vulgaris

Anti-Dsg3 IgG4 antibody  
5 mg/kg IV

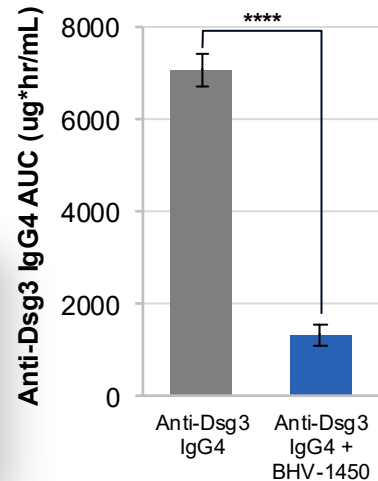
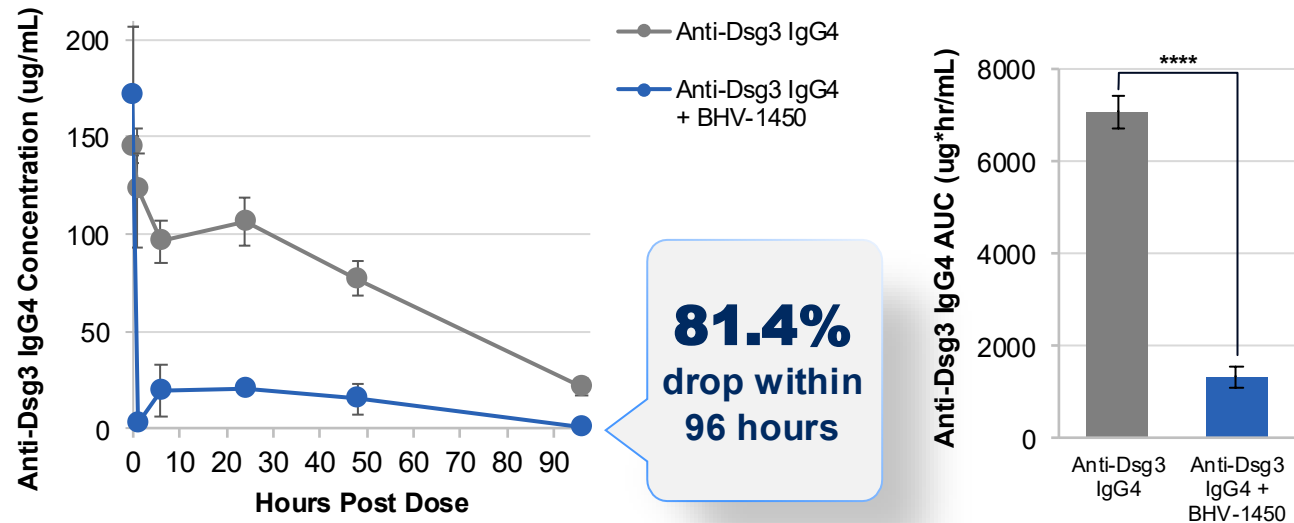


- Hair loss
- Body weight loss
- Skin histology
- Plasma anti-Dsg3 IgG4 antibody levels

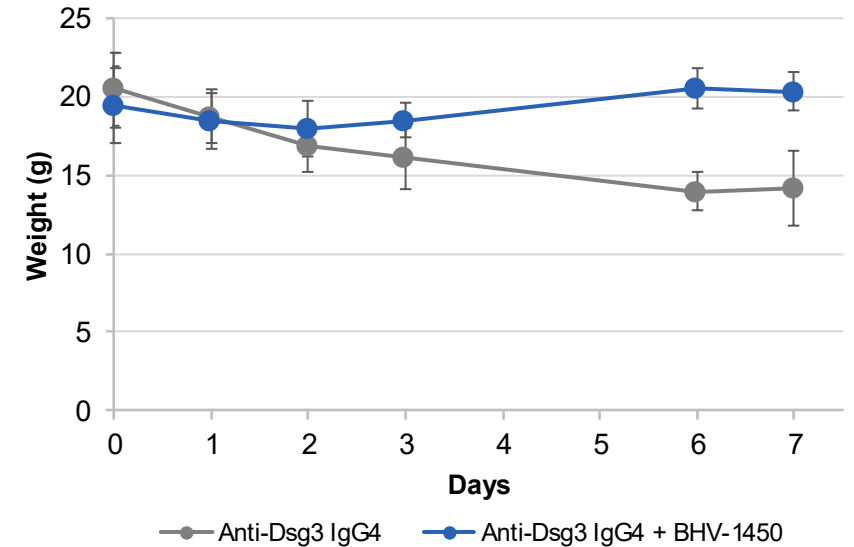


## The pharmacodynamic effect of BHV-1450 on anti-Dsg3 IgG4 antibodies in mouse plasma and its effect on body weight

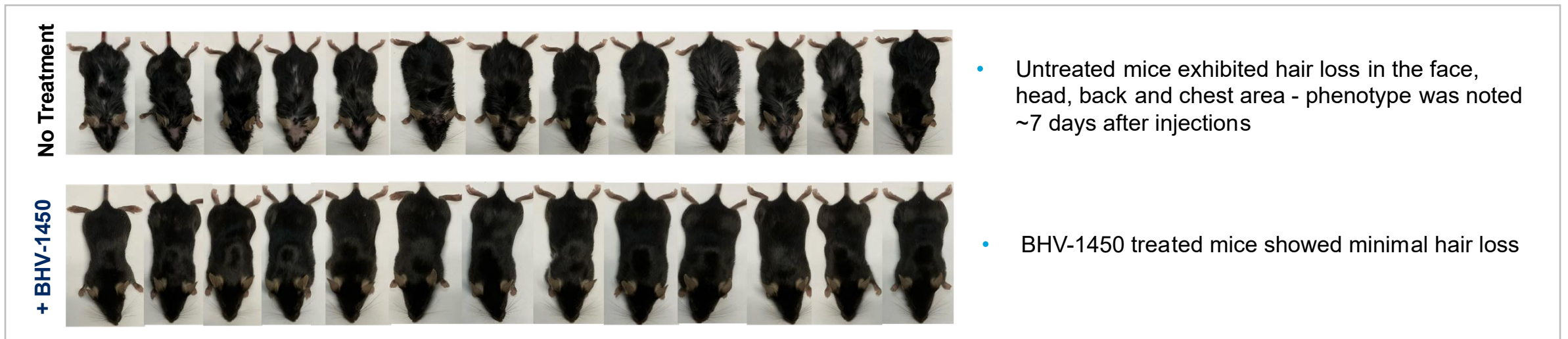
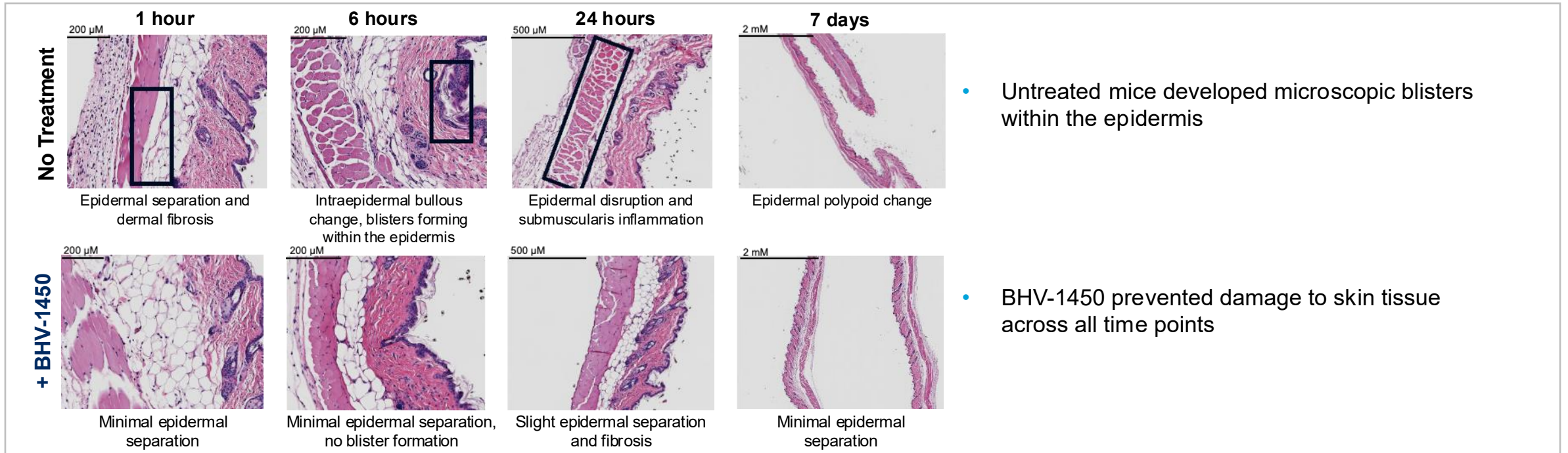
Plasma concentrations of anti-Dsg3 IgG4 antibodies decreased rapidly post-BHV-1450 treatment compared to no treatment control



BHV-1450 treatment mitigated disease-associated weight loss

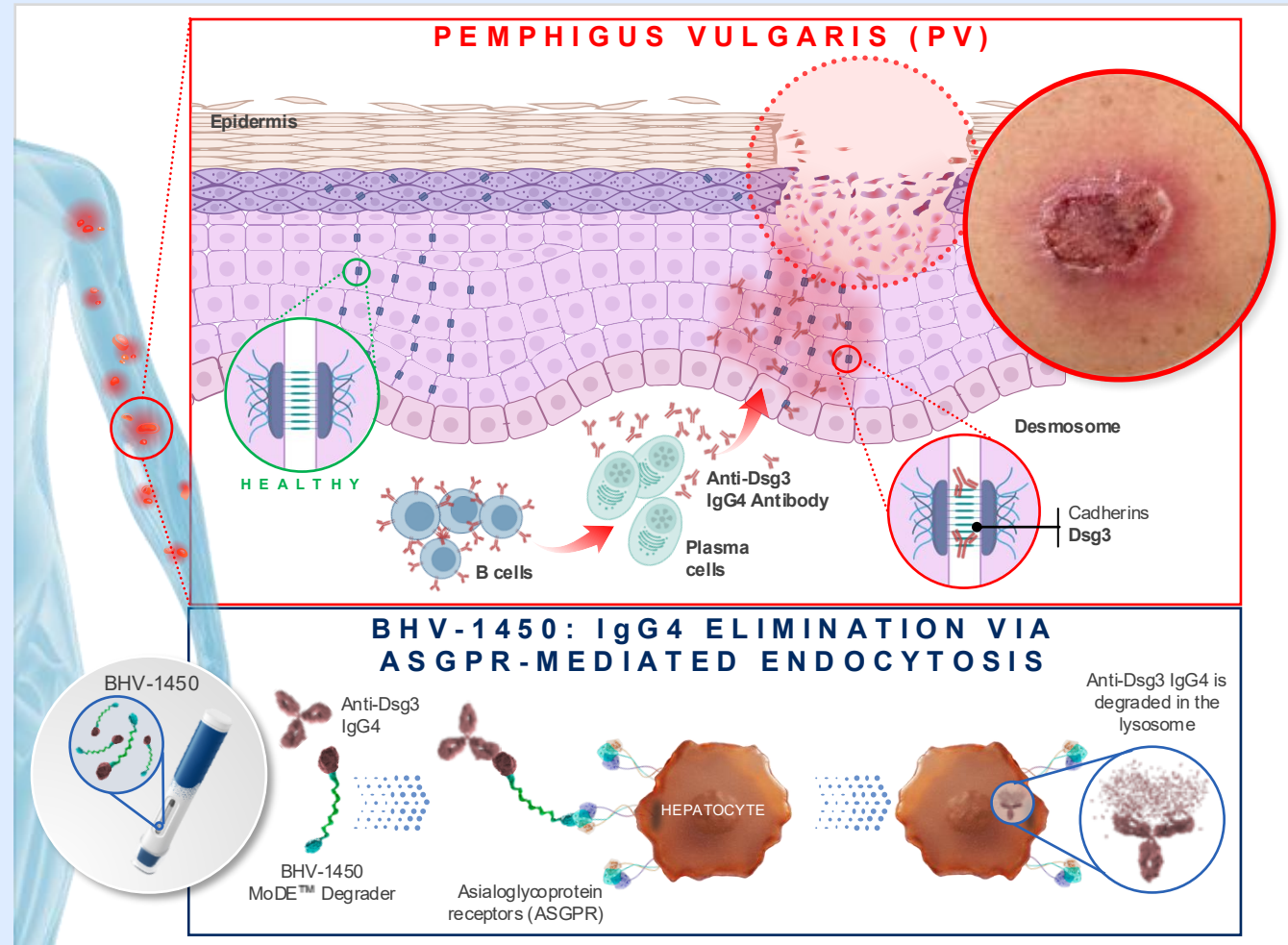


## BHV-1450 dosed 16 hours post anti-Dsg3 IgG4 administration alleviates skin damage



## CONCLUSIONS

- ▶ BHV-1450 is a novel MoDE degrader designed to selectively bind and degrade IgG4 auto-antibodies via hepatic ASGPR mediated endocytosis and lysosomal degradation, without affecting other IgG subclasses and immunoglobulin isotypes
- ▶ A mouse model of PV was established to evaluate the efficacy of BHV-1450. Anti-Dsg3 IgG4 antibodies induced a PV-like phenotype, including weight loss, hair loss, and histopathological changes in the skin
- ▶ A single SC dose of BHV-1450 significantly reduced circulating anti-Dsg3 IgG4 levels by more than 80%. BHV-1450 treatment reduced damage to skin, prevented weight loss, improved survival, and alleviated clinical symptoms
- ▶ **These findings demonstrate that BHV-1450 selectively targets IgG4 and underscore its promise as a first-in-class disease-modifying therapy for Pemphigus vulgaris**



## Disclosures:

Hanna Yousuf, Aikaterini Karagianni, Jared Head, Julie M. Silverman, Brian M. Linhares, Wes Kazmierski, Sampat Ingale, Anna Bunin, Bruce Car, Vlad Coric and Tova Gardin are employed by and hold stock/stock options in Biohaven Pharmaceuticals

## References:

1. Yeh. *Clin Immunol.* 2006. 2. Anhalt. *N Engl J Med.* 1982. 3. Schulze. *J Invest Dermatol.* 2012. 4. Hofrichter. *Front Immunol.* 2018. 5. Amagai. *J Clin Invest.* 1998. 6. Tsunoda. *J Immunol.* 2003. 7. Ono. *J Allergy Clin Immunol.* 2017. 8. Wormser. *J Am Acad Dermatol.* 2017. 9. Joly. *Lancet.* 2017. 10. Goebeler. *Br J Dermatol.* 2021. 10. Caianiello. *Nat Chem Biol.* 2021.

Support provided by  
Biohaven Company Inc.

Presented at The American Academy of  
Dermatology Association (AAD 2026),  
Denver, CO, USA