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Safety, tolerability, pharmacokinetics and pharmacodynamic effects of desmoglein 3 peptide-coupled tolerizing nanoparticles in pemphigus

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Abstract

Background Pemphigus vulgaris (PV) is a CD4$^+$ T-cell-dependent autoantibody-mediated blistering disease associated with human leucocyte antigen (HLA) class II molecules. IgG autoantibodies against the primary autoantigen desmoglein 3 (Dsg3), a desmosomal adhesion protein on epidermal keratinocytes, cause loss of epidermal cell adhesion.

Objectives To assess the clinical applicability of an innovative nanoparticle platform for the induction of immune tolerance exploiting the natural tolerance potential of liver sinusoidal endothelial cells. An open-label first-in-human study was conducted with TPM203, a mixture of four nanoparticle-coupled immunodominant Dsg3 T-cell peptides.

Methods The efficacy and mechanism of action of TPM203 were first tested in a humanized HLA-DRB1*0402-transgenic PV mouse model. In the clinical phase I trial, TPM203 was administered intravenously in patients with PV with no-to-moderate disease activity in single ascending and multiple doses (three doses of TPM203 two weeks apart). Primary endpoints included safety and tolerability. As a secondary endpoint, pharmacokinetics were assessed. Exploratory endpoints comprised changes in Dsg3-specific and bulk T- and B-cell frequencies, anti-Dsg3 IgG levels and autoantibody-induced keratinocyte dissociation. The trial was registered with EudraCT (2019-001727-12).

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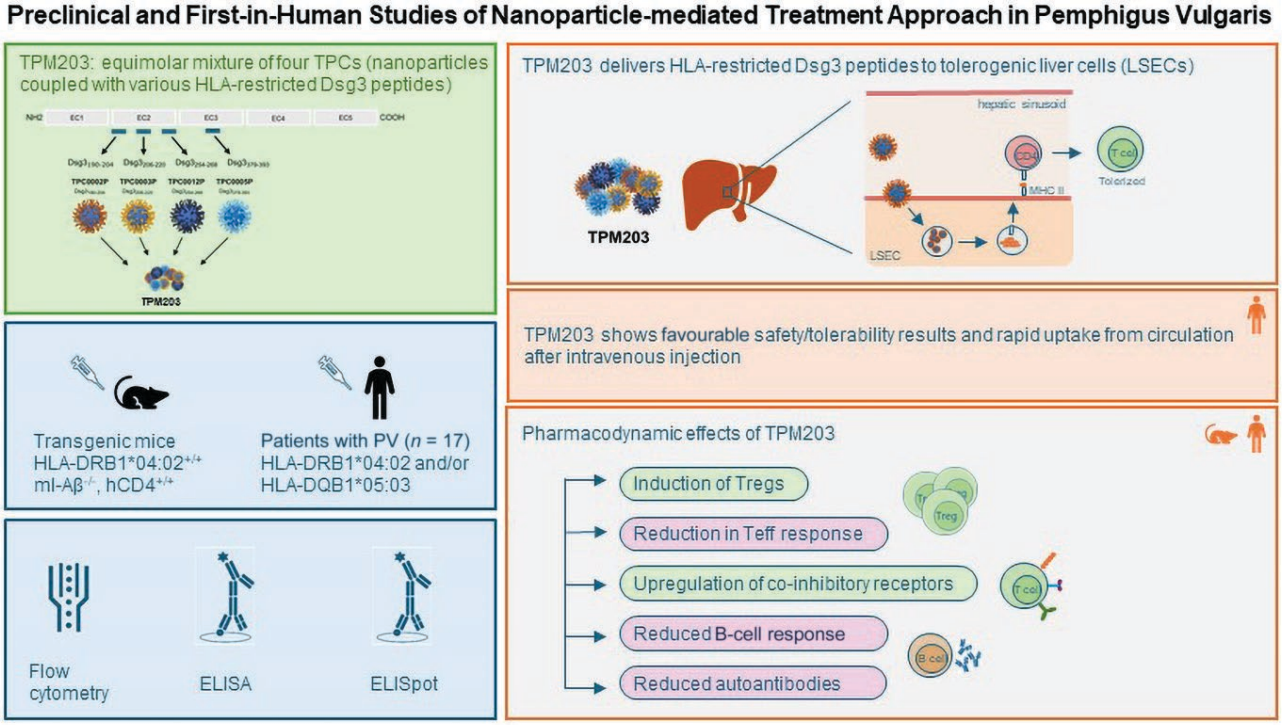
Results In the PV mouse model, two administrations of TPM203 significantly reduced anti-Dsg3 IgG. On the cellular level, TPM203 led to a significant decrease in $CD4^+$ T cells in the spleen, accompanied by increased frequencies of regulatory T (Treg) cells. In the clinical trial, the 17 patients with PV enrolled across single- and multiple-dose groups did not experience any serious or severe adverse events, or treatment-related PV worsening. Pharmacokinetics confirmed rapid TPM203 clearance from the circulation. Significant TPM203-induced modulations in bulk lymphocyte subsets included an increase in Treg cells, and reductions in T helper 17.1 and $CD27^+$ memory B cells, when dose groups were combined for analysis. Dsg3-specific T cells were found to be significantly reduced at week 8 following single administration of TPM203. Anti-Dsg3 IgG levels trended downward in the three lower single ascending dose groups, while IgG-induced keratinocyte-dissociating capacity was significantly reduced after multiple doses.

Conclusions Administered for the first time in humans, TPM203 was shown to be a safe and well-tolerated nanoparticle-based therapeutic approach with the potential to promote tolerance induction in PV, justifying further clinical development in this and other autoimmune diseases.

An author video to accompany this article is available online.

Graphical Abstract



Dsg3: Desmoglein 3; HLA: human leucocyte antigen; LSEC: liver sinusoidal endothelial cell; MHC: major histocompatibility complex; PV: pemphigus vulgaris; TPC: Topas Particle Conjugates; Teff: effector T cell; Treg: regulatory T cell

Lay summary

Pemphigus is a rare but potentially life-threatening disease. It causes blisters to form on the skin, mouth and genitals. It can lead to the loss of body fluids and proteins. It is also associated with severe infections. Blisters are caused by 'autoantibodies' (misguided defence proteins in the immune system) that bind to a component of the skin called Dsg3. The autoantibodies are produced by specialized immune cells known as 'B cells' with the help of another group of immune cells called 'T cells'. These cells play an important role in starting autoimmune responses.

In this study, we tried to block the effects of T cells in pemphigus. We did this using 'nanoparticles' to deliver pieces of Dsg3 to the liver. These nanoparticles have the potential to inhibit (or stop) the misdirected immune response. We carried out a study in Germany, Italy and the UK and gave increasing doses of Dsg3-loaded nanoparticles to a group of 17 patients with the disease. We found that the treatment was well-tolerated by the patients. They did not experience any severe side effects. We also found changes in the patients' blood. This provided the first hints that T cells and activated B cells that promote inflammation could be blocked, leading to a decrease in pemphigus autoantibodies.

Our study findings suggest that Dsg3-loaded nanoparticles should be further developed. The aim would be to treat pemphigus, and maybe even other autoimmune diseases, in a safe and specific way.

What is already known about this topic?

- Pemphigus vulgaris (PV) is a rare, potentially fatal autoimmune blistering disease of the skin and mucosa, which is CD4+ T-cell-dependent and autoantibody-mediated.
- Current treatment for PV relies on prolonged general immunosuppression and B-cell depletion by anti-CD20 monoclonal antibodies, with the risk of severe side effects.
- There is an urgent need for antigen-specific therapies with the objective of reinstating immune tolerance without compromising the immune system.

What does this study add?

- Based on proof-of-concept in a humanized mouse model and its first administration in humans, this nanoparticle-based platform technology shows a favourable safety, pharmacokinetics and immunomodulatory profile.
- In addition, initial signs of tolerance induction were observed, justifying further clinical development in PV and other autoimmune diseases.

What is the translational message?

- Nanoparticle-based delivery of Dsg3 peptides results in the first signs of the induction of T-cell tolerance.
- T-cell inhibition shows a tendency towards downregulation of B cells and a reduction in serum IgG autoantibodies against Dsg3.
- Our observations support the concept that T-cell tolerance is linked to downregulation of proinflammatory T cells and upregulation of regulatory T cells.

Pemphigus vulgaris (PV), a potentially lethal bullous disorder of mucosa and skin, is considered a paradigm of an organ-specific human autoimmune disease.[1–3] Specifically, IgG autoantibodies target desmosomal components, desmoglein (Dsg) 1 and 3, disrupting adhesion between epidermal keratinocytes.[4] There is increasing evidence that autoreactive T cells, preferentially expressing type 2 and type 17 signatures, are crucial for the induction and perpetuation of B-cell activation, leading to the secretion of pathogenic autoantibodies. PV is strongly associated with HLA-DRB1*04:02 and HLA-DQB1*05:03, which are critically involved in presenting a limited set of immunodominant Dsg3 peptides to autoreactive T cells.[5–8]

PV manifests as progressive fragile blisters of the oral mucosa and skin, resulting in impaired epidermal barrier function and increased infection risk.[2] Overall, PV treatment largely depends on long-lasting immunosuppression, associated with an increased risk of severe comorbidities.[9] The anti-CD20 monoclonal antibody rituximab has shown efficacy in PV,[10,11] becoming a first-line treatment option for moderate-to-severe pemphigus. Nevertheless, PV remains a major therapeutic challenge given the high relapse rate and the significant treatment-related comorbidities.[9] Antigen-specific therapies aimed at reinstating immune tolerance without broadly suppressing the immune system might represent a valuable approach to addressing this urgent medical need.

To tackle the well-described T-cell-driven autoimmune pathogenesis of PV, Topas Therapeutics (Hamburg, Germany) has developed a nanoparticle-based platform for inducing antigen-specific tolerance by leveraging the natural tolerogenic potential of liver sinusoidal endothelial cells (LSECs).[12] Autoantigenic peptide epitopes are chemically coupled to nanoparticles to generate Topas particle conjugates (TPCs). Following infusion, TPCs preferentially deliver disease-relevant peptides to LSECs, which act as unconventional antigen-presenting cells capable of inducing tolerance in CD4+ and CD8+ T cells reactive to the delivered peptides.[13,14] Proof-of-concept for this mode of action comes from preclinical animal models, where TPC application induces regulatory T (Treg) cells, anergy and/or deletion of proinflammatory effector T cells.[13,14]

The efficacy and mechanism of action of TPM203, a mixture of four TPCs carrying distinct immunodominant Dsg3 CD4+ T-cell epitopes, were investigated in a PV-related humanized HLA-DRB1*04:02 mouse model (Figure S1; see Supporting Information). Based on robust preclinical proof of concept, TPM203 was subsequently tested in a study of patients with PV.

Patients and methods

In this phase I open-label single ascending (part A) and multiple (part B) dose study adults with PV with either no or mild-to-moderate disease activity were treated at five sites. The study duration was 12 weeks (part A) and 16 weeks (part B). The study was registered with EudraCT (2019-001727-12). The protocol intended to enrol 24 patients with PV: 12 in part A and 12 in part B (Figure S2; see Supporting Information).

TPM203 was to be administered as single or multiple (three at 2-week intervals) infusions at the following escalating doses: 0.03 μmol (dose 1), 0.09 μmol (dose 2), 0.3 μmol (dose 3) and 0.9 μmol (dose 4) hDsg3 peptide for each of the individual four TPCs in part A; and 0.09 or 0.9 μmol hDsg3 peptide in part B.

The primary endpoint was safety and tolerability, measured by the frequency and severity of treatment-emergent adverse events and worsening of PV. Pharmacokinetics

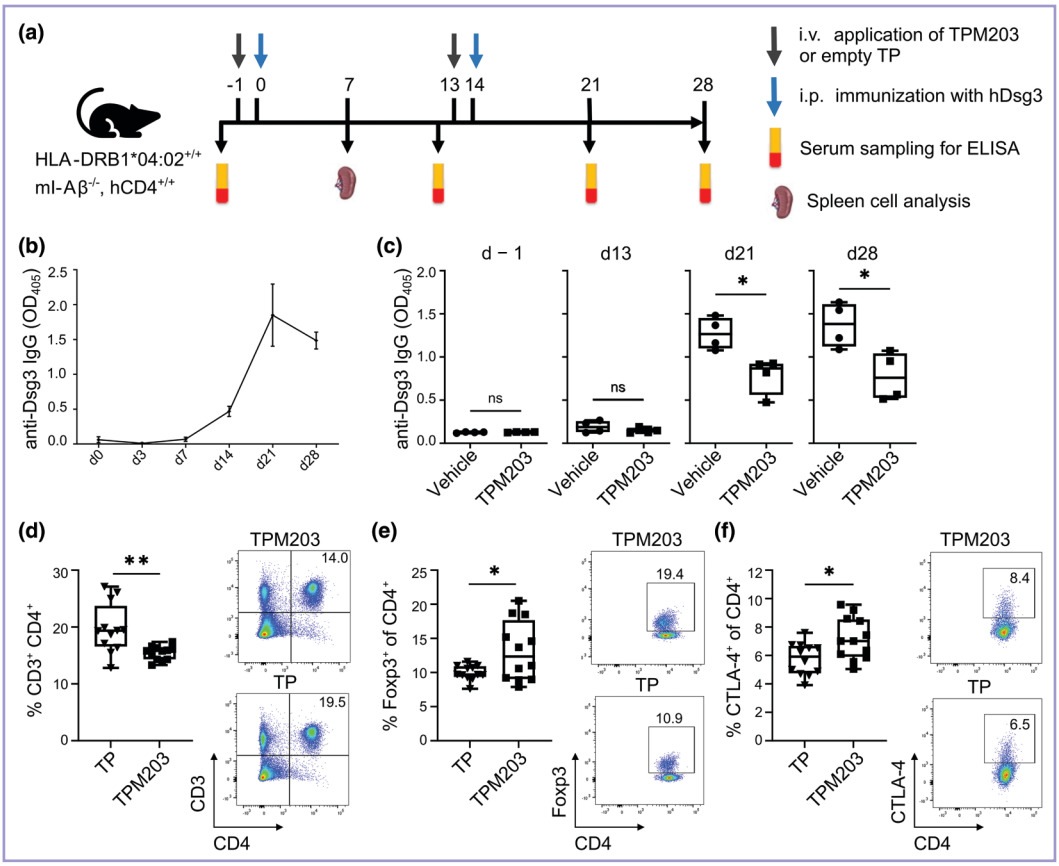


Figure 1 TPM203 reduces anti-desmoglein 3 (Dsg3) IgG and induces regulatory T cells in a humanized mouse model of pemphigus vulgaris. (a) Experimental design. (b) Kinetics of anti-hDsg3 IgG antibody titres in transgenic mice following intraperitoneal immunization with hDsg3 at days 0 and 14 ($n=4$). Results of a representative experiment are shown as optical density (OD) values [mean (SEM)] from hDsg3 IgG-specific enzyme-linked immunosorbent assays (ELISAs). (c) Comparison of anti-hDsg3 IgG antibody titres analysed by ELISA between TPM203- and vehicle control-treated sensitized transgenic mice at different timepoints ($n=4$/group). OD_{405}, absorbance measured at 405 nm using a plate reader. (d) Flow cytometric analysis of splenocytes at day 7. Frequency of $CD3^+$ $CD4^+$ cells within all live splenocytes, Frequency of $Foxp3^+$ cells and of cytotoxic T lymphocyte antigen 4 $(CTLA\text{-}4)^+$ cells within the $CD4^+$ T cells. Each subfigure consists of representative dot plots of (right, upper) TPM203-treated vs. (right, lower) tolerizing particle (TP)-treated animals and the statistical representation of 12 animals per group (left). Data in (b) and (c) are representative of up to six independent experiments. Data in (d) were pooled from two independently conducted experiments. Box-and-whisker plots show the median, range and individual datapoints. d, day; ns, not significant (i.e. $P>0.05$). $^*P\leq0.05$, $^{**}P\leq0.01$ [(c) Mann–Whitney *U* test; (d) unpaired Student's *t*-test].

were the secondary endpoint. Exploratory endpoints included the analysis of humoral and cellular parameters of Dsg3-specific autoimmune and tolerance mechanisms, such as serum anti-Dsg3 IgG titres, frequency of Dsg3-specific $CD4^+$ T cells and changes in peripheral blood T- and B-cell subset composition.

Descriptive statistics were performed for the primary and secondary endpoints. The statistical tests used for preclinical experiments and exploratory endpoints are specified in the figure legends. Full details of the study methodology can be found in Appendix S1 (see Supporting Information).

Results

TPM203 reduces anti-Dsg3 IgG and induces regulatory T cells in a HLA transgenic mouse model of pemphigus vulgaris

Following two immunizations with hDsg3, HLA-DRB1*04:02/DQB1*03:02 transgenic mice developed robust Dsg3-specific IgG responses on days 21 and 28 (Figure 1a, b). Two administrations of TPM203, each 1 day prior to immunization, consistently resulted in significantly reduced anti-hDsg3 IgG levels on days 21 and 28 compared with the vehicle control (Figure 1c). To assess TPC-mediated tolerance in early $CD4^+$ T-cell responses, we used the same study design but euthanased the animals on day 7. TPM203 treatment led to a significant decrease in $CD4^+$ T cells in the spleen, a significant increase in $Foxp3^+$ Treg cells and upregulation of cytotoxic T lymphocyte antigen 4 $(CTLA\text{-}4)^+$ $CD4^+$ T cells compared with tolerizing particle (TP) administration (Figure 1d).

Patient characteristics

Thirty-six patients underwent screening and 17 received TPM203 (12 in part A, 5 in part B): 13 in Germany, 2 in Italy and 2 in the UK. The study was prematurely terminated due to slow recruitment from a rare population and COVID-19 restrictions. At screening, the majority of patients were in complete clinical remission ($n=12$) or had low disease

Table 1 Baseline characteristics of the patients with pemphigus vulgaris (PV) included in this study

	Concentration of TPM203					
	0.12 μmol × 1 (*n* = 3)	**0.36 μmol × 1 (*n* = 3)**	**1.2 μmol × 1 (*n* = 3)**	**3.6 μmol × 1 (*n* = 3)**	**0.36 μmol × 3 (*n* = 5)**	**Total (*n* = 17)**
Age (years) when informed consent provided						
Mean (SD)	47.0 (18.1)	50.3 (12.2)	57.0 (5.0)	58.7 (8.7)	52.4 (7.2)	53.0 (10.1)
Median (range)	49.0 (28.0–64.0)	53.0 (37.0–61.0)	57.0 (52.0–62.0)	61.0 (49.0–66.0)	54.0 (41.0–61.0)	54.0 (28.0–66.0)
Sex, *n* (%)						
Female	1 (33)	3 (100)	2 (67)	1 (33)	2 (40)	9 (53)
Male	2 (67)	0 (0)	1 (33)	2 (67)	3 (60)	8 (47)
BMI (kg m^{-2})						
Mean (SD)	26.2 (4.1)	31.8 (1.5)	27.6 (0.9)	28.3 (3.0)	27.1 (5.6)	28.1 (3.9)
Median (range)	26.1 (22.2–30.4)	31.1 (30.7–33.5)	27.8 (26.6–28.4)	27.8 (25.5–31.5)	24.5 (23.9–37.0)	27.8 (22.2–37.0)
PV duration (years)						
Mean (SD)	14.4 (9.6)	4.1 (3.5)	4.0 (4.4)	12.4 (7.0)	4.0 (3.8)	7.3 (6.8)
Median (range)	15.7 (4.2–23.3)	2.2 (1.8–8.1)	2.5 (0.6–8.9)	15.6 (4.3–17.1)	3.5 (0.6–10.3)	4.2 (0.6–23.3)
Anti-Dsg3 autoantibodies						
Mean (SD)	379.7 (324.7)	692.0 (92.8)	226.3 (212.0)	199.3 (166.2)	340.6 (325.5)	364.4 (280.8)
Median (range)	432.0 32.0–675.0)	726.0 (587.0–763.0)	112.0 (96.0–471.0)	176.0 (46.0–376.0)	241.0 (61.0–897.0)	324.0 (32.0–897.0)
ABSIS score						
Mean (SD)	1.0 (1.0)	2.0 (2.7)	5.2 (7.3)	0.3 (0.6)	0.5 (0.5)	1.6 (3.3)
Median (range)	1.0 (0.0–2.0)	1.0 (0.0–5.0)	2.0 (0.0–13.5)	0.0 (0.0–1.0)	0.5 (0.0–1.0)	1.0 (0.0–13.5)
PDAI (total score at day –1)						
Mean (SD)	3.0 (3.6)	0.7 (0.6)	2.0 (2.0)	0.3 (0.6)	1.0 (1.2)	1.4 (1.9)
Median (range)	2.0 (0.0–7.0)	1.0 (0.0–1.0)	2.0 (0.0–4.0)	0.0 (0.0–1.0)	1.0 (0.0–3.0)	1.0 (0.0–7.0)
PGA (at day –1)						
Mean (SD)	1.0 (1.0)	0.3 (0.6)	0.7 (0.6)	0.3 (0.6)	0.6 (0.6)	0.6 (0.6)
Median (range)	1.0 (0.0–2.0)	0.0 (0.0–1.0)	1.0 (0.0–1.0)	0.0 (0.0–1.0)	1.0 (0.0–1.0)	1.0 (0.0–2.0)
Prednisolone or equivalent (mg daily)[a]						
Mean (SD)	11.3 (1.8)	12.5 (0)[b]	10.0 (0.0)		12.5 (0.0)	11.7 (1.3)
Median (range)	11.3 (10.0–12.5)	12.5 (12.5–12.5)	10.0 (10.0–10.0)		12.5 (12.5–12.5)	12.5 (10.0–12.5)

ABSIS, Autoimmune Bullous Skin Disorder Intensity Score; BMI, body mass index; Dsg3, desmoglein 3; PDAI, Pemphigus Disease Activity Index; PGA, Physician's Global Assessment. [a]No patient in the 0.36 μmol TPM dose group had steroids at study entry. [b]Only one patient had steroids at study entry.

activity (*n* = 5); eight patients received glucocorticoids at study entry. All patients completed the study. The characteristics of the enrolled patients are summarized in Table 1.

Safety of TPM203

Single and multiple infusions of TPM203 were safe and well tolerated. Sixteen of 17 patients (94%) reported at least one adverse event (AE) up to 28 days post-treatment or during follow-up (Table 2). AEs were not serious or severe; in the vast majority, they were mild. There were no AE- or treatment-related withdrawals: six patients (35%) reported treatment-related AEs, all of mild intensity. All AEs were nonspecific (e.g. headache), except for two (oral blood blister and oral mucosal erosion), reported as being related both to TPM203 and PV (neither required systemic treatment).

Seven AEs in seven patients were reported by investigators as being related to PV. All but one were mild; the moderate event, reported as 'worsening of PV after vaccination', was coded 'condition aggravated'. At the time of these AEs, none of the patients presented significant PV disease activity based on clinical scores [Pemphigus Disease Area Index (PDAI)], with the exception of two patients [Figure 2a; Table S1 (see Supporting Information)]. As per the investigator's assessment, Autoimmune Bullous Skin Disorder Intensity Score and PDAI score, these patients experienced mild and moderate PV worsening, respectively, in the context of SARS-CoV-2/influenza vaccinations. Clinical symptoms were accompanied by increased anti-Dsg3 IgG levels (in one of these patients, levels had already been rising before vaccination). Symptoms improved following high-dose prednisolone in one patient and prednisolone plus azathioprine in the other (Figure 2b).

No AEs or laboratory abnormalities potentially related to the mode of action of TPM203 or the nature of the disease were observed. Specifically, there were no reports of infusion-related reactions (including complement activation-related pseudoallergy), cytokine release syndrome, hepatotoxicity or treatment-related worsening of PV (Table 2).

Pharmacokinetics of TPM203 upon single administration

Pharmacokinetics were assessed up to 23 h after the start of single TPM203 administrations based on the concentration data of the four immunodominant peptides conjugated with the nanoparticles, namely TPC0002, TPC0003, TPC0005 and TPC0012. Based on long-term storage pharmacokinetic sample stability (LTS) tests in plasma, stable storage periods at –70 °C or lower for TPC0002 and TPC0003 were found to be shorter than those for the other TPCs. Samples exceeding LTS margins included those from two patients at TPC0002 dose level 1, all patients at TPC0003 dose level 1 and one patient at TPC0003 dose level 2. Due to this limited LTS, these results were considered invalid.

After a single TPM203 infusion over 30 min, TPCs were rapidly cleared from the circulation (Figure 3). TPC-bound

Table 2 Safety data for TPM203 administered in single doses (study part A) or multiple doses (part B) in patients with pemphigus vulgaris (PV)

	Concentration of TPM203									
	0.12 μmol×1 (*n*=3)		0.36 μmol×1 (*n*=3)		1.2 μmol×1 (*n*=3)		3.6 μmol×1(*n*=3)		0.36 μmol×3(*n*=5)	
MedDRA Preferred Term	**Treatment**	**FU**	**Treatment**	**FU**	**Treatment**	**FU**	**Treatment**	**FU**	**Treatment**	**FU**
Anaemia	–	–	1	–	–	–	–	–	–	–
Lymphopenia	–	–	–	–	–	1	–	–	–	–
Sinus arrhythmia	–	–	–	–	–	–	–	–	1	1
Abdominal pain, upper	1[a]	–	1	–	–	–	–	1	–	–
Lip swelling	–	1	–	–	–	–	–	–	–	–
Nausea	–	–	1	–	–	–	–	–	1	–
Tongue coated	–	–	–	–	1	–	–	–	–	–
Lip erosion	–	1[b]	–	–	–	–	–	–	–	–
Oral dysesthesia	–	–	–	–	–	–	–	–	1[b]	–
Oral blood blister	–	–	–	–	–	–	1[c]	–	–	–
Oral mucosa erosion	–	–	–	1[c]	–	–	–	–	–	–
Diarrhoea	1[a]	–	–	–	–	–	–	–	–	–
Flatulence	1[a]	–	–	–	–	–	–	–	–	–
Chest pain	–	–	–	–	–	–	–	–	–	1
Fatigue	–	–	–	–	–	–	1	–	–	–
Condition aggravated	–	–	–	1[b]	–	1[b]	–	1[b]	–	–
Feeling cold	–	–	–	–	–	–	1[a]	–	–	–
Infusion site pain	–	–	–	–	–	–	–	–	1[a]	–
COVID-19	–	–	–	–	–	–	–	–	–	1
Influenza	–	–	–	–	–	–	–	–	–	1
Laryngitis	–	–	–	–	–	–	1	–	–	–
Lower respiratory tract infection	–	–	–	–	–	–	1	–	–	–
Oral candidiasis	–	–	1	–	–	1	–	–	–	–
Pulpitis dental	–	1	–	–	–	–	–	–	–	–
Blood pressure increased	1[a]	–	–	–	–	–	–	–	–	–
Fall	–	–	1	–	–	–	–	–	–	–
Immunization reaction	–	–	–	–	–	–	–	1	–	–
Arthralgia	–	–	1	–	–	–	–	–	–	–
Back pain	–	–	–	–	–	–	–	1	–	–
Headache	–	–	–	–	–	–	1[a]+1	–	1[a]+1	1
Paraesthesia	1[a]	–	–	–	–	–	–	–	–	–
Sleep disorder	–	–	–	–	–	–	1	–	–	–
Vaginal haemorrhage	–	–	1	–	–	–	–	–	–	–
Epistaxis	–	–	1	–	–	–	–	1	–	–
Hypertension	–	–	–	–	1	–	1	–	–	–
Total	5	3	8	2	2	3	9	5	6	5

FU, follow-up. [a]Investigational medicinal product (IMP)-related adverse events; [b]PV-related adverse events (red); [c]PV- and IMP-related adverse events.

peptide levels were below the lower limit of quantification of 10 ng mL^{-1} following TPM203 administration at the lowest dose. Detectable drug concentrations were only present up to 30 min (corresponding to end of infusion) at 0.36 μmol total peptide (except for TPC0012), up to 1.5 h (postadministration) at 1.2 μmol total peptide and up to 3 h (2.5 h postadministration) at 3.6 μmol total peptide. Dose-normalized concentrations did not clearly overlap between the two highest doses, precluding a sufficient assessment of pharmacokinetic dose proportionality. At the highest TPM203 dose, TPC0002, TPC0003 and TPC0005 peptide concentrations were shown to decline, with half-lives of 12–44 min. For TPC0012, the half-life was incomputable due to limited concentration observations.

Impact of TPM203 on peripheral blood T-cell subsets

The criteria for the pharmacodynamically evaluable population excluded single datapoints from some patients due to confounding factors (i.e. SARS-CoV-2/influenza vaccination). Given the small sample size and exploratory nature of the trial, pharmacodynamic data were presented by dose/frequency of administration and separately combined for all 12 patients in part A and the 5 patients included in part B.

The dynamic changes in bulk T-cell subsets are shown in Figure 4(a). Notably, marked decreases in proinflammatory T helper (Th)17 and Th17.1 cells, and reductions in their follicular counterparts, were observed at week 12

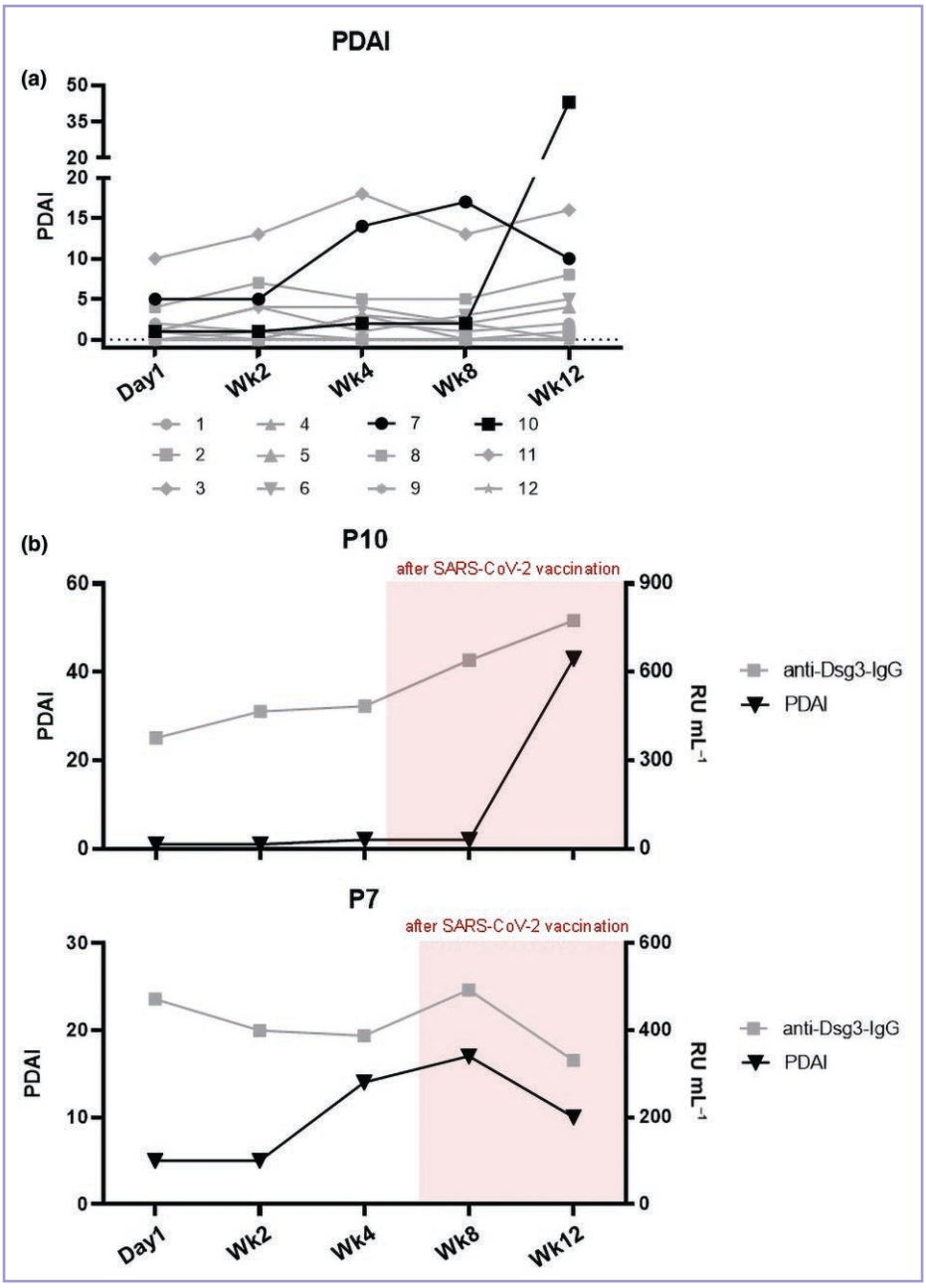


Figure 2 Safety of single and multiple administrations of TPM203 in patients with pemphigus vulgaris (PV) and the impact of SARS-CoV-2 vaccination. (a) Clinical course over the entire observation period of 12 weeks [shown as Pemphigus Disease Area Index (PDAI) score] of 12 patients with PV upon administration of single incremental doses [0.03 μmol, 0.09 μmol, 0.3 μmol and 0.9 μmol (dose levels 1–4, respectively); study part A] of TPM203 at day 1 (D1). (b) PDAI scores vs. anti-desmoglein 3 (Dsg3) serum IgG from patients 10 (dose level 1; upper panel) and 7 (dose level 3; lower panel). RU, relative units; Wk, week.

vs. baseline at dose levels 1–3, along with increases in Treg and follicular Treg (Tfr) cells, but were not seen at dose level 4. Analysis of combined part A data showed a significant decrease in Th17.1 cells at weeks 1 and 12 and an increase in Treg cells at week 12 (Figure 4b). Repeated TPM203 administration (part B) displayed a similar trend towards the study end, albeit with more fluctuations before week 8 and without reaching statistical significance. The ratios of Treg to Th17, Th17.1 and Th1, but not Th2, cells showed an ascending trend following an initial decline at TPM203 dose levels 1–3, which was less apparent when dose level 4 of the part A cohort was included (Figure S3; see Supporting Information). In part B, the ratios (except for Treg : Th2) exhibited fluctuations from day 1 to week 8, with a noticeable increase at week 12.

For numerical and functional assessment of Dsg3-specific autoreactive T cells, flow cytometry using Dsg3 peptide–HLA-DRB1*04:02 dextramers and an enzyme-linked immunospot (ELISpot) assay were performed (Figure 4c–e).[15] Given the low precursor frequency of autoreactive T cells in patients with PV (1–10 per 10^6 T cells),[16] both protocols included an *ex vivo* enrichment step with hDsg3.

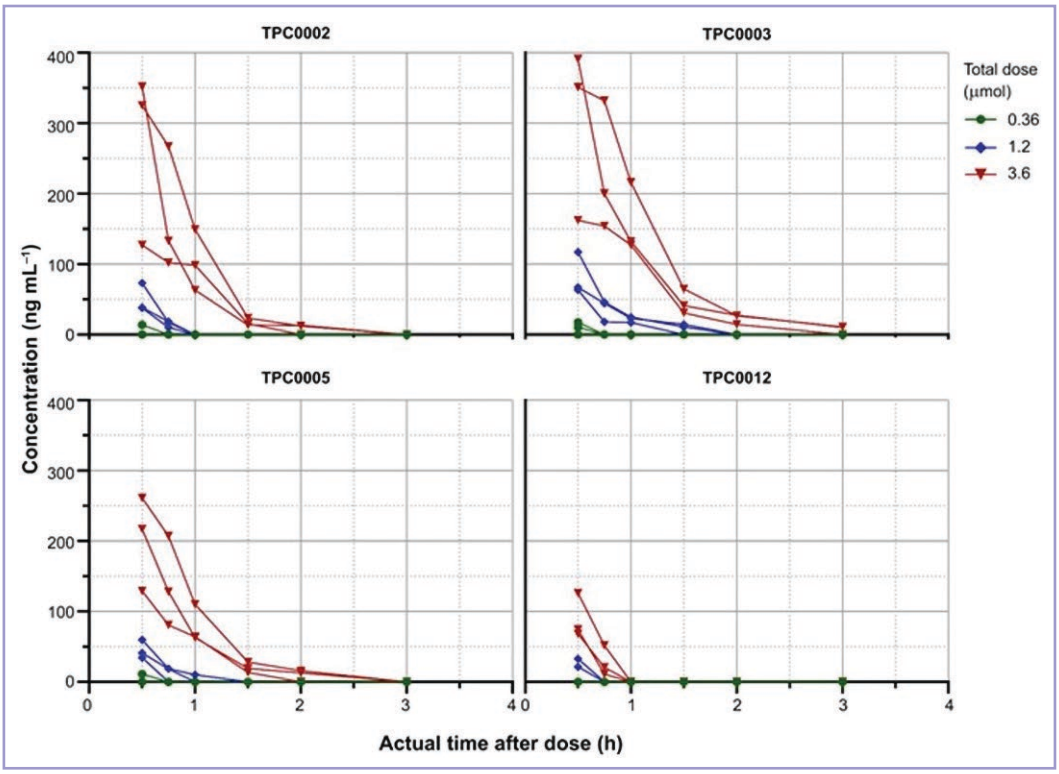


Figure 3 Pharmacokinetics of TPM203 in patients with pemphigus vulgaris. Shown are plasma concentrations and elimination rates for the Topas particle conjugates (TPCs) TPC0002, TPC0003, TPC005 and TPC0012, which form the study drug TPM203. At dose level 3 (1.2 μmol total peptide/0.3 μmol peptide for each of the four TPCs), peak plasma levels reached 37.8–73.1 ng mL^{-1} for TPC0002, 63.4–117 ng mL^{-1} for TPC0003, 34.4–59.7 ng mL^{-1} for TPC0005 and 21.6–32.8 ng mL^{-1} for TPC0012. At the highest dose administered (dose level 4: 3.6 μmol total peptide/0.9 μmol peptide for each of the four TPCs), peak plasma levels reached 127–352 ng mL^{-1} for TPC0002, 162–391 ng mL^{-1} for TPC0003, 129–261 ng mL^{-1} for TPC0005 and 68.1–126 ng mL^{-1} for TPC0012.

Specifically, dextramer staining revealed low but detectable Dsg3 peptide-specific T cells in patients included in part A (Figure S4; see Supporting Information), allowing qualitative assessment, albeit insufficient to assess individual treatment efficacy. However, the combined part A dataset showed a significant reduction in Dsg3 peptide dextramer$^+$ CD4$^+$ T cells at week 8, suggesting that TPM203 probably downregulated Dsg3-reactive T cells (Figure 4c). ELISpot results showed a trend towards reduced interferon-γ-secreting T cells at dose level 1 by week 12, which was more pronounced in part B (Figure 4d, e). Downregulation of other interleukin (IL)-5- and IL-10-secreting T-cell subsets was observed at week 12 (part A) and week 16 [part B; Figure S5a (see Supporting Information)].

Impact of TPM203 on peripheral blood B cells and anti-Dsg3 IgG

We further investigated whether modulation of autoreactive CD4$^+$ T-cell subsets might affect Dsg3-specific B-cell responses. In the combined part A dataset, a marked reduction in activated CD27$^+$ memory B cells was seen across all post-treatment timepoints vs. baseline at dose levels 1–3 (Figure 5a), reaching significance at weeks 1, 2 and 8. In part B, the frequency of these B cells remained stable initially, with a slight decrease at week 6 and an increase starting at week 8 (Figure 5a). Notably, while other B-cell subsets generally showed no significant changes from baseline, transitional B cells increased at dose levels 1–3 and in part B at weeks 2 and 12 (Figure S6; see Supporting Information).

Anti-Dsg3 IgG autoantibody levels varied across dose levels (Figure 5b). Dose levels 1–3 exhibited a trend towards reduced levels from weeks 8 to 12, while dose level 4 showed an increase starting at week 4. In part B, none of the five patients had significant changes in anti-Dsg3 IgG levels vs. baseline during follow-up. To analyse post-treatment functional changes in patients' anti-Dsg3 IgG antibodies, we performed the monolayer dissociation assay using isolated IgG from patient serum samples (150 and 500 μg mL^{-1} IgG for parts A and B, respectively),[17] to quantitatively assess the dissociating capacities that lead to a different degree of keratinocyte monolayer fragmentation (Figure 5c–e). In part B, a significant reduction in the relative fragmentation was noted from baseline to weeks 8, 12 and 20 (i.e. 4, 8 and 12 weeks after the last TPM203 treatment; Figure 5e).

Potential associations between anti-Dsg3 IgG autoantibodies and disease-promoting vs. immunoregulatory T- and B-cell subsets were summarized in a heatmap [Figure 5f; Figure S7 (see Supporting Information)]. At dose levels 1–3, anti-Dsg3 IgG decreased alongside reductions in memory B cells and type 17 T cells, while Treg and Tfr cells increased. At dose level 4, anti-Dsg3 IgG, memory B cells and Th17 cells increased despite increased Treg/Tfr cells and decreased Th17.1/Tfh17/Tfh17.1 cells, similarly to dose levels 1–3. Repeated TPM203 administrations showed the same trends. Overall, Th2/Tfh2 and Tfh1 cells increased in both

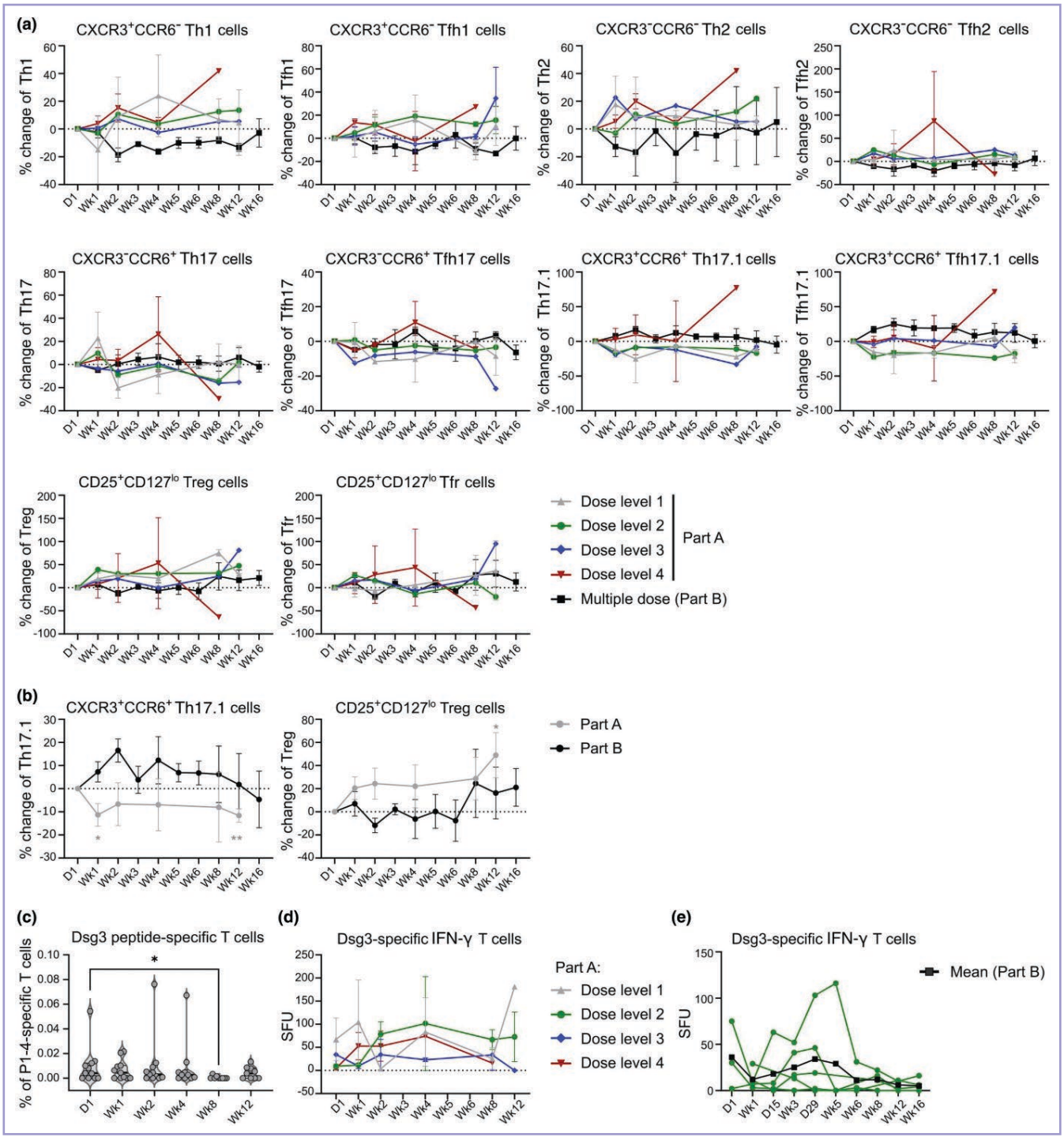
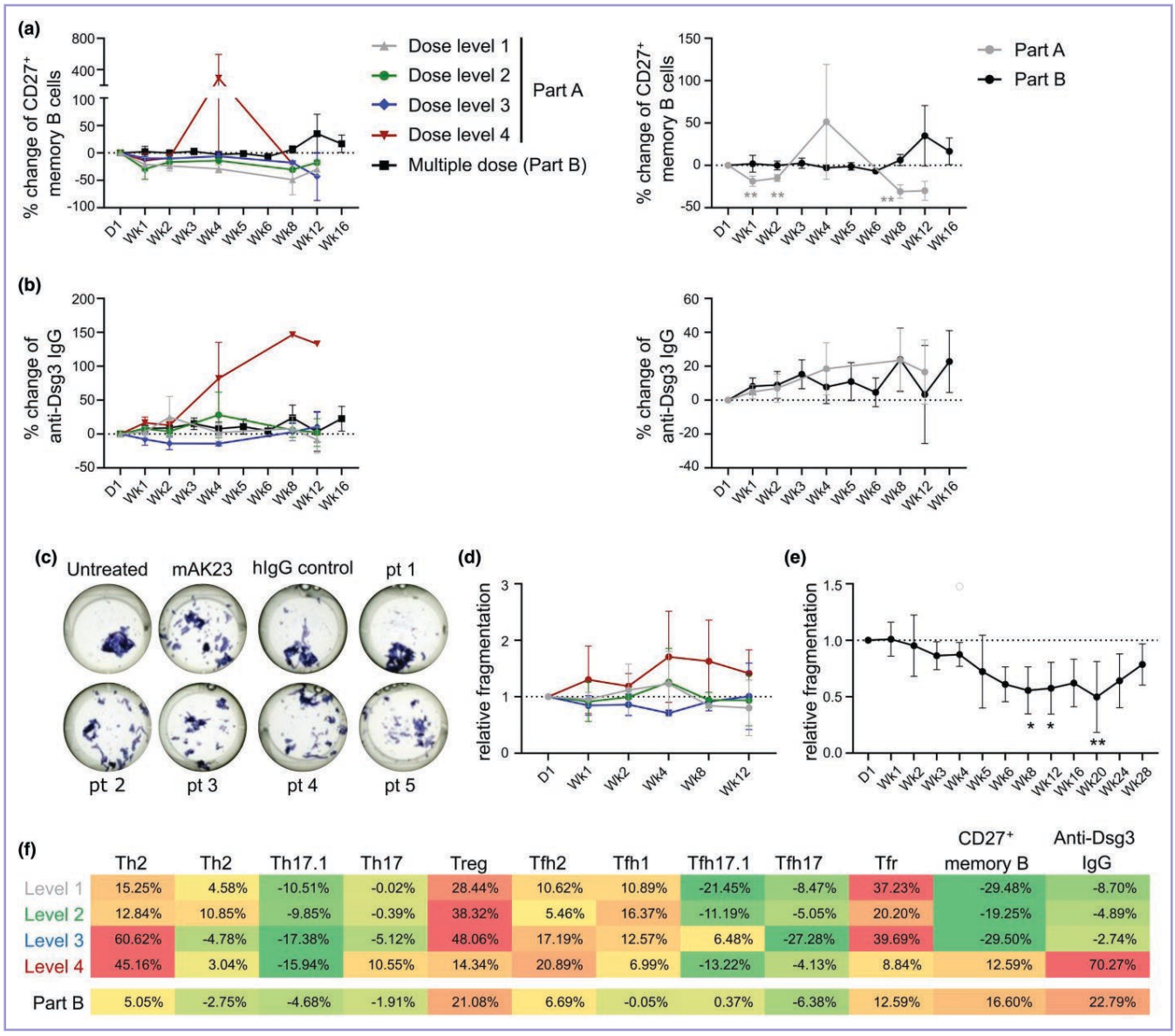


Figure 4 TPM203 reduces T helper (Th) and follicular regulatory T-cell (Tfh) subsets and induces regulator T (Treg) cells in patients with pemphigus vulgaris. (a) Frequencies of T-cell subsets expressed as percentage change from baseline [day 1 (D1)] for Th1, Tfh1, Th2, Tfh2, Th17, Tfh17, Th17.1, Tfh17.1, Treg and Tfr cells in the peripheral blood of patients with PV treated with TPM203 at incremental single doses [0.03 μmol, 0.09 μmol, 0.3 μmol and 0.9 μmol (dose levels 1–4, respectively); study part A] over 12 weeks, and repeated administration of TPM203 at dose level 2 (study part B) over 16 weeks. (b) Mean percentage change of Th17.1 and Treg cells from baseline (D1) for combined dose groups (part A, grey) and part B (black). (c) Mean frequencies of desmoglein 3 (Dsg3) peptide–HLA-DRB1*04:02 dextramer-positive T cells within CD4+ T cells (combined part A dose groups). P1–P4, peptides 1–4 of Dsg incorporated into one of the four dextramers (which are also present in TPM203). (d, e) Frequencies of interferon (IFN)-γ-secreting cells [expressed as spot-forming units (SFU)]. Peripheral blood mononuclear cells from patients in (d) study part A and (e) study part B were stimulated *ex vivo* with Dsg3. Graphs in (a, b, d) show mean (SEM). The data from dose level 4 (grey line) at week 8 consist only of one patient sample. Dose groups are colour-coded: 1 = grey; 2 = green; 3 = blue; 4 = red; part B = black. Wk, week. **P* < 0.05, ***P* < 0.01 (paired *t*-test).



(f)

	Th2	Th2	Th17.1	Th17	Treg	Tfh2	Tfh1	Tfh17.1	Tfh17	Tfr	CD27+ memory B	Anti-Dsg3 IgG
Level 1	15.25%	4.58%	-10.51%	-0.02%	28.44%	10.62%	10.89%	-21.45%	-8.47%	37.23%	-29.48%	-8.70%
Level 2	12.84%	10.85%	-9.85%	-0.39%	38.32%	5.46%	16.37%	-11.19%	-5.05%	20.20%	-19.25%	-4.89%
Level 3	60.62%	-4.78%	-17.38%	-5.12%	48.06%	17.19%	12.57%	6.48%	-27.28%	39.69%	-29.50%	-2.74%
Level 4	45.16%	3.04%	-15.94%	10.55%	14.34%	20.89%	6.99%	-13.22%	-4.13%	8.84%	12.59%	70.27%
Part B	5.05%	-2.75%	-4.68%	-1.91%	21.08%	6.69%	-0.05%	0.37%	-6.38%	12.59%	16.60%	22.79%

Figure 5 TPM203 reduces memory B cells and anti-Dsg3 IgG autoantibodies in patients with pemphigus vulgaris (PV). (a) Mean percentage change from baseline [day 1 (D1)] of CD27+ B memory cells at different timepoints post-treatment. (Left) Stratified into the four dose groups of study part A [0.03 μmol, 0.09 μmol, 0.3 μmol and 0.9 μmol (dose levels 1–4), respectively] and study part B. (Right) Combined dose groups from part A vs. part B. (b) Mean percentage change from baseline in anti-desmoglein 3 (Dsg3) IgG at different timepoints post-treatment. (Left) Stratified into the four dose groups of part A, and part B. (Right) Combined dose groups of part A vs. part B. (c) Representative images of hTert keratinocyte fragmentations by isolated IgG tested in a monolayer dissociation assay (MDA), including negative (untreated, hIgG) and positive (AK23) controls, and samples from patients with PV (pts 1–5). (d, e) Changes in the keratinocyte dissociating capacity of IgG isolated from serum samples from (d) part A and (e) part B across post-treatment timepoints vs. baseline. Serum samples, from which IgG was isolated for the MDA assay, were collected at predefined study timepoints, indicated on the *x*-axis. On a voluntary basis, patient samples from study part B were provided until week 28. (f) Heatmap of mean percentage change from baseline in T-cell subsets, CD27+ B cells and anti-Dsg3 IgG at the four dose levels of study part A at week 12 and part B at week 16. Dose groups are colour-coded: 1 = grey; 2 = green; 3 = blue; 4 = red; part B = black. *$P<0.05$, **$P<0.01$ [(a) paired *t*-test; (e) one-way ANOVA with Dunnett's post-test]. Wk, week.

parts A and B, with variable Th1 cell numbers across dose levels.

Discussion

Here, we present the results of the first-in-human-study of an innovative nanoparticle-based tolerizing approach targeting LSECs in patients with PV, corroborated by data gathered from proof-of-concept studies in a disease-relevant humanized animal model treated with the same mixture of nanoparticles.

TPM203 was designed to deliver Dsg3-specific CD4+ T-cell epitopes to LSECs, thereby modulating PV-related autoreactive T- and B-cell responses to reinstate tolerance towards Dsg3. This was demonstrated in the HLA-DRB1*04:02-transgenic PV mouse model which, upon administration of TPM203 prior to immunization with Dsg3,

showed a statistically significant reduction in anti-Dsg3 IgG and a significant increase in Foxp3+ Treg and CTLA-4+ T cells, highly suggestive of T-cell suppression as Treg cells and CTLA-4 play immunoregulatory roles.[18,19] In the same HLA transgenic PV mouse model, the induction of Treg cells by a superagonistic anti-CD28 antibody (D665) resulted in reduced pathogenic IgG antibodies.[20] Indeed, the critical role of Treg cells in maintaining peripheral tolerance against Dsg3 has been described.[21] The efficacy of TPM203 in tolerizing autoreactive Dsg3-specific T- and B-cell responses in this PV model also confirms our selection of a well-characterized set of Dsg3-derived CD4+ T-cell epitopes,[5,15,22] described as strong binders to HLA-DRB1*04:02 and HLA-DQB1*05:03 in patients with PV.[5,7] These results corroborated the rationale to investigate TPM203 in patients with PV. However, future animal models mimicking clinical onset may help validate the therapeutic potential of the investigational medicinal product. TPM203 was rapidly cleared from the circulation following intravenous administration, with drug concentrations detectable only up to 2.5 h after administration. This behaviour was expected based on the pharmacokinetic characteristics of the particles and the outstanding clearance function of LSECs, where the processing of TPCs preferentially occurs, as demonstrated in nonclinical targeting and excretion studies (data not shown). This rapid clearance allows for flexibility in the frequency of administration that can be explored in future clinical trials. TPM203 showed a favourable safety and tolerability profile in a population of patients with PV with no or low disease activity at study entry and no or low-dose glucocorticoid treatment. Three of the 17 patients experienced PV worsening assessed as being unrelated to TPM203: 1 event lacked a temporal relationship with TPM203 (occurring 57 days after the last TPM203 administration), while the other 2 occurred after SARS-CoV-2 and influenza vaccination, consistent with the PV reactivation often described in patients after vaccinations.[23–25]

PV pathogenesis has been linked to autoreactive Th2 cells, Th2-regulated anti-Dsg3 IgG4 and IgE, and the accumulation of Th2 cells in skin lesions.[5,15,24] Surprisingly, Th17/Th17.1 cells were found to be the primary T-cell subsets significantly reduced by TPM203 at low doses, with no similar changes seen in Th2 or Th1 cells. This finding aligns with recent observations strongly associating PV pathogenesis with Th17 cells, as Th17/Tfh17 cells were found to be increased in active PV and capable of inducing anti-Dsg3 IgG via B-cell help *ex vivo*.[26,27] Moreover, PV skin lesions exhibit a prominent type 17 signature in addition to the presence of Th2 cells, suggesting that both Th cell subsets are critical drivers of the disease.[28–30] Following administration of TPM203, Treg cells increased at week 12 and CD27+ memory B cells decreased at weeks 1, 2 and 12, indicating that exploiting the tolerogenic potential of LSECs by TPM203 may counteract the Treg/Th17 imbalance described in PV.[30–32] This notion is further supported by the observed trend towards increased Treg : Th17 and Treg : Th17.1 ratios across dose levels 1–3 following single TPM203 administrations, with a peak at week 12 in patients receiving three TPM203 administrations.

During the short observation period, a trend towards a reduction in anti-Dsg3 IgG was observed only in patients receiving a single infusion of lower TPM203 doses. *Ex vivo*, a significant reduction in the cell-dissociating capacity of serum IgG of the treated patients was noted 4–12 weeks after repeated TPM203 administration in the five patients included in part B, suggesting a qualitative change in anti-Dsg IgG. Further investigations will clarify whether this change arises from shifted IgG subclass distribution or changes in IgG Fab or Fc N-glycosylation profiles,[33–35] as observed in some patients with PV treated with TPM203 (data not shown).

Overall, the three lower TPM203 doses (dose 1–3) consistently reduced Th17.1 and CD27+ B cells and increased Treg cells through week 12; however, this was not seen in the highest dose group (dose 4). Despite this observation, the study was not powered to determine whether there was a difference between the low- and high-dose groups, given the small number of patients included. Moreover, due to the early termination of the study, the efficacy and safety at higher cumulative doses could not be fully assessed. This needs to be further investigated in future dose–response studies.

In conclusion, the findings of this study suggest that exploiting the tolerogenic potential of LSECs by TPM203 provides a novel therapeutic avenue to downregulate disease-promoting Th17 cells and induce tolerogenic Treg cells in PV. Despite the intraindividual variability of certain immunological parameters, the small sample size, the short observation period and the absence of a placebo group, the favourable observations definitively warrant further development steps in this indication and beyond.

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Conflicts of interest

Topas Therapeutics (Topas) was the sponsor of the preclinical and clinical study. M. Hertl and H.G. served as consultants to Topas, and R.T. received financial support from Topas for laboratory services. D.K., S.-H.W., S.R., S. Huguenin, V.A., C.d.M. and S. Fleischer are current employees of Topas. R.D., R.S., F.S.Z., E.v.S., J. Hummel and J.P. are former employees/consultants of Topas. R.T. reports a

relationship with Argenx BV that includes funding grants. M. Hertl has received honoraria from and was an adviser to Argenx BV, Janssen Cilag and Novartis. M.S. has received scientific support, honoraria as a member of speaker and advisory boards, and clinical study support from AbbVie, Almirall, Amgen, BMS, Boehringer Ingelheim, Janssen, LEO Pharma, Eli Lilly, MSD, Novartis, Pfizer, Regeneron, Sandoz, Sanofi and UCB. The other authors declare no conflicts of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki, all applicable laws and regulations, and Good Clinical Practice Guidelines. The Ethics Committees of the participating clinical centres approved the research protocol.

Patient consent

All patients gave written informed consent prior to study entry.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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