CLINICAL STUDY REPORT

A multi-centre, open-label, phase 1 study, Part A single ascending dose and Part B multiple dose, to evaluate the safety, tolerability and pharmacokinetics, and to explore early signs of effectiveness of induction of antigen-specific immune tolerance with TPM203 in pemphigus vulgaris patients

TPV11 study

Investigational Product:	TPM203
Indication:	Pemphigus vulgaris
Development Phase:	Phase 1a/1b (first-in-human)
Study Initiation Date:	12 December 2019
Study Completion Date:	25 July 2023
Report Completion Date:	4 December 2023
Name and Address of Co-ordinating Investigator:	Prof Dr Michael Hertl Director of the Department of Dermatology and Allergology of the Phillips-University Marburg, Baldingerstr, 35043 Marburg, Germany
Name and Address of Sponsor:	Topas Therapeutics GmbH Falkenried 88, 20251 Hamburg, Germany Phone +49 40 302089044
Responsible for Sponsor:	Dr Cristina de Min Chief Medical Officer Topas Therapeutics GmbH

GCP STATEMENT

This study was conducted in compliance with Good Clinical Practices, according to the ICH Harmonised Tripartite Guideline.

CONFIDENTIALITY STATEMENT

SYNOPSIS

Title of Study:
A multi-centre, open-label, phase 1 study, Part A single ascending dose and Part B multiple dose, to evaluate the safety, tolerability and pharmacokinetics, and to explore early signs of effectiveness of induction of antigen-specific immune tolerance with TPM203 in pemphigus vulgaris patients

Co-ordinating Investigator:
Michael Hertl, MD
Department for Dermatology and Allergology of the Philipps-University Marburg
Baldingerstraße, 35043 Marburg, Germany

Study Centre(s):
19 investigational centres initiated in Germany, Italy, Israel and United Kingdom, of which 12 screened patients

Publication (reference):
N/A

Study Period (years):	**Clinical Phase:**
December 2019 - July 2023	Phase 1a/1b

Objectives:
Primary: to evaluate the safety and tolerability of the intravenous infusion of TPM203 in pemphigus vulgaris (PV) patients
Secondary: to describe the pharmacokinetics of TPM203 in PV patients
Exploratory: to explore early signs of effectiveness of induction of antigen-specific immune tolerance with TPM203 in PV patients

Methodology:
- Part A:
  an open design with single doses at four dose levels. Data from each dose-level group was to be reviewed before escalation to the next higher dose level. At each dose level, a sentinel patient was to be treated first
- Part B:
  an open design with three (3) doses at two (2) dose levels, given at 2-week intervals.
  The lower dose level was the second-lowest dose tested as a single dose in Part A. Upon review of the initial data for this group and for the highest dose level from Part A, the second multiple-dose group was to be treated, using the highest dose from Part A. At each dose level, a sentinel patient was to be treated first
- Follow-up of Part B participants (optional):
  once the patient completed the last study visit for Part B, she/he were asked to return for blood draw at Week 20, 24 and 28 to determine the anti-Dsg3-Ig-antibody titres

Number of Subjects (total and for each dosage):
- Part A: 12 patients in total, 3 at each dose level
- Part B: 12 patients in total, 6 at each dose level

Study TPV11 had been prematurely terminated because of very slow recruitment (rare disease population and Covid-19 pandemic) and, because of this early termination, the 2nd cohort planned in

Part B did not recruit any patients. A total of 17 patients have been treated in the trial: 12 in Part A and 5 in Part B (1 patient in Part B did not receive IMP because of Covid onset shortly before treatment). This abbreviated CSR provides full details of the safety and PK datasets only, in line with relevant regulatory guidelines and requirements

Diagnosis and Criteria for Inclusion:
Key inclusion criteria

1. Written informed consent to take part in the study
2. Patient (male or female) age ≥18 years and ≤70 years
3. Body weight of ≥50 kg and a body mass index ≥18.5 and ≤32 kg/m^2
4. Diagnosis with PV (documented) and -at screening- complete clinical remission or low to moderate clinical disease activity (i.e. ABSIS ≤17 **and** PDAI ≤15)
5. Presence of anti-Dsg3 IgG (immunoglobulin G) antibodies
   and
   peripheral blood CD4+ T cells specific for at least one of the Dsg3 peptides employed in TPM203 in blood samples at screening or presence of human leucocyte antigen (HLA)-DRB1*04:02 and/or HLA-DQB1*05:03.

Key exclusion criteria

1. Immunosuppressive or immunomodulatory treatment other than prednisolone ≤10 mg/d for patients with body weight <70 kg or ≤12.5 mg/d for patients with body weight ≥ 70 kg (or equipotent doses of other steroids)
2. Conditions including previous or concomitant medication that might present a risk to the patient and/or impede the attainment of the study's objectives

Test Product, Dose, Mode of Administration, Batch No.:
- Part A:
  TPM203 dose escalation at four (4) different dose levels (3 patients per dose level) of the four Topas Particle Conjugates (TPC) constituting TPM203
  Dose level 1: 0.03 µmol peptide for each of the four TPCs (0.12 µmol total peptide)
  Dose level 2: 0.09 µmol peptide for each of the four TPCs (0.36 µmol total peptide)
  Dose level 3: 0.3 µmol peptide for each of the four TPCs (1.2 µmol total peptide)
  Dose level 4: 0.9 µmol peptide for each of the four TPCs (3.6 µmol total peptide)
- Part B:
  two dose levels, with three doses of TPM203 given at 2-week intervals (6 patients per dose level):
  Dose levels 2 and 4 tested as single dose in Part A to be used in the multiple-dose part B.
  Every dose administered to a patient was prepared individually and has its individual batch number. (Refer to Appendix **Error! Reference source not found.** for a complete list of batches used in this trial)

Duration of Treatment:
- Part A:
  Single dose
- Part B:
  6 weeks (3 TPM203 infusions at intervals of 2 weeks)

Reference Therapy, Dose, Mode of Administration, Batch No.:
N/A

Criteria for Evaluation:
Safety: frequency and severity of treatment-emergent adverse events and worsening of PV

PK: concentrations of the individual peptide components TPC0002, TPC0003, TPC0005 and TPC0012 following intravenous dosing of TPM203. The secondary endpoints include the following PK parameters:

- Maximum observed plasma concentration after dosing (C_{max})
- Time when C_{max} is observed (t_{max})
- Last measurable plasma concentration (C_{last})
- Time when C_{last} is observed (T_{last})
- Area under the plasma concentration-time curve from time zero to the time of the last quantifiable sample (AUC_{last})
- Area under the plasma concentration-time curve from time zero extrapolated to infinity (AUC_{inf}), if available
- Apparent terminal elimination half-life (t1/2), if available

Statistical Methods:
No formal power calculation was performed to establish the sample size, owing to the early development phase of this study.
No confirmatory hypothesis-testing was to be performed. Any statistical tests applied was to be at a descriptive or exploratory level

SUMMARY – CONCLUSIONS

Safety Results: no serious adverse event, no IMP-related discontinuation and no adverse event of special interest has been reported in the trial. No safety signal has been identified, specifically not related to any of the anticipated potential risks.

PK Results: TPCs were rapidly cleared from the systemic circulation after the intravenous infusion of TPM203. Concentrations were only measurable for up to 3 hours after dosing at the highest dose.

Conclusion: the PK and safety data collected in this study support further development of TPM203 in PV, a severe disease with high unmet medical need