A double-blind, randomized, placebo-controlled, phase 2a study to evaluate the safety, tolerability, and pharmacodynamic (PD) effects of two infusions of escalating doses of TPM502 in adults diagnosed with celiac disease (CeD)

Published: 08-02-2023
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Main objective:To evaluate the safety and tolerability of two i.v. infusions of escalating doses of TPM502 in CeD patients.Secondary objectives:• To identify PD effects consistent with the induction of antigen-specific immune tolerance following the...

Ethical review	Approved WMO
Status	Completed
Health condition type	Gastrointestinal conditions NEC
Study type	Interventional

Summary

ID

NL-OMON53376

Source
ToetsingOnline

Brief title
TPM502 in adults diagnosed with celiac disease (CeD)

Condition

- Gastrointestinal conditions NEC

Synonym
Coeliac disease; Gluten intolerance

Research involving
Human

Sponsors and support

Primary sponsor: Topas Therapeutics GmbH
Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: Celiac disease, Pharmacodynamic effects, TPM502

Outcome measures

Primary outcome

Incidence, severity, causality and outcomes of TEAEs (serious and nonserious), including hypersensitivity reactions, CRS, hepatotoxicity and other AEs suggestive of these conditions.

Secondary outcome

• Ratio "Interleukin 2 (IL-2) after GC post-TPM502 treatment/IL-2 after GC at screening" compared to the placebo group

• Modified Celiac disease patient*reported outcome (CeD PRO®) and GloSS (Global Symptom Survey) 1 hour before and then hourly up to 6 hours post GC/ TPM502 compared to placebo

• Maximum observed plasma concentration after dosing (Cmax), area under the plasma concentration-time curve from time zero to the time of the last quantifiable sample (AUC0-last).

Study description

Background summary

CeD is an autoimmune chronic inflammatory disease of the small intestine triggered by gluten ingestion in genetically predisposed individuals, and it is characterized by a specific serological and histological profile.

Gluten is the general term for alcohol-soluble proteins present in various cereals, including wheat, rye, barley, spelt, and kamut. The main pathological intestinal manifestations of CeD are villus atrophy and crypt hyperplasia, as well as inflammatory lymphocyte infiltration of the gut epithelium. This leads to diarrhoea, abdominal pain, malabsorption and other - often serious - clinical manifestations. Up to 30% of patients have severe symptoms and/or persisting inflammation in spite of adhering to a gluten-free diet (GFD) (3).
CeD may also be associated with intestinal lymphoma and enhanced extra-intestinal autoimmunity, such as Type 1 diabetes (4-6).
CeD is one of the most common autoimmune disorders, with a reported prevalence of 0.5-1% of the general population, with the exception of areas showing low frequency of CeD predisposing genes and low gluten consumption (e.g., sub-Saharan Africa and Japan). CeD prevalence is increasing in Western countries (7).
Despite the high medical need, there are currently no effective non-dietary therapies available to patients, and the only treatment option is lifelong strict adherence to a GFD. This poses not only multiple restrictions that impact the patients* physical and mental health and quality of life, but often fails to completely prevent inflammatory flares, as undeclared or *hidden* gluten in food products is often consumed involuntarily.

The inflammatory responses triggered by gluten depend on CD4+ T cell-induced immunity to certain gluten-derived peptides. These peptides are rendered strongly antigenic through tissue transglutaminase-mediated deamidation of certain glutamine residues. The resulting charged glutamates bind with high affinity into peptide binding pockets of the human major histocompatibility complex (MHC) class II molecules HLA-DQ2 and DQ8 (8).

The causative genetic link between CeD and HLA-DQ2 and HLA-DQ8, together with insight into disease-associated immune responses against HLA-DQ2 and DQ8-restricted antigenic gluten peptides, makes CeD a suitable setting to investigate novel antigenic peptide-specific immunotherapies aiming at restoring immunological tolerance. Topas particle mix (TPM) 502, which is the investigational drug tested in this study, represents a targeted (it addresses specific epitopes) and a personalized (it is addressed to specific individuals within the diseased population) approach to the disease. In fact, CeD is one of the few autoimmune conditions for which the key genetic elements, the auto-antigen involved (tissue transglutaminase) and the environmental trigger (gluten) are known and well-defined.

Study objective

Main objective:

To evaluate the safety and tolerability of two i.v. infusions of escalating doses of TPM502 in CeD patients.

Secondary objectives:
• To identify PD effects consistent with the induction of antigen-specific immune tolerance following the administration of TPM502
• To describe the severity of gastrointestinal (GI) symptoms following the administration of TPM502 and a GC
• To determine TPM502 PK

Study design

Multi center, double-blind, randomized, placebo-controlled study

Intervention

TPM502

Study burden and risks

TPM502 has not been administered to humans, therefore there are no clinical data yet indicating a benefit for CeD patients.
Any potential benefit for the patients in the study is theoretical, based on the assumed mechanism of action and on preclinical results in relevant animal models, and may be restricted to some of the study groups only or not be present at all.
Importantly, the safety, tolerability, and PD data obtained from this study will form the basis for any further clinical development of TPM502 and are thus expected to be fundamental for the development of a new treatment approach for CeD and other autoimmune diseases.

Given all the above, the potential long-term benefit of obtaining a safe and effective treatment for patients with CeD is considered to outweigh any potential individual risks, and the benefit/risk of conducting the study is positive.
This benefit/risk will be regularly monitored by the iDMC, to ensure it remains positive and the patients in the study are adequately protected.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Availability of a documented biopsy-confirmed diagnosis of CeD OR documented tissue transglutaminase >10x upper limit of normal (ULN) and documented positive immunoglobulin A (IgA) anti-endomysial antibody (EMA) at time of CeD diagnosis (as per local guidelines) 2. Serum anti-tissue transglutaminase 2 immunoglobin A antibodies within normal range at screening 3. Serum IL-2 levels (AUC1-6h) > 2x AUC1-6h at the lower level of quantification (LLOQ) (i.e., 8x LLOQ) following the GC at screening 4. Patients must have been on gluten-free diet (GFD) for >= 6 months 5. Patients must have well-controlled CeD, defined as mild or with no ongoing signs or symptoms felt to be related to active CeD, as per investigator`s assessment 6. Human leukocyte antigen (HLA)-DQ2.5 positive (homozygous and heterozygous) but HLA-DQ8 and HLA-DQ2.2 negative

Exclusion criteria

1. Known or suspected refractory CeD (refractory CeD type I or II)
2. Known intolerable symptoms following previous GCs, as per investigator`s assessment
3. Treatment with systemic immunosuppressants (e.g., glucocorticoids), ongoing or administered in the 12 weeks preceding the first investigational medicinal

product (IMP) administration

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	09-03-2023
Enrollment:	12
Type:	Actual

Ethics review

Approved WMO Date:	08-02-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	22-02-2023
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-01-2024
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-03-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-05-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-05-2024
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2022-001656-41-NL
CCMO	NL83574.056.23