Unveiling the strong safety profile and high target engagement of OPM-101, a first-in-class orally available RIPK2 Inhibitor, in healthy volunteers, a Phase 1 Clinical trial

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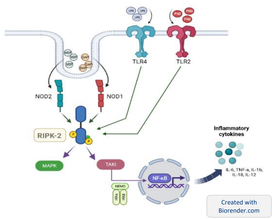
Introduction

Oncodesign Precision Medicine has designed and developed OPM-101, an active substance, chemically-defined, small synthetic molecule, that specifically binds and inhibits RIPK2.
The NOD2/RIPK2 pathway is a key driver of IBDs as its hyperactivation will result in an over production of proinflammatory cytokine including notably tumor necrosis factor (TNF)-α, which plays an essential role in the induction and maintenance of inflammation and tissue damage in the intestine.
Consequently, targeting RIPK2 has emerged as a promising therapeutic strategy for mitigating inflammation and ameliorating disease progression in IBD. It is expected that blocking RIPK2 pathway could become a possible strategy for severe steroid refractory or dependent IBD patients, and lead to a normalization of proinflammatory cytokines (including TNFα) generation that play an essential role in the induction and maintenance of inflammation in the intestine in IBD.

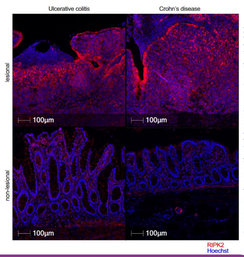
OPM evaluated the safety profile, the pharmacokinetic (PK) and pharmacodynamic (PD) properties of **OPM-101** in a Phase 1 clinical trials, including Single Ascending Dose (SAD) in male and female healthy volunteers.

RIPK2 is highly expressed in lesional human IBD tissue

RIPK2 pathway

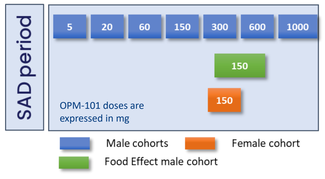


RIPK2 expression in lesional human IBD tissue
RIPK2 fluorescence immunohistochemistry demonstrating differences in immunoreactivity between patient matched lesional and nonlesional **ulcerative colitis** (left, representative of n = 6) and **Crohn's disease** (right, representative of n = 5) colonic resection tissue.



Study design

In this First-in-Human phase 1 clinical trial, OPM-101 was administered using a Single Ascending Dose (SAD) regimen with doses ranging from 5-1,000 mg. The SAD study design is shown below:



Data collected for each cohort:
- Safety
- Laboratory parameters
- ECG
- Holters
- Blood for PK analyses (up to 24h for cohorts 1-4, and up to 72h for cohorts 5-10)
- Blood for PD analyses (up to 24h for cohorts 1-4, and up to 48h for cohorts 5-10)

The Investigational Medicinal Product (IMP) was administered as hard gelatin capsules containing 5, 25 or 100 mg of OPM-101 or a matching placebo. The IMP was administered in male and female healthy volunteers in fasted state in the morning.
Healthy volunteers in the food effect cohort were administered IMP sequentially in fasted and in fed state, a week apart. For fed state administration, they received a standardized high fat breakfast 30 minutes prior to IMP administration.
9 cohorts were conducted during the SAD part. A single dose ranging from 5 to 1,000 mg was administered in male volunteers and a single dose of 150 mg was administered in female volunteers. An additional group of male volunteers received, a week apart, two single doses of 150 mg in fasted and in fed conditions.

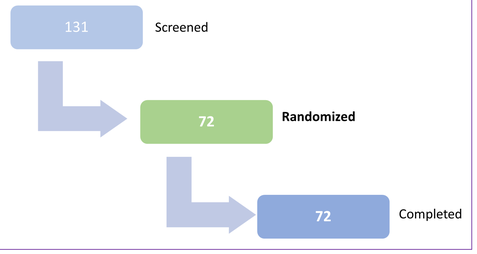
At the end of each cohort, a Data Review Committee meeting was held to review all data collected and to decide on the study continuation and on dose to be used for the next cohort.

Subject disposition

Male and female healthy volunteers were included in the phase 1 study.

The screening visit was conducted within 4 weeks of the randomization.

A total of 131 volunteers were screened and 72 were randomized in 9 cohorts.
In each cohort, Healthy volunteers were randomized 6:2 between OPM-101 (6 healthy volunteers) and placebo (2 healthy volunteers).



OPM-101 Safety – TEAEs

8.3% of subjects reported at least 1 treatment-related TEAEs

8 treatment-related TEAEs were reported
6 mild
2 moderate

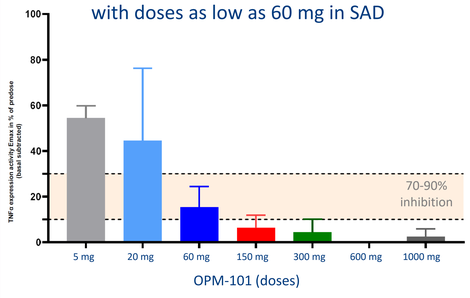
No SAE
No severe treatment-related TEAE
No study withdrawal

Dose (mg)	Subject #	Reported Term	Onset day	Duration	Outcome	Treatment	Causality	Intensity	SAE
5	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
20	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
60	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
150	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*	*NA*
300	S036	Headache	D1	24min	Resolved	Paracetamol	Possible	Moderate	No
600	S120	Bloating	D1	1h 50min	Resolved	*NA*	Possible	Mild	No
		Bloating	D3	1h	Resolved	*NA*	Possible	Mild	No
		Diarrhea	D3	5h	Resolved	*NA*	Possible	Mild	No
1000	S146	Sensation of palpitations	D1	5min	Resolved	*NA*	Possible	Mild	No
150 (FE)	S092	Headache	D1	1h 10min	Resolved	*NA*	Possible	Mild	No
	S113	One loose stool	D2	1h	Resolved	*NA*	Possible	Mild	No
150 (F)	S086	Headache	D1	12h 30min	Resolved	*NA*	Possible	Moderate	No

FE: food effect cohort F: female volunteers

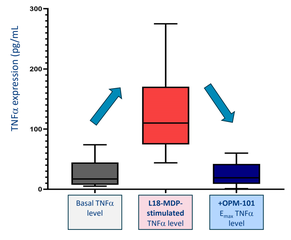
OPM-101 Pharmacodynamics

High target engagement, evaluated by TNFα expression inhibition was observed with doses as low as 60 mg in SAD



Ex vivo stimulation of TNFα expression triggered by L18-MDP (specific activator of the NOD2-RIPK2 pathway)

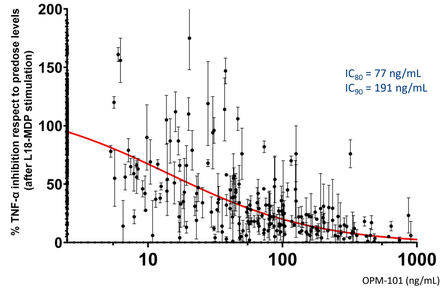
OPM-101 appears to exhibit an immunomodulatory effect rather than an immunosuppressive effect.



Pooled data of TNFα expression from cohorts 60-1,000 mg

PK/PD relationship

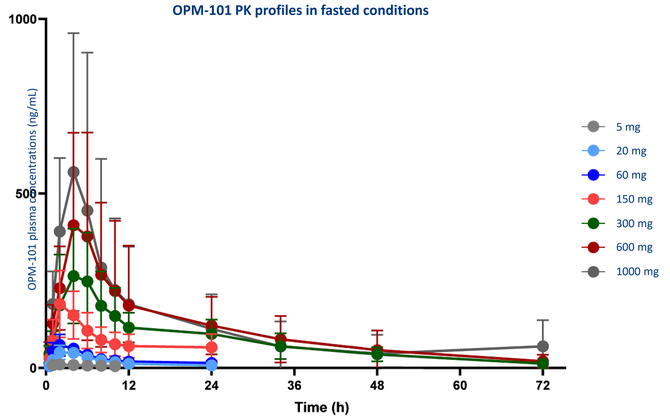
The relationship between plasma concentrations of OPM-101 and target engagement (% of stimulated TNFα inhibition) showed that OPM-101 concentrations in the range of 50-157 ng/mL can induce a 80% inhibition.

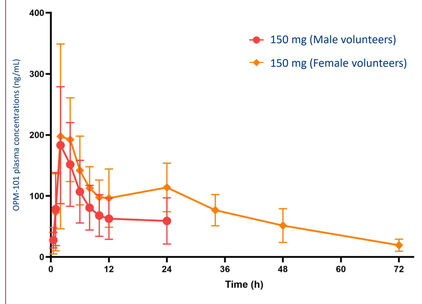


OPM-101 Pharmacokinetics

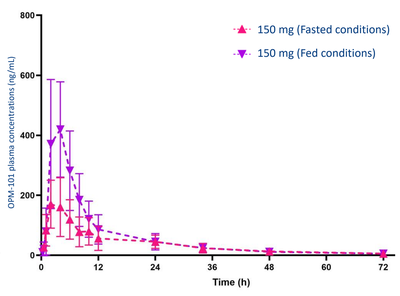
OPM-101 is
- **Orally bioavailable**
- **Rapidly** absorbed: T_{max} observed after 2-4h
- **Long** terminal half life: 12-15h in all SAD cohorts

OPM-101 PK profiles in fasted conditions





Exposure in female with a **150 mg dose** is twice that observed in males with the same dose



Exposure in fed conditions with a dose of **150 mg** is twice that observed in fasted condition

Conclusions

This phase 1 study unveils OPM-101 as a potent RIPK2 inhibitor paving the way for groundbreaking therapeutic advancements in IBD
- **Very good safety profile for OPM-101 in male and female healthy volunteers over a 200-fold range (doses from 5 to 1,000 mg)**
- **Orally bioavailable** and **rapidly absorbed**
- **Long terminal half life**
- **High target engagement over 24h**
- **Immunomodulation** (rather than immunosuppression)
  - 70-80% inhibition of stimulated TNFα expression at T_{24h}
  - TNFα expression returning to basal levels
- The MAD part of the study is ongoing