

# Digestive Disease Week<sup>®</sup>, Washington, 2018

## Novel Orally Administered Recombinant Anti-TNF alpha Fusion Protein for the Treatment of Ulcerative Colitis: Phase 2a Clinical Trial Showing Promising Results

E. Almon<sup>\*</sup>, Y. Shaaltiel<sup>\*</sup>, E. Goldin<sup>1</sup>, W. Sbeit<sup>2</sup>, E. Israeli<sup>3</sup>, D. Schwartz<sup>4</sup>, O. Ben-Basat<sup>5</sup>, M. Waterman<sup>6</sup>, N. Milinic<sup>7</sup>, B. Vladimirov<sup>8</sup>, M. Szlaifer<sup>\*</sup>, H. Reuveni<sup>\*</sup>, B. Amit-Cohen<sup>\*</sup>, S. Alon<sup>\*</sup>, R. Chertkoff<sup>\*</sup>, A. Paz<sup>\*\*</sup>, Y. Ilan<sup>3</sup>.

<sup>1</sup>Shaare Zedek Medical Center, Jerusalem, Israel, <sup>2</sup>Western Galilee Hospital, Nahariya, Israel, <sup>3</sup>Hadassah Medical Center, Jerusalem, Israel, <sup>4</sup>Ichilov Medical Center, Tel Aviv, Israel, <sup>5</sup>Maccabi, Tel Aviv, Israel, <sup>6</sup>Rambam Medical Center, Haifa, Israel, <sup>7</sup>Medical Center Bezanjska Kosa (MCBK) Clinic for Internal Medicine, Belgrade, Serbia, <sup>8</sup>University Hospital for Active Treatment (UMHAT) "Tzaritza Yoanna – ISUL, Sofia, Bulgaria, <sup>\*</sup>Protalix, Carmiel, Israel, <sup>\*\*</sup>Medical consultant to Protalix, Carmiel, Israel

# Disclosure Information

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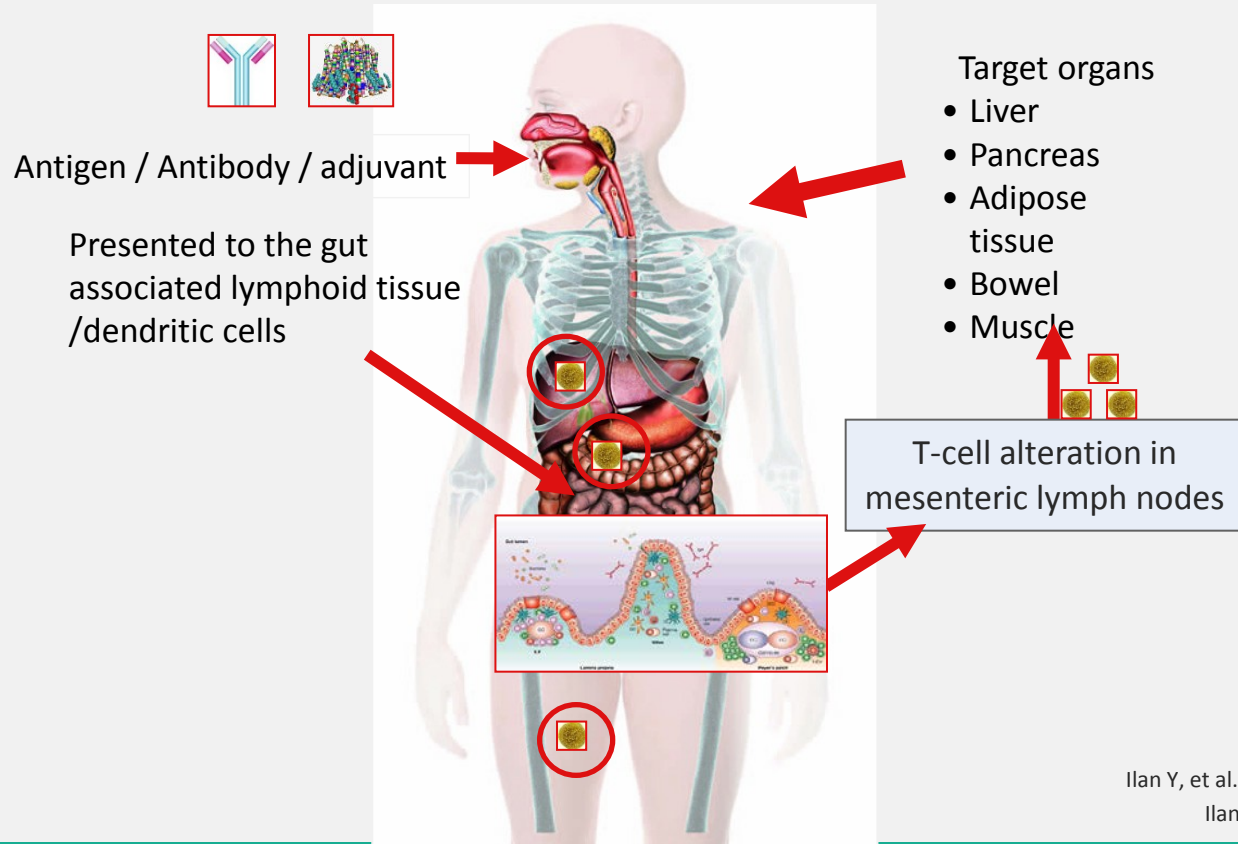
- Y. Ilan is a consultant to Protalix Biotherapeutics
- E. Almon, Y. Shaaltiel, S. Alon, R. Chertkoff, B. Amit-Cohen are employees of Protalix Biotherapeutics
- The study was supported by Protalix Biotherapeutics

# Forward-looking statement

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Please be advised that the information and projections provided in this presentation may include forward-looking statements with respect to plans, projections or future performance of the compounds and companies presented, the occurrence of which involves certain risks and uncertainties and is not under the control of these companies, including, but not limited to, changes in regulatory environment and success in implementing its research, development, sales, marketing and manufacturing plans, protection and validity of patents and other intellectual property rights, the impact of currency exchange rates and the effect of competition by other companies.

# Oral immunotherapy: modulation of the systemic immune response via alteration of the gut immune system without immune suppression

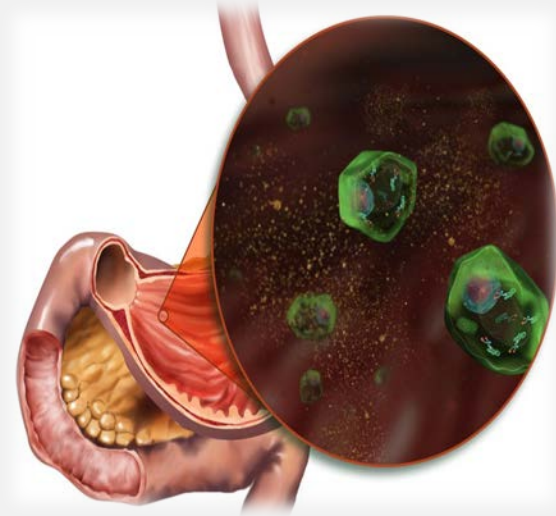


Ilan Y, et al. Immunol Cell Biol 2009;87:514–24  
Ilan Y, Hum Immunol. 10:768-76, 2009

# Oral delivery of plant cell encapsulated anti-TNF fusion protein for treatment of IBD

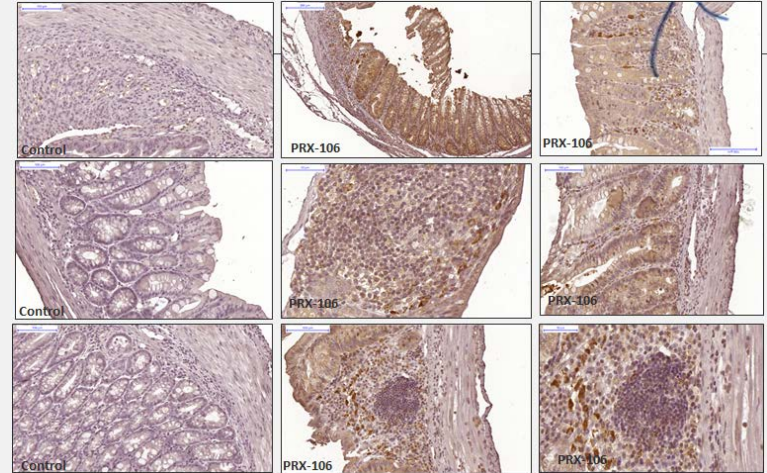
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- OPRX-106 consists of lyophilized *Nicotiana Tabacum* (BY2) tobacco plant cells expressing the recombinant TNFR2-Fc fusion protein (rTNFR2-Fc), cultivated in a bioreactor system ProCellEx®.
- The rTNFR2-Fc consists of the soluble form of the human TNF2 receptor fused to the Fc component of a human IgG1 antibody domain which imparts a longer serum half-life.
- Plant cell wall, cellulose, serves as protective agent against the gastric environment.
- The amino acid sequence of rTNFR-Fc is similar to the sequence of the approved anti TNFR agent etanercept.



# OPRX 106 - preclinical studies

- OPRX-106 localization in duodenum of DSS-colitis
- Reduction of colitis severity
- Inhibition of macrophage recruitment to inflammation site
- Reduction in serum TNF $\alpha$  levels & promotion of IL-10 levels
- Change in functional spleen regulatory T cells



Localization of OPRX-106 into the duodenum of DSS induced colitis mice model shown by staining with anti- drug antibodies.

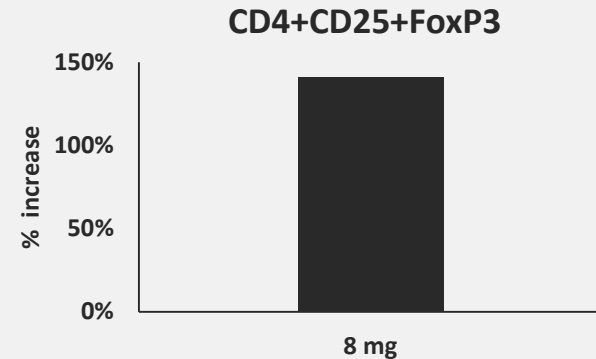
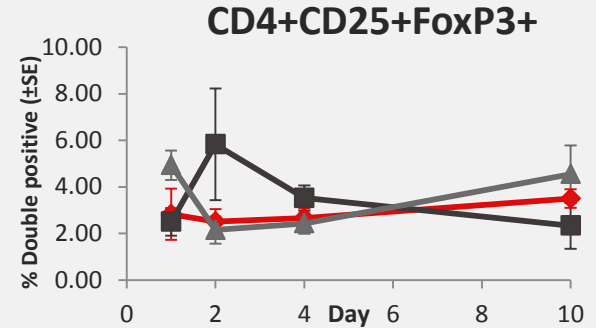
# OPRX 106: A biologically active anti-TNF $\alpha$ protein naturally encapsulated in a plant cell

## Objectives

- Potential for better safety relative to currently approved anti-TNF $\alpha$  proteins
- Potential to exert a local biological effect in the gut
- No systemic absorption

## Phase I - Healthy Volunteers

- Safe, well tolerated
- No systemic absorption
- Induced peripheral regulatory T cells
- No major effects were noted on serum cytokines



Almon E, J Immunol Methods. 2017 Jul;446:21-29.



## Phase IIa

An Open Label, Proof of Concept Study to Assess the Safety, PK and Explore Efficacy of OPRX-106 in Patients with Active Mild to Moderate Ulcerative Colitis

### **Objective:**

To determine the safety, efficacy and immune modulatory effect of oral administration of plant cells expressing the human TNFR fusion protein in patients with Ulcerative Colitis.

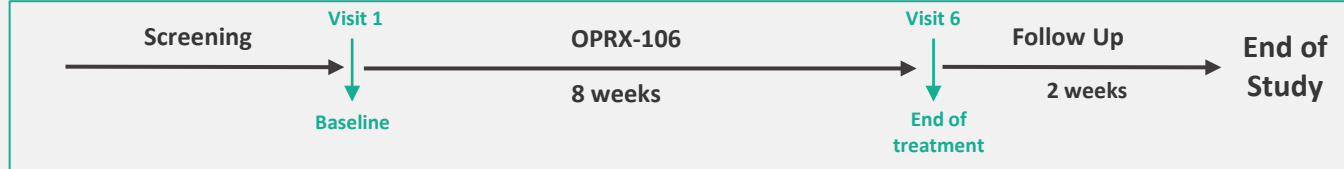


# Study Design

## Phase IIa - multi center

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- 24 mild to moderate ulcerative colitis patients
  - Age:  $\geq 18$  years
  - Active mild to moderate UC, as defined by a Mayo score of 4 to 9 (inclusive) at screening
  - High level of calprotectin ( $>100$  mg/kg of stool)
- Oral once daily administration one of two doses (2mg or 8mg) of OPRX-106 for 8 weeks



- Evaluating:
  - Safety and tolerability
  - Pharmacokinetics
  - Exploratory efficacy

# Main Exclusion Criteria

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- Severe ulcerative colitis
- Ulcerative proctitis: disease limited to less than 15 cm from the anal verge
- Use >4.8 g 5-ASA or equivalent, corticosteroid or 5-ASA enemas, foams, or suppositories within 2 weeks prior to the screening or at any time during the study
- Use of anti-inflammatory drugs (cromones, xanthines, leukotriene antagonists) or natural remedies (Probiotics, omega-3 fatty acids) within 4 weeks prior to screening or any time during the study
- Use of chronic non-steroidal anti-inflammatory (NSAID) therapy
- Use of immune suppressive agents including anti-TNF agents, Azathioprine, 6MP, Methotrexate 12 weeks prior to screening or at any time during the study

# Efficacy endpoints

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- Clinical response or clinical remission at week 8 (V6) vs. baseline (V1)
  - **Clinical response** :
    - A decrease in the Mayo score of at least 3 points, AND either a decrease in the sub-score for rectal bleeding of at least 1 point, or a rectal bleeding sub-score of 0 or 1
  - **Clinical remission** :
    - Clinically symptom free, Mayo Score  $\leq 2$ , with no individual sub-score exceeding 1 point, after treatment
- Histopathological improvement in **Geboes histological grading**
- Improvement in **hs-CRP**
- Improvement in **fecal calprotectin** levels
- Change in **systemic immune modulation parameters**

# Demographics & Baseline Characteristics

	2 mg/day (n=13)*	8 mg/day (n=11)**
<b>Mean age (years) ± SD (range)</b>	42.62 ± 10.41 (28-63)	42.64 ± 17.43 (23-73)
<b>Male : Female</b>	6:7	5:6
<b>Ethnicity</b>		
Caucasian	13	11
<b>Mean baseline values (± SD)</b>	<b>2 mg/day</b>	<b>8 mg/day</b>
Mayo score***	7.69±1.11	6.82±1.83
Geboes score	12.00±4.76	11.00±6.60

\* 2 subjects discontinued due to UC exacerbation, one subject discontinued due to lack of response, one subject discontinued due to usage of antibiotics treatment

\*\* 2 subjects discontinued due to lack of response

- Patient were enrolled in Israel, Serbia and Bulgaria
- Most of the patients were classified as having moderate UC based on Mayo score. 22/24 (92%) were 6 and above
- No discontinuations were due to adverse events.
- Dropout rate consistent with other trials in similar populations

# Pharmacokinetics and Anti Drug Antibodies

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- **Pharmacokinetics**

- The plasma pharmacokinetics results indicated that OPRX-106 is not absorbed into the circulation

- **Anti Drug Antibodies**

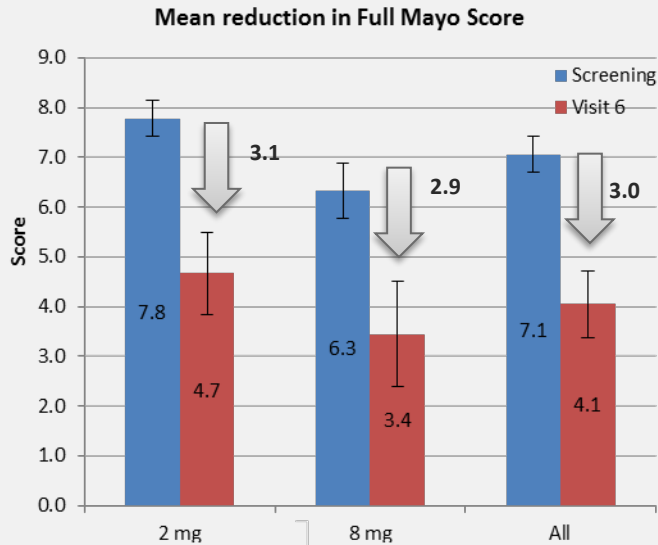
- All tested samples were reported negative to the presence of anti-drug antibodies against OPRX-106

# Safety

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- **Oral PRX-106 was well tolerated showing a potential good safety profile**
  - No SAE was reported
  - Total 40 adverse events (AEs) reported in 15 (63%) patients
    - 95% (38) were mild and moderate
    - 5% - (2) severe AEs ( nausea – possibly related, ulcerative colitis –non related)
  - 16/40 (40%) were reported as treatment related :
    - headache(4), increased CPK(2), and 1 of each of the following : Dysphagia, nausea, chills , fatigue , peripheral edema , increase appetite , dizziness , pruritus , hypertension , eosinophilia
  - 24/40 (60%) of AEs were reported as not related
  - No difference between doses (2mg or 8 mg)

# Clinical efficacy: Mayo Score



**% of patients achieving clinical remission**

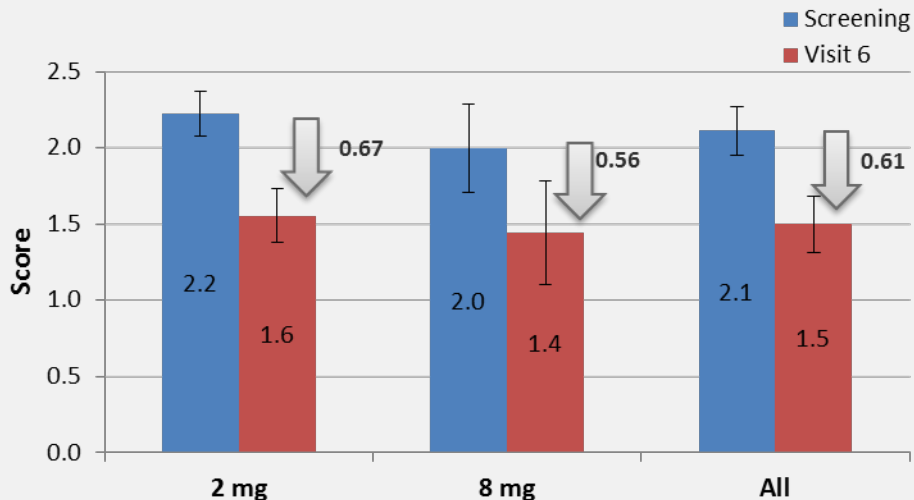


**% of patients achieving clinical response**

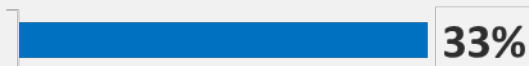


# Mucosal healing & improvement

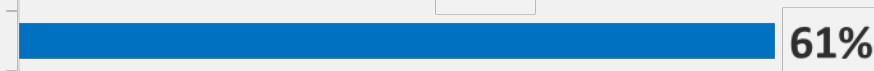
## Mean Reduction in Mayo Endoscopy Sub-score



**% of patients achieving mucosal healing**



**% of patients with improved mucosal endoscopy score**



1. Patients achieving mucosal healing- pts. with endoscopy sub-score  $\leq 1$  at V6
2. Patients with mucosal improvement- all pts. with a decrease in endoscopy sub-score at V6 (including the one patient who started with sub-score of 1 at BL)



# Improvement in Geboes Calprotectin, hs-CRP Levels

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- **Improved Geboes Score**

- 11/18 (61%) patients had an improved Geboes score

- **Reduction in Fecal Calprotectin Levels**

- A reduction in Calprotectin levels was demonstrated in 13/18 (72%) patients

- **Reduction in hs-CRP Levels**

- 14/18 (78%) of patients had an improved CRP result or had a result within the normal range (<3mg/L)

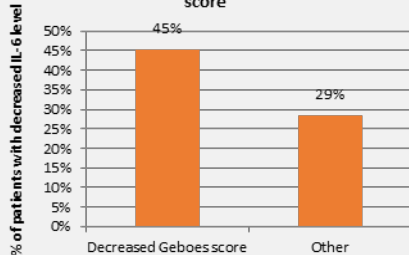
# Systemic immune-modulation by subsets of lymphocytes & serum cytokines levels

No. of patients with decreased levels of cytokine at week 8 compared to baseline			
Clinical response or remission (based on Mayo score)			
	All (n=18)	Yes (n=12)	No (n=6)
<b>IL-6</b>	7	6	1
<b>TNF<math>\alpha</math></b>	11	7	4
<b>IFN<math>\gamma</math></b>	10	7	3
Decreased Geboes score			
	All (n=18)	Yes (n=11)	No (n=7)
<b>IL-6</b>	7	5	2
<b>TNF<math>\alpha</math></b>	11	6	5
<b>IFN<math>\gamma</math></b>	10	6	4

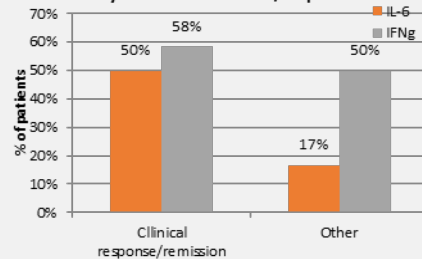
No. of patients with increased CD3+ CD4+ CD25+ FoxP3+ population at week 8 compared to baseline	
Achieving clinical response or remission (n=11)	Others* (n=6)
<b>6</b>	<b>3</b>
* Patients who did not achieved clinical response/remission in the study	

- Response to therapy was associated with a decrease in IFN $\gamma$ , TNF $\alpha$ , and IL6 pro-inflammatory cytokines.
- Response to therapy was associated with an increase in CD3+ CD4+ CD25+ regulatory lymphocytes.

Percent of patients with decreased IL-6 level – sorted by decrease in Geboes score



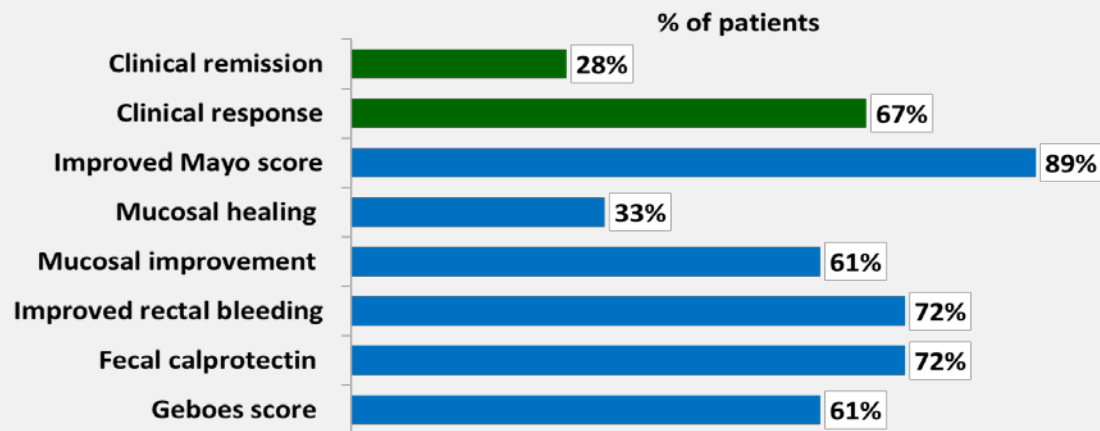
Percent of patients with decreased levels of cytokine at week 8 compared to BL – sorted by – clinical remission/response



# Summary & Conclusions

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- Oral administration using OPRX-106 was effective, safe and well tolerated.
- OPRX-106 was not absorbed systemically.
- OPRX-106 was effective as demonstrated by clinical response and improvement in various disease parameters and not associated with immune suppression.
- OPRX-106 may provide an oral, safe and effective anti-TNF $\alpha$  based therapy for IBD.



# Acknowledgements

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## Special thanks to:

- Patients participating in the study
- Study Investigators and Co-authors
- Study sites clinical teams





Thank You

# Responder analysis

Patient	Dose	Age	Sex	Full Mayo score					Mayo endoscopic sub-score				Geboes			hs-CRP				Calprotectin		
				Screening	Change from Sc	Clinical remission	Clinical response	Improved	Screening	Change from Sc	Mucosal healing	Mucosal improvement	Screening	Change from Sc	Improved	Baseline	Change from BL	Improved	Remained within normal range	Baseline	Change from BL	Improved
1	2 mg	38	Female	6	-5	v	v	v	2	-1	v	v	10	2		0.8	10.5			125	-86	v
2	2 mg	49	Female	7	-4		v	v	2	-1	v	v	12	-7	v	0.4	-0.2	v		1118	32	
3	2 mg	46	Male	8	-1			v	2	0			7	1		2.2	0.7		v	1859	-412	v
4	2 mg	54	Female	9	-4		v	v	2	-1	v	v	16	-5	v	11.3	0.5			1976	-1663	v
5	2 mg	31	Female	9	0				2	0			16	-6	v	38.5	-8	v		4640	-2939	v
6	2 mg	63	Female	8	-4		v	v	2	-1	v	v	15	-3	v	11.9	-10	v		1943	-135	v
7	2 mg	56	Male	7	-1			v	2	0			5	8		1	1.4		v	590	-348	v
8	2 mg	41	Female	9	-4		v	v	3	-1		v	7	11		14.7	-3.8	v		2075	-673	v
9	2 mg	28	Female	7	-5		v	v	3	-1		v	10	7		0.3	0.7		v	66	36	
10	8 mg	63	Female	8	-6	v	v	v	2	-1	v	v	15	-13	v	1.3	-0.8	v		65	-50	v
11	8 mg	41	Female	4	-4	v	v	v	1	-1		v	9	-5	v	0.6	0.7		v	63	-21	v
12	8 mg	31	Male	6	-2			v	3	-1		v	19	-5	v	4.3	-1.8	v		1041	-147	v
13	8 mg	27	Male	4	-3	v	v	v	1	0			1	2		0.7	0.1		v	238	-156	v
14	8 mg	33	Male	7	-6	v	v	v	2	-2	v	v	13	-12	v	6.1	-0.5	v		134	29	
15	8 mg	73	Female	7	-2			v	3	0			16	-5	v	61.3	-20.8	v		1812	-1448	v
16	8 mg	23	Female	6	4				1	1			5	6		1.9	1.1			813	-305	v
17	8 mg	68	Male	6	-4		v	v	2	0			7	-3	v	11.3	65			798	742	
18	8 mg	44	Male	9	-3		v	v	3	-1		v	14	-7	v	32.9	-26.2	v		245	619	