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

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PROTALIX Biotherapeutics

Disclosure Information

- 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

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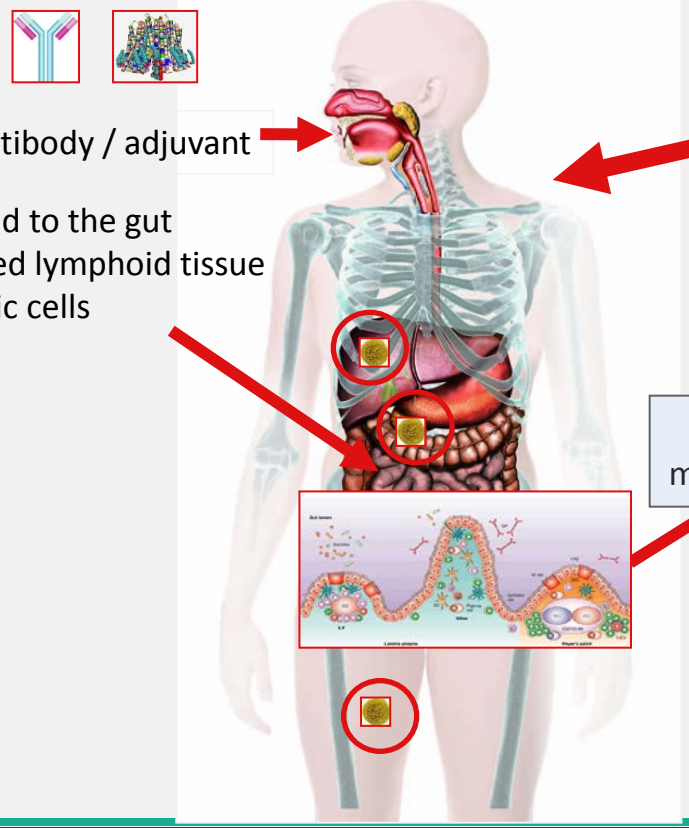
Oral immunotherapy: modulation of the systemic immune response via alteration of the gut immune system without immune suppression



Antigen / Antibody / adjuvant

Presented to the gut associated lymphoid tissue /dendritic cells

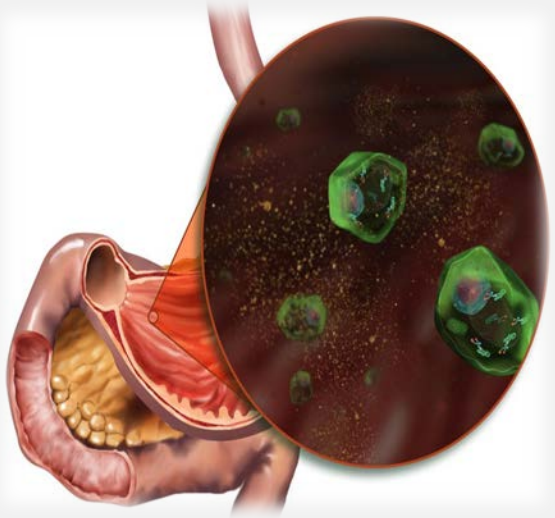
Target organs
- Liver
- Pancreas
- Adipose tissue
- Bowel
- Muscle

T-cell alteration in mesenteric lymph nodes

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

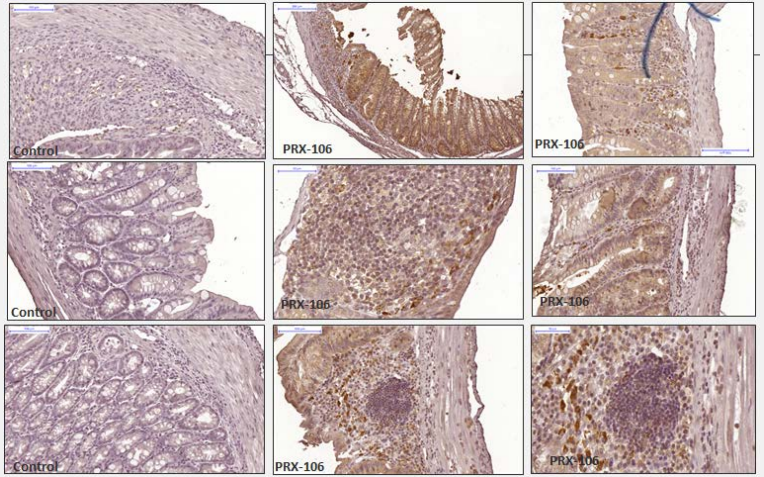
Oral delivery of plant cell encapsulated anti-TNF fusion protein for treatment of IBD

- 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 TNFα 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.

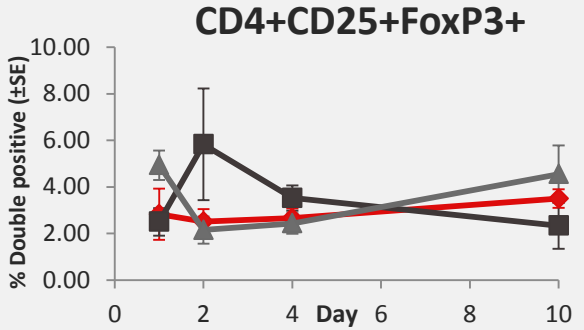
OPRX 106: A biologically active anti-TNFα protein naturally encapsulated in a plant cell

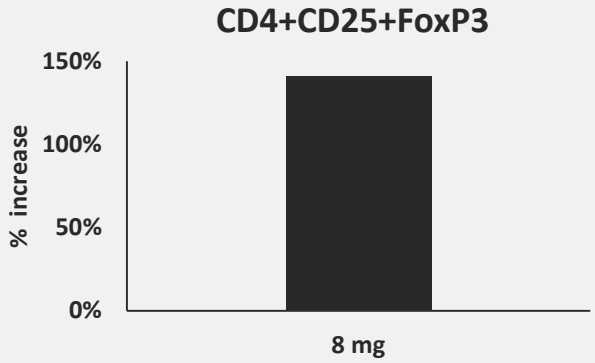
Objectives

- Potential for better safety relative to currently approved anti-TNFα 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

- 24 mild to moderate ulcerative colitis patients
  - Age: ≥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

- 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

- 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 ≤ 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)**
Mean age (years) ± SD (range)	42.62 ± 10.41 (28-63)	42.64 ± 17.43 (23-73)
Male : Female	6:7	5:6
Ethnicity		
Caucasian	13	11
Mean baseline values (± SD)	**2 mg/day**	**8 mg/day**
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

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

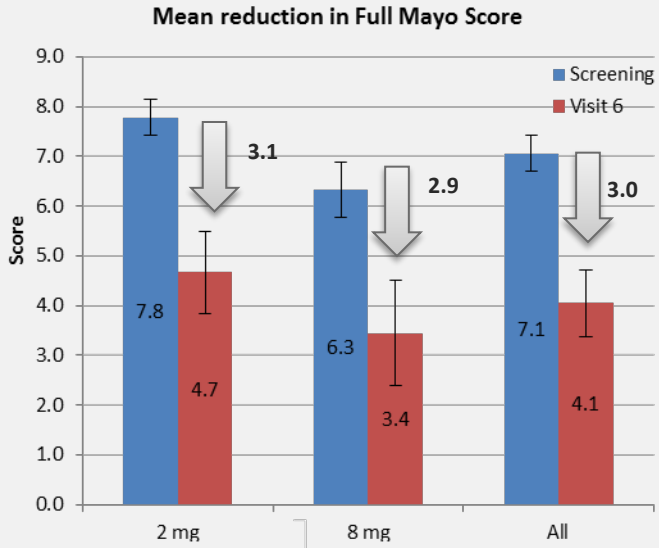
- **Anti Drug Antibodies**
  - All tested samples were reported negative to the presence of anti-drug antibodies against OPRX-106

Safety

- **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)

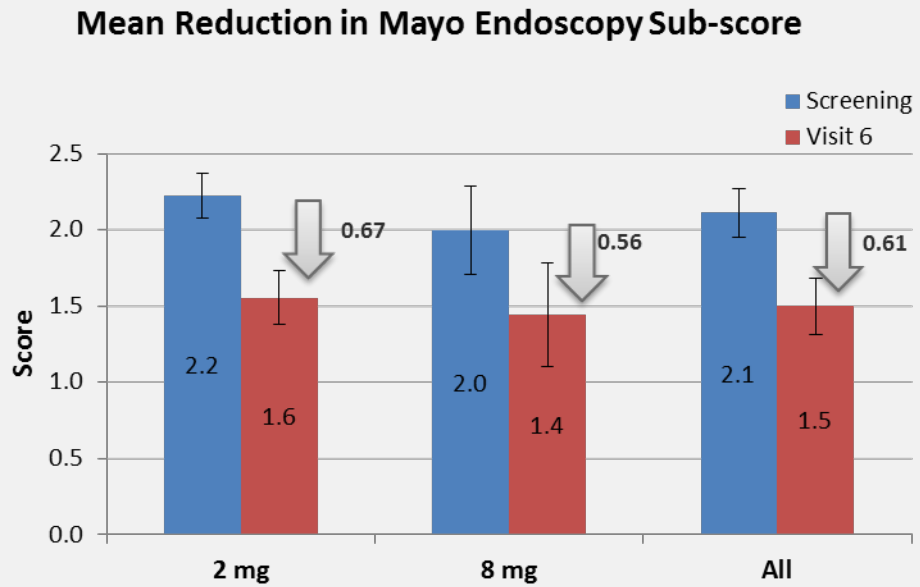
Clinical efficacy: Mayo Score



% of patients achieving clinical remission — 28%

% of patients achieving clinical response — 67%

Mucosal healing & improvement



1. Patients achieving mucosal healing- pts. with endoscopy sub-score ≤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)

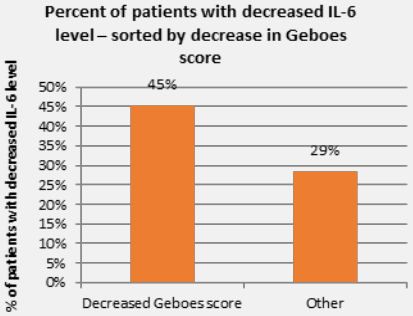
Improvement in Geboes Calprotectin, hs-CRP Levels

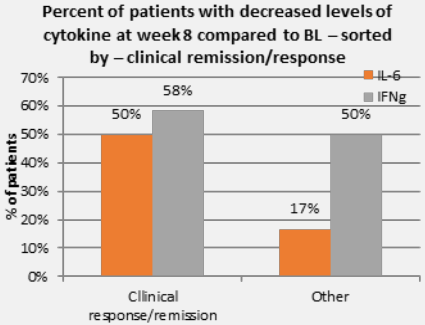
- **Improved Geboes Score**
  - 11/18 (61%) patients had an improved Geboes score
- **Reduction in Fecal Calprotectin Levels**
  - A reduction in Calprotectin levels was demonstrated in 13/18 (72%) patients
- **Reduction in hs-CRP Levels**
  - 14/18 (78%) of patients had an improved CRP result or had 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)**
IL-6	7	6	1
TNFα	11	7	4
IFNγ	10	7	3
Decreased Geboes score			
	All (n=18)	**Yes (n=11)**	**No (n=7)**
IL-6	7	5	2
TNFα	11	6	5
IFNγ	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)**
6	**3**
* Patients who did not achieved clinical response/remission in the study	

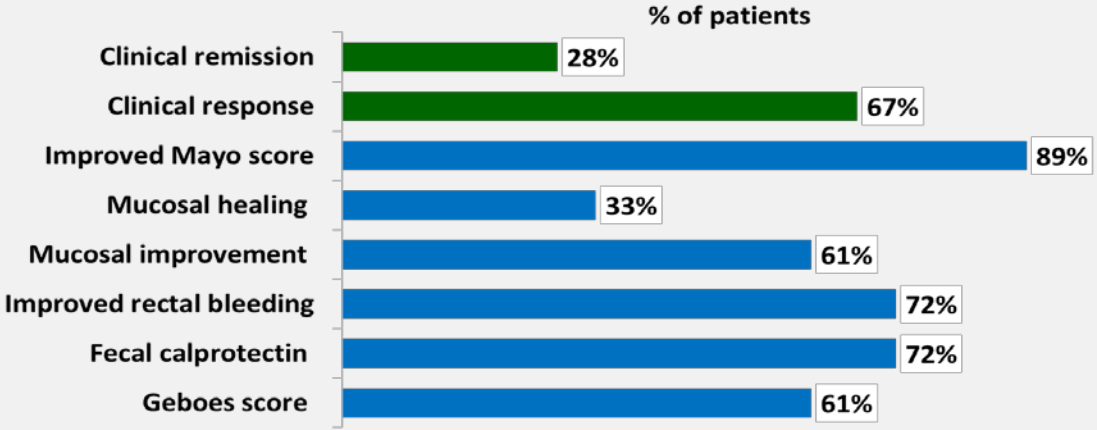




- Response to therapy was associated with a decrease in IFNγ, TNFα, and IL6 pro-inflammatory cytokines.
- Response to therapy was associated with an increase in CD3+ CD4+ CD25+ regulatory lymphocytes.

Summary & Conclusions

- 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-TNFα based therapy for IBD.



Acknowledgements

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

Thank You

Responder analysis

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