Phase II, Randomized, Double Blind, Controlled Trial of the Efficacy of Active Therapeutic Immunization with TNF-Kinoid in Patients with Moderate to Severe Crohn's Disease with Secondary Resistance to TNFα Antagonist

Dewit, Olivier1; Hebuterne, Xavier2; Dupas, Jean-Louis3; Howaldt, Stefanie M.4; Bures, Jan5; Schreiber, Stefan6; Pace, Andrea 7; Klaus, Jochen8; Bouhnik, Yoram9; Reinshagen, Max10; Allez, Matthieu11; Hoffmann, Peter12; D'Haens, Geert R.13; van Bodegraven, Adriaan A.14; Stimac, Davor15; Goetz, Martin16; Kahi, Sandrine17; Vandepapeliere, Pierre17; Colombel, Jean-Frédéric18; Rutgeerts, Paul J.19; Vermeire, Severine19

1. Saint-Luc Hospital, Brussels, Belgium. 2. L'Archet 2 Hospital, Nice, France. 3. CHU Hôpital Nord, Amiens, France. 4. Hamburgisches Forschungsinstitut für CED, Hamburg, Germany. 5. Faculty Hospital in Hradec Kralove, Hradec Kralove, Czech Republic. 6. University Medical Center Schleswig-Holstein, Kiel, Germany. 7. Universitätsklinikum Hamburg-Eppendorf , Hamburg, Germany. 8. Universitätsklinikum Ulm, Ulm, Germany. 9. Beaujon Hospital, Clichy, France. 10. Klinikum Braunschweig, Braunschweig, Germany. 11. Saint-Louis Hospital, Paris, France. 12. Kliniken-Essen-Mitte/Evang. Huyssenstiftung, Essen, Germany. 13. Academisch Medisch Centrum, Amsterdam, Netherlands. 14. VU University Medical Center, Amsterdam, Netherlands. 15. Clinical Hospital Centre Rijeka, Rijeka, Croatia. 16. Johannes Gutenberg University, Mainz, Croatia. 17. Neovacs, Paris, France. 18. Claude Huriez Hospital, Lille, France. 19. UZ Gasthuisberg, Leuven, Belgium.

Contact: pvandepapeliere@neovacs.com

1. ABSTRACT

Background: TNFα antagonists have largely demonstrated their efficacy in both induction and maintenance of clinical response and remission in patients with Crohn's disease (CD). However up to 40% of the patients do not fully respond to induction therapy and a complete response is maintained over a year in less than 50% of patients. In a first phase I/II study in patients with moderate to severe active CD, immunization with a TNF-Kinoid induced self, polyclonal anti-TNFα antibodies in 89% of the patients. No safety issue was detected. Furthermore, clinical disease appeared to be positively affected by the treatment: up to 50% of the patients in the two highest dose groups were in clinical remission (CDAI≤ 150) from week 4 to week 20. These promising results supported a confirmatory randomized study of treatment with TNF-K in patients with CD. Objectives: We evaluated the clinical efficacy, safety and immunogenicity of TNF-K in patients with moderate to severe active CD who have developed secondary resistance and/or intolerance to at least one TNFα antagonist.

Material and Methods: TNF-Kinoid (TNF-K, Neovacs SA, Paris, France) is an immunotherapeutic composed of recombinant human TNFα conjugated to Keyhole Limpet Hemocyanin (KLH) as a carrier protein, inactivated and adjuvanted with ISA-51 emulsion. Sixty-eight patients with moderate to severe active CD (CDAI between 220 and 450) have been enrolled in a randomized doubleblind, placebo-controlled study. All patients had evidence of mucosal ulcerations at ileocolonoscopy and a history of positive clinical response followed by secondary failure and/or intolerance to at least one TNFα antagonist. Patients randomized in the TNF-K group were receiving TNF-K at days 0, 7, 28, 84 and placebo at days 91 and 112. Patients randomized in the control group were receiving placebo at days 0, 7, 28, and TNF-K at days 84, 91 and 112. TNF-K was injected intramuscularly at the dose of 180 mcg per injection. The primary end point was CDAI clinical remission (CDAI≤150) at week 8. Other efficacy end-points included mucosal healing at week 12 and evolution of calprotectin and C-reactive protein. Immune responses were evaluated through titration of anti-TNFα and anti-KLH antibodies.

Results: All patients have been recruited. Few mild or moderate transient local and systemic reactions have been recorded following immunizations. The only serious adverse event reported by the investigator as potentially related to the study drug was a deterioration of CD one month following administration of blinded treatment. There were no other safety concerns. Full analysis is ongoing.

Conclusions: Active immunization with TNF-K in patients with Crohn's disease is safe. Full immunogenicity and clinical efficacy results will be presented.

2. INTRODUCTION

The TNFα kinoid (TNF-K) is a biological TNFα-specific, selective and active immunotherapeutic designed for the treatment of TNFα-mediated chronic and auto-immune diseases, including Crohn's disease (CD), rheumatoid arthritis and psoriasis.

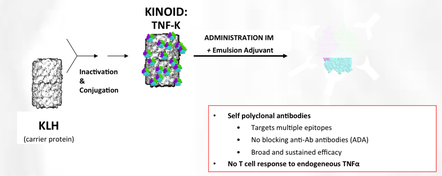

Figure 1. TNF-K structure. TNF-K is a heterocomplex consisting of inactivated recombinant human (rhu)-TNFα coupled to a T-helper carrier protein, Keyhole Limpet Hemocyanin (KLH). The injectable form for intramuscular administration consists of TNF-K emulsified with the adjuvant ISA-51vg at a 1:1 (v/v) ratio.

3. PATIENT POPULATION:

Inclusion criteria: Male or female aged 18 to 65 years, Crohn's Disease for at least 6 months; Crohn's Disease Activity Index (CDAI) score ≥ 220 and ≤ 450, and presence of mucosal ulcerations in at least 2 segments, or ulcerations on ≥ 10% of the mucosal surface if only one segment is involved. Have developed secondary resistance to anti-TNFα therapy that must have followed at least 6 months of continuous anti-TNFα therapy during which a positive clinical response has been observed; or Have developed intolerance to an anti-TNFα treatment

Exclusion criteria: Primary non-response to a previously received treatment directed against TNFα, Or Intolerance related to the primary pharmacological effect of anti-TNFα; History of severe systemic bacterial, fungal, viral, or parasitic infections within the 3 months prior to screening; or the occurrence of any acute infection within 2 weeks of the first administration of study drug.

Treatment with immunosuppressive or immunomodulatory drugs, including, but not limited to:

B-cell depleting therapy within 1 year of the first administration of study drug;

Cyclophosphamide , Cyclosporine , TNFα blockers other than infliximab, adalimumab or certolizumab, Biological agents other than TNFα blockers , Use of any investigational or non-registered product (drug or vaccine) within 12 weeks of the first administration of study drug;

Need for emergency surgery (uncontrollable hemorrhage, persistent non-inflammatory intestinal obstruction - at the Investigator's discretion - or perforation), or surgery in the 4 weeks preceding the first administration of study drug.

4. END POINTS and ANALYSIS:

Primary: rate of remission (≤150) at week 8 as compared to baseline

Secondary:

- Clinical responses (CDAI-70; CDAI-100)
- Endoscopic responses (CDEIS-50%; SES-CD-50%) at week 12
- Mucosal healing (no ulcerations) at week 12
- Steroid sparing and steroid free remission at week 12
- Biological responses: calprotectin levels in stools and CRP serum levels
- Inflammatory Bowel Disease Questionnaire
- Immunogenicity: anti-TNFα and anti-KLH antibodies; anti-drug antibodies
- Safety: recording of AE's throughout the study; recording on diary cards of local and systemic reactions during 7 days following each administration; vital signs; ECG; Biology

Interim analysis is performed after a first cohort of 66 patients has completed week 12 visit.

If p≥0.05 for primary end-point, recruitment of a second cohort of 66 patients

5.STUDY DESIGN

Double-blind, placebo controlled, partially cross-over, double-dummy trial

Patients were randomized 1:1 to receive kinoid (180 mcg per dose) or matching placebo at day 0, 7 and 28

Kinoid recipients were administered a fourth dose at week 12, followed by placebo at week 13 and 16

Placebo recipients then received 3 kinoid doses at week 12, 13 and 16

Ileocolonoscopy at week 0 and 12, central reading

	W0	W4	W8	W12	W16	W20	W24	W28
	D0-D7	D28		D0-D7	D28			
KINOID	K1-K2	K3		K4-P1	P2			
PLACEBO	P1-P2	P3		K1-K2	K3			
	ILEO-COLONOSCOPY		PRIMARY ANALYSIS CDAI	ILEO-COLONOSCOPY				FINAL ANALYSIS

6. RESULTS

Only the blinded baseline characteristics of the first cohort of patients are presented here. The results of the interim analysis are not available yet.

Between February and December 2011 , 89 patients have been screened and 72 randomized in the study. 68 patients have received at least one injection of kinoid or placebo, 63 have received 3 injections.

Kinoid administration was generally well tolerated.15 Serious Adverse Events have been reported in 14 patients: 12 complications related to Crohn's disease, 1 urinary tract infection, 1 pneumonia and 1 pregnancy.

Two episodes of CD worsening were rated as SAEs possibly related to study medications by the investigators.

		GROUP A	GROUP B	TOTAL
N PATIENTS		36	36	72
GENDER	FEMALE	25 (69%)	21 (58%)	46 (64%)
	MALE	11 (31%)	15 (42%)	26 (36%)
AGE	MEAN	35.8	37.3	36.5
	STD	13.20	9.51	11.45
ETHNICITY	WHITE-CAUCASIAN	34 (94%)	35 (97%)	69 (96%)
	OTHERS	2 (6%)	1 (3%)	3 (4%)
SMOKING STATUS	CURRENT SMOKER	9 (25%)	16 (44%)	25 (35%)
	FORMER SMOKER	7(19%)	8(22%)	15 (21%)
	NEVER SMOKED	20 (56%)	12(34%)	32 (44%)

CROHN'S DISEASE CHARACTERISTICS		GROUP A	GROUP B	TOTAL
	N	36	36	72
CDAI score	Mean	316.5	305.3	310.7
	Std	78.9	57.56	68.46
CRP	HIGH ≥ 6 mg/L	20 (56%)	25 (69%)	45 (63%)
	LOW < 6 mg/L	16 (44%)	10 (28%)	26 (31%)
	Missing	-	1 (3%)	1 (1%)
CALPROTECTIN LEVEL IN STOOLS (mg/kg)	Mean	523.7	423.1	473.4
	Std	541.62	312.22	441.57
CDEIS score	Mean	21.8	18.7	20.2
	Std	13.83	10.01	12.02
SES-CD score	Mean	17.2	16.8	17.0
	Std	8.98	8.32	8.58
N segments with mucosal ulcerations	1 (≥ 10% surface)	15 (42%)	9 (25%)	24 (33%)
	2	13 (36%)	15 (42%)	28 (39%)
	3	6 (16%)	8 (22%)	14 (19%)
	4	1 (3%)	3 (8%)	4 (6%)
	5	1 (3%)	1 (3%)	2 (3%)

PRIOR ANTI-TNFα THERAPY	GROUP A	GROUP B	TOTAL
N	36	36	72
IFX	11(31%)	9 (25%)	20 (28%)
IFX – CTZ	-	1 (3%)	1 (1%)
ADA	9 (25%)	8 (22%)	17 (24%)
ADA – IFX	13 (36%)	16 (44%)	29 (40%)
ADA – IFX - CTZ	3 (8%)	2 (6%)	5 (7%)

IFX: Infliximab; CTZ: Certolizumab; ADA: Adalimumab

CONCOMMITANT THERAPY	GROUP A	GROUP B	TOTAL
N	36	36	72
Corticosteroids (≤ 25mg/d)	8 (22%)	10 (28%)	18 (25%)
Methotrexate (≤ 25mg/w)	1 (3%)	5 (14%)	6 (8%)
Azathioprine (≤ 2.5mg/kg/d)	7 (19%)	6 (17%)	13 (18%)
Sulfazalazinz or mesalazine (≤4g/d)	7 (19%)	9 (25%)	16 (22%)

8. DISCUSSION AND CONCLUSIONS

- The patients characteristics are similar in both groups
- The mean CDAI and endoscopic scores as well as the biological markers indicate a severe disease.
- Close to 50 % of the patients had developed secondary resistance and/or intolerance to more than 1 TNFα antagonist
- Safety results available thus far indicate the absence of safety concern related to TNF kinoid administration
- Full results will be available soon

Acknowledgements:

The following investigators have also randomized one patient: Belgium: P Bossuyt, Bonheiden, M Devos, Gent - Croatia: M Kozic, Zadar - Czeck Republic: M Konecny, Olomouc; M Lukas, Praha. - France: P Desreumaux, Lille ; D Laharie, Bordeaux; E Lerebourg, Rouen; J Moreau, Toulouse; L Peyrin-Biroulet, Nancy; JM Reymund, Caen - Germany: A Stallmach, Iena; A Sturms, Berlin; N Teich, Leipzig - Hungary: P Lakatos, Budapest;

Author Disclosures

Xavier Hebuterne - Board Membership: UCB, Baxter Healthcare Corporation; Consulting: Nestlé Clinical Nutrition; Grant/Research Support: Fresenius Kabi; Speaking and Teaching: Nutricia, Abbott Laboratories , MSD; Stefan Schreiber - Advisory Committees or Review Panels: Abbott, AstraZeneca Pharmaceuticals, Bayer AG, Berlex Laboratories, Bristol-Myers Squibb, Centocor, Chemocentryx, Ferring Pharmaceuticals, Otsuka Pharma., Progenika Biopharma , Genentech, Schering-Plough, Shire Pharmaceuticals Group, UCB Pharma, Novartis Pharmaceuticals, Pfizer Inc , NovoNordisk; Grant/Research Support: AstraZeneca Pharmaceuticals, UCB Pharma, Shire Pharmaceuticals Group; Speaking and Teaching: Falk Foundation

Yoram Bouhnik - Advisory Committees or Review Panels: Norgine Ltd., Ferring Pharmaceuticals Inc , Bristol-Myers Squibb Co. ; Speaking and Teaching: Abbott Laboratories, Schering-Plough Corp; Max Reinshagen - Grant/Research Support: Falk Pharma; Matthieu Allez - Advisory Committees or Review Panels: Novo Nordisk A/S, Ferring Pharmaceuticals Inc, TxCell; Speaking and Teaching: Abbott, MSD; Geert R. D'Haens - Advisory Committees or Review Panels: Jansen Biologics, Abbott, TEVA, Glaxo SmithKline, Shire Pharmaceuticals Inc., Nova Nordisk A/S, Pfizer Inc ; Consulting: MSD, UCB, Inc.; Grant/Research Support: Falk Pharma, MSD; Speaking and Teaching: MSD, UCB, Inc., Abbott, Ferring Pharmaceuticals Inc ; Adriaan A. van Bodegraven - Advisory Committees or Review Panels: Abbott, Merck & Co; Grant/Research Support: Ferring Pharmaceuticals Inc ; Speaking and Teaching: Abbott, Ferring Pharmaceuticals Inc

Martin Goetz - Grant/Research Support: Optiscan; Speaking and Teaching: PENTAX, Abbott Laboratories, MSD, Falk Foundation; Sandrine Kahi - Employment: Neovacs; Pierre Vandepapeliere - Patent Held/Filed: Neovacs; Jean-Frederic Colombel - Advisory Committees or Review Panels: Abbott, Centocor, Inc.; Consulting: Abbott, ActoGeniX, Albireo Pharma, AstraZeneca Pharmaceuticals LP, Bayer AG, Biogen Idec, Boehringer Ingelheim GmbH, Bristol-Myers Squibb Co. , Cellerix SL, Centocor, Inc, Chemocentryx, Cosmo Technologies Ltd, Danone Research, Elan Pharmaceuticals, Inc., Genentech Inc., Giuliani SpA, GlaxoSmithKline, Given Imaging , Hutchison MediPharma Limited; Speaking and Teaching: Abbott, Centocor, Inc., Elan Pharmaceuticals, Inc. , Given Imaging ; Paul J. Rutgeerts - Consulting: UCB Pharma, Merck, Bristol-Myers Squibb, Genentech Inc., Abbott, Centocor, Inc., Millenium, Neovacs, Actogenics, Robarts, Amgen; Grant/Research Support: UCB Pharma, Abbott, Centocor, Merck & Co; Speaking and Teaching: Abbott, Merck & Co; Severine Vermeire - Advisory Committees or Review Panels: Ferring Pharmaceuticals, Shire Pharmaceuticals Group, Pfizer; Consulting: AstraZeneca Pharmaceuticals, Ferring Pharmaceuticals; Grant/Research Support: UCB Pharma; Speaking and Teaching: Abbott, Schering-Plough, Ferring Pharmaceuticals, UCB Pharma

The following people have nothing to disclose: Olivier Dewit, Jean-Louis Dupas, Stefanie M. Howaldt, Jan Bures, Andrea Pace, Jochen Klaus, Peter Hoffmann, Davor Stimac