OP006
Correlation of durability of response, serum trough concentrations and outcome parameters: long-term follow-up of the Trough Concentration Adapted Infliximab Treatment (TAXIT) trial

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Background: The Trough Concentration Adapted Infliximab Treatment (TAXIT) randomized controlled trial [1] showed that targeting patients' infliximab trough concentrations in a 3–7 μg/mL window resulted in a more efficient use of the drug in patients with inflammatory bowel disease (IBD). However, following dose optimization, continued concentration-based dosing was not superior to clinically-based dosing for achieving a co-primary endpoint of clinical and biological remission after 1 year.
Methods: This was a retrospective analysis of the long-term outcome of all 226 patients who completed the TAXIT maintenance phase. Durability of response to infliximab was correlated with serum trough concentrations and important quality of care outcome parameters, including need for IBD-related hospitalization, need for abdominal surgery and steroid use.
Results: With a median follow-up of 41 months after the completion of the TAXIT trial, 167/215 (78%) patients were still on continued treatment with infliximab, and 48/215 (22%) patients needed to stop (11 patients were lost to follow-up). Among the 48 patients who discontinued infliximab, 10/27 (37%) randomized previously to the clinically-based dosing arm did so within 1 year, compared to 2/21 (10%) patients randomized to the concentration-based dosing arm ($p<0.05$).
Among the 167 patients who continued infliximab, the dosing scheme was intensified in 56 patients and de-intensified in 27 patients, compared to the end of the TAXIT maintenance phase. Median trough concentrations of infliximab at the end of follow-up were 4.73 μg/mL (IQR=3.3–6.42). Five patients developed immunogenicity within 1 year after TAXIT and all had been randomized to the clinically-based dosing arm. In patients continuing on infliximab, the rates of IBD-related hospitalization (16/167 patients or 9.6%), abdominal surgery (4/167 patients or 2.4%) and steroid use (6/167 patients or 3.6%) during the entire follow-up period were very low and significantly better than in patients who had to discontinue infliximab.

Table 1. Outcome parameters in patients who continued infliximab vs. patients who discontinued infliximab

	Continuation of infliximab (n=167)	Discontinuation of infliximab (n=48)	p-value
Hospitalization	16 (9.6%)	16 (33.3%)	<0.001
Abdominal surgery	4 (2.4%)	10 (20.8%)	<0.001
Steroid use	6 (3.6%)	16 (33.3%)	<0.001

Conclusions: In this long-term follow-up of the TAXIT trial, infliximab discontinuation occurred earlier in patients treated in the clinically-based dosing arm than in patients treated in the concentration-based dosing arm. Targeting infliximab trough concentrations to a therapeutic window led to a highly durable treatment response, and was associated with very good outcomes including very low (<5%) surgical rates and steroid use.

References:
[1] Vande Casteele et al, (2015), Trough concentrations of infliximab guide dosing for patients with inflammatory bowel disease, Gastroenterology

OP007
A multi-centre double blind randomised placebo-controlled study of the use of rectal tacrolimus in the treatment of resistant ulcerative proctitis

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Background: Resistant ulcerative proctitis can be extremely difficult to manage. Topically administered tacrolimus, however, may be effective in difficult-to-treat proctitis
Methods: This was randomized, double-blind, placebo-controlled induction trial of rectal tacrolimus in patients with active ulcerative colitis funded by the Broad Medical Research Program (Clinicaltrials.gov registration: NCT01418131). Eleven patients received rectal tacrolimus (0.5mg/ml), and 10 placebo, for 8 weeks. The primary endpoint was clinical response by using the Mayo clinic score.
Results: An interim analysis after 20 patients had completed the study demonstrated highly significant differences between the groups and the study was closed due to ethical considerations with patients already recruited allowed to complete the study. The primary endpoint was met in 8/11 (73%) patients receiving rectal tacrolimus and 1/10 patients receiving placebo (10%; p=0.004). Of the secondary endpoints, 5 (45%) rectal tacrolimus patients achieved clinical remission compared to none receiving placebo (p=0.015). Mucosal healing at week 8 was achieved in 8 (73%) patients receiving rectal tacrolimus compared to 1 (10%) receiving placebo (p=0.004). The IBDQ increased ≥16 points over baseline in 5 (45%) of the

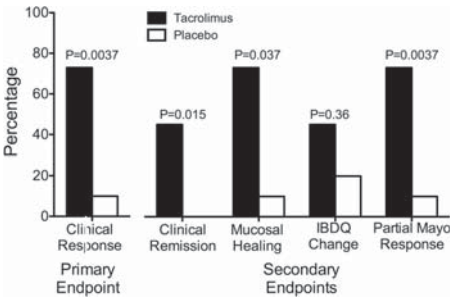

Figure 1. Primary and secondary endpoints.

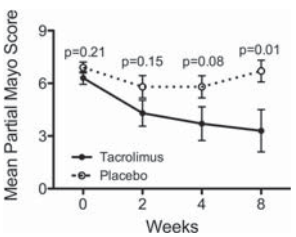

Figure 2. Mean partial Mayo score.

tacrolimus and 2 (20%) of the placebo patients (p=0.36). Finally, the average partial Mayo score was numerically lower in the tacrolimus-treated group compared to placebo at week 2 (4.3±0.74 vs. 5.8±0.64; p=0.15) and week 4 (3.7±0.96 vs. 5.8±0.6; p=0.08) but was significantly lower at week 8 (3.3±1.2 vs. 6.7±0.62; p=0.01). There were no safety issues identified with rectal tacrolimus use.

Conclusions: Rectal tacrolimus was more effective than placebo for induction of a clinical response, clinical remission and mucosal healing in resistant ulcerative proctitis

OP008
An innovative treatment for refractory perianal fistulas in Crohn's disease: local micro reinjection of autologous fat and adipose derived stromal vascular fraction

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Background: Mesenchymal cell therapy is promising for the treatment of perianal Crohn's fistulas refractory to conventional therapy. Autologous adipose-derived stromal vascular fraction (ADSVF) is recognized as an easily accessible source of cells with angiogenic, anti-inflammatory, immunomodulatory and regenerative properties. ADICROHN pilot study is based on the innovative hypothesis that combined action of ADSVF associated with trophic charasteristics of microfat graft could be beneficial to Crohn patients with refractory perianal fistulas.

Methods: This is a prospective, open, non-comparative, single center, phase I-II clinical trial. Eligible patients are aged >18 years and diagnosed with complex perianal fistula associated with Crohn's disease at least for 6 months with controlled luminal disease (CDAI<220). Fistula(s) had to be refractory to conventional treatment. It was planned to enroll 10 patients. Patients are first subjected to an exam under anaesthesia with drainage by seton placement if indicated, followed at least one week later on the same day by adipose tissue extraction, ADSVF and microfat preparation then injected into the fistula. Patients are monitored at baseline and at 1, 2, 6, 12, 16 and 48 weeks after injection for safety and efficacy analysis. Safety analysis includes at every visits clinical assessment of adverse events. Efficacy analysis includes at every visit clinical evaluation of fistula closure, evaluation of disease activity by PDAI/CDAI scores, and assesment of quality of life by SIBDQ. Fistula closure is also evaluated via radiological assessment with MRI (confirmation of absence of collections >2 cm of the treated perianal fistula) at week 12 and 48.

Results: Since October 2015, 9 patients were treated by this innovative local treatment (among 10 cc of microfat and about 30 millions of ADSVF viable cells subsequently injected into the soft tissue around the fistulas). No serious adverse events have been described. The only side effect were moderate pain on lipoaspiration site. Preliminary efficacy datas at week 12 for the first 7 treated patients showed 71% of response and 28% of complete healing, significant reduction of discharge (p<0.001), significant reduction of severity of perianal disease (p=0.045) and significant improvement of quality of life (p=0.039).

Conclusions: This first study evaluating co-local administration of ADSVF in association with fat graft appears to be a simple, safe and efficient surgical regenerative therapy for perianal Crohn's fistula refractory to conventional therapy.

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OP009
Long-term efficacy and safety of Cx601, allogeneic expanded adipose-derived mesenchymal stem cells, for complex perianal fistulas in Crohn's disease: 52-week results of a phase III randomised controlled trial

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Background: Existing therapies for perianal fistulas in Crohn's disease (CD) are associated with a high failure rate and few have been evaluated in randomised controlled trials (RCTs) using hard endpoints. The 24-week results of a RCT showed that Cx601 added onto standard of care was safe and effective for treatment-refractory complex perianal fistulas with a significantly greater proportion of patients achieving clinical and radiological combined remission (CR) compared with placebo+standard of care. We aimed to determine whether this efficacy and safety was maintained over the long-term (52 weeks) (NCT01541579).

Methods: Patients with inactive or mildly active luminal CD and treatment-refractory, draining, complex perianal fistulas were randomised (1:1) to Cx601 (single injection of 120 million eASC to all tracts+standard of care) or control (placebo+standard of care) in this phase III, double-blind, parallel-group multicentre study. An unblinded surgeon administered the treatment and a blinded gastroenterologist evaluated the therapeutic effect. Efficacy was evaluated in the mITT (randomised, treated and ≥1 post-baseline efficacy assessment) population at week 52. Pre-specified endpoints included CR (closure of all treated external openings [EOs] that were draining at baseline assessed clinically, and absence of collections >2 cm in the area of the treated perianal fistulas by blinded central MRI reading) and clinical remission (closure of all treated EOs). Sustained CR at week 52 was also evaluated.

Results: 212 patients were randomised to Cx601 (n=107) or control (n=105); 61.8% completed the 52-week follow-up (Cx601, n=70; control=61). The beneficial effect observed at week 24 (CR in Cx601 51.5%, control 35.6%; p=0.021) was sustained at week 52; a significantly greater proportion of patients receiving Cx601 vs control achieved CR (56.3% vs 38.6%; p=0.010), and clinical remission (59.2% vs 41.6%; p=0.013) at week 52. Of patients with CR at week 24, a greater proportion of those treated with Cx601 vs control had no relapse at week 52 (75.0% vs 55.9%). Rates and types of treatment related adverse events were similar in both groups (20.4%, Cx601 vs 26.5%, control).

Conclusions: The efficacy of Cx601 in treatment-refractory complex perianal fistulas of CD patients was sustained for up to 1 year after a single administration. The results also support the favourable tolerability of Cx601 over the long-term.