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Phase IIB, Randomized, Placebo-Controlled Evaluation of the Efficacy and Safety of Induction Therapy With Eldelumab (Anti-IP-10 Antibody; BMS-936557) in Patients With Active Ulcerative Colitis

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Background: Interferon-γ-inducible protein-10 (IP-10) is involved in inflammatory cell migration and the survival and migration of gut epithelial cells. IP-10 expression is increased in patients with ulcerative colitis (UC).[1] Eldelumab, a fully human monoclonal antibody to IP-10, has been investigated as induction therapy in an 11-week, Phase IIb study of patients with UC. Methods: Adult patients with Mayo score ≥6 and endoscopic subscore ≥2 were randomized 1:1:1 to placebo or eldelumab 15 or 25 mg/kg IV and received study drug on Days 1 and 8 and then every other week thereafter. The primary endpoint was clinical remission (Mayo score ≤2 points with no individual subscale score >1) at Week 11. Key secondary endpoints were clinical response (reduction from baseline ≥3 and ≥30% in Mayo score, reduction ≥1 in rectal bleeding subscore, or absolute rectal bleeding subscore ≤1) and mucosal healing (endoscopic subscore ≤1) at Week 11. Results: Overall, 252 patients were randomized, with 84.3, 89.3, and 87.1% of patients in the placebo and eldelumab 15 and 25 mg/kg groups, respectively, completing induction therapy. Baseline characteristics were comparable across the groups. Neither eldelumab dose resulted in significant increases versus placebo in the proportion of patients achieving the primary endpoint at Week 11 (p=0.515 and p=0.158, for eldelumab 15 and 25 mg/kg, respectively). However, numerically higher remission and response rates were reported for both eldelumab 25 mg/kg (17.6 and 47.1%, respectively) and 15 mg/kg dose (13.1 and 44.0%) compared with placebo (9.6 and 31.3%). Clinical remission and response rates were higher in anti-TNF-Naive patients across both eldelumab treatment arms versus anti-TNF failures (Table 1). Adverse events were comparable across treatment groups; serious adverse events were more common with placebo (driven by discontinuation due to exacerbation; Table 2). Infection was more common in the eldelumab 25 mg/kg group compared with eldelumab 15 mg/kg or placebo. Acute infusion reactions were more common with eldelumab than placebo; 90.6% (29/32) of infusion reactions with eldelumab were mild to moderate in severity. Conclusion: Induction treatment with eldelumab 15 or 25 mg/kg did not achieve the primary endpoint, although there were trends towards efficacy in the overall population and in patients who were anti-TNF Naive. Safety signals were consistent with those reported previously for eldelumab.[2]

1. Uguccioni M, et al. Am J Pathol 1999;155:331-36. 2. Mayer L, et al. Gut 2013 [Epub ahead of print; doi:10.1136/gutjnl-2012-303424].

Table 1. Subgroup analyses according to anti-TNF status

	Anti-TNF status					
	Placebo (n=83)		Eldelumab 15 mg/kg (n=84)		Eldelumab 25 mg/kg (n=85)	
	Naïve (n=53)	Failure (n=30)	Naïve (n=54)	Failure (n=30)	Naïve (n=48)	Failure (n=37)
Clinical remission						
n (%)	6 (11.3)	2 (6.7)	9 (16.7)	2 (6.7)	10 (20.8)	5 (13.5)
95% CI	2.8, 19.9	0.8, 22.1	6.7, 26.6	0.8, 22.1	9.3, 32.3	2.5, 24.5
Δ vs placebo	NA	NA	5.3	0.0	9.5	6.8
95% CI	NA	NA	-7.8, 18.4	-16.8, 16.8	-4.8, 23.8	-11.1, 22.9
Clinical response						
n (%)	17 (32.1)	9 (30.0)	26 (48.1)	11 (36.7)	26 (54.2)	14 (37.8)
95% CI	19.5, 44.6	13.6, 46.4	34.8, 61.5	19.4, 53.9	40.1, 68.3	22.2, 53.5
Δ vs placebo	NA	NA	16.1	6.7	22.1	7.8
95% CI	NA	NA	-2.2, 34.4	-17.1, 30.5	3.2, 41.0	-14.8, 30.5

Δ=treatment difference; NA=not applicable; CI=confidence interval

Table 2. AEs during 11 weeks of induction treatment with eldelumab

	Placebo (n=83)	Eldelumab 15 mg/kg (n=84)	Eldelumab 25 mg/kg (n=85)
AEs	57 (68.7)	56 (66.7)	60 (70.6)
Serious AEs	8 (9.6)	4 (4.8)	4 (4.7)
Deaths	0	0	0
Related serious AEs	0	1 (1.2)	2 (2.4)
Serious AEs resulting in discontinuation	4 (4.8)	2 (2.4)	2 (2.4)
Serious infections	1 (1.2)	0	0
Related AEs	16 (19.3)	27 (32.1)	33 (38.8)
AEs resulting in discontinuation	4 (4.8)	5 (6.0)	4 (4.7)
Infections and infestations	15 (18.1)	15 (17.9)	22 (25.9)
Infusion reaction*	4 (4.8)	12 (14.3)	16 (18.8)

All data are n (%). AE=adverse event *Potentially infusion-related AEs occurring from the start of study drug infusion until 1 hour after the end of infusion

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Development of an Algorithm Incorporating Pharmacokinetics of Adalimumab in Inflammatory Bowel Diseases

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Introduction Several decision algorithms based on the measurement of infliximab (IFX) trough levels and antibodies to infliximab (ATI) have been proposed. Whether such algorithms can be extrapolated to the pharmacokinetics of adalimumab (ADA) has yet to be determined. Patients and Methods A prospective study included all consecutive patients with IBD having a disease flare while being on ADA 40 mg every two weeks monotherapy were included. All patients were primary responders to ADA and anti-TNF naive. ADA trough levels and antibodies to adalimumab (AAA) were measured in blindly to clinical data (Elisa LISA-Tracker, Theradiag). All patients were optimized with ADA 40 mg weekly. Four months later, in the absence of clinical remission (CDAI < 150 for Crohn's disease (CD), and Mayo score < 2 for ulcerative colitis (UC)), patients were treated with IFX therapy. Patients were y divided into three groups based on ADA trough levels based on previous studies: Group A: ADA>4.9 µg/mL Group B: ADA< 4.9 µg/mL and undetectable levels of AAA (< 10 ng/mL) Group C: ADA<4.9 µg/mL and AAA > 10 µg/mL Results 82 patients were included (55% CD, mean age = 43 years, disease duration = 7.4 years, duration of ADA therapy= 17 months). After optimization of ADA treatment, 29.2% of patients achieved clinical remission in the group A (N = 41), 67% in the group B (N = 24), and 12% in the group C (N = 17) (p < 0.01 between groups A/B and B/C). CRP level at the time of relapsee, disease duration, duration of ADA therapy and type of IBD were not predictive of clinical remission after optimization by univariate analysis. The response to ADA optimization was significantly more durable in the group B (15 months) than in groups A and C (respectively 4 and 5 months). Fifty seven patients who failed following ADA optimization (69%) were treated with IFX and 31.6% of them achieved clinical remission. Clinical remission rates following IFX initiation were 12 %, 25% and 80% in groups A, B and C (p < 0.01 between groups C/A and C/B), respectively. Duration of response to IFX was significantly higher in the group C than in groups A and B (14 vs. 3 and 5 months, respectively, p <0.01). Conclusions The presence of low ADA trough levels in serum without AAA is strongly predictive of a favorable clinical response after ADA optimization (67%). Conversely low ADA levels with detectable AAA are associated with failure of ADA optimization and a switch to IFX should be considered. ADA trough levels > 4.9 µg/mL are associated with clinical response to two anti- TNF (optimisation and switch) in only 10% of cases and must provide an other treatment than anti-TNF (class change).

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Anti-MAdCAM Monoclonal Antibody PF-00547659 Does Not Affect Immune Surveillance in the Central Nervous System of Crohn's Disease Patients Who Are Anti-TNF Inadequate Responders: Results From the Tosca Study

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Background: Therapies that inhibit white blood cell (WBC) trafficking from the bloodstream to gut mucosa have shown promise for treatment of inflammatory bowel disease. Such treatment has been limited by the risk of progressive multifocal leukoencephalopathy (PML) in patients (pts) treated with the nonselective α4 integrin blocker, natalizumab. PML is an opportunistic central nervous system (CNS) infection caused by the highly prevalent JC virus. Reduced CNS immune surveillance from inhibition of leukocyte migration is a likely element in the pathogenic cascade. We have previously shown that in cerebrospinal fluid (CSF) sampled from study pts before treatment, cell counts and lymphocyte markers were stable in TransFix® transport medium for at least 48h, within-pt values did not change over 2 weeks, and pre-treatment cell counts and subsets were similar to healthy volunteers.(D-'Haens UEGW-2013). PF-00547659, a fully human monoclonal antibody, is highly selective and binds to MAdCAM on endothelial cells, blocks its interaction with WBC bearing α4β7 integrin, and prevents their entry into the gut mucosa. The CNS, which is constitutively devoid of MAdCAM, should be unaffected. This report of the TOSCA study is the first to describe effects of the anti-MAdCAM antibody PF-00547659 on immune surveillance in the central nervous system of pts with Crohn's disease (CD). Methods: Patients with moderate to severe CD, (ie, Harvey Bradshaw Index (HBI) > 8 + highly sensitive C-reactive protein (hsCRP)>5.0mg/L or active lesions on endoscopy or imaging) and prior treatment with both anti-TNF and immunosuppressant (azathioprine, 6-MP or methotrexate) underwent a lumbar puncture (LP) followed by 3 monthly injections of 225 mg PF-00547659. 2±1 weeks after the last dose of PF-00547659 a 2nd LP was performed. CSF was analyzed by flow cytometry in a central laboratory adjusting with TruCount beads for enumeration of lymphocytes and T cell subsets. Results: 24 CD pts enrolled (16F/8M). Mean (sd) entry values were age: 38.0 (9.7) years; CD duration: 11.7 (6.1) years; HBI (16 pts without stoma): 8.6 (1.4); hsCRP:12.0 (18.7) mg/L. 14 had a 2nd LP after completing treatment. Cell counts by flow cytometry were not available for 1 pt; 1 pt was excluded for a traumatic tap. Results of CSF flow cytometry are shown in Table 1. Conclusion: In anti-TNF and immunosuppressant experienced pts with moderate to severe CD, a full induction course of the highest clinical dose of PF-00547659 did not affect CSF lymphocytes. The results of the TOSCA study support the gut selectivity and the CNS-sparing mechanism proposed for PF-00547659

Table 1: CSF lymphocytes (cells per mL) before and after treatment (Geometric Mean (CV%))

	N	Lymphocytes	CD3+	CD3+/CD4+	CD3+/CD8+	CD4:CD8
LP1	24	471 (132%)	435 (132%)	294 (141%)	122 (119%)	2.40 (50%)
LP2	12	626 (185%)	595 (188%)	409 (197%)	160 (171%)	2.52 (52%)