PP0757

Efficacy, safety and immunogenicity of Subcutaneous Infliximab (CT-P13 SC) monotherapy versus combination therapy with Immunosuppressants from LIBERTY-CD study and LIBERTY-UC study

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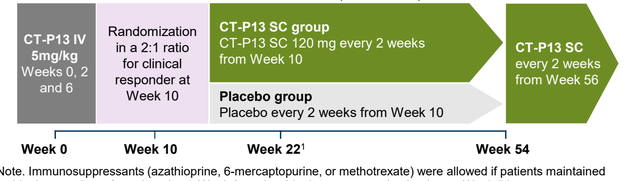
BACKGROUND / AIMS

- CT-P13 subcutaneous (SC) infliximab formulation demonstrated superiority over placebo as maintenance therapy in Crohn's disease (CD) and ulcerative colitis (UC) patients through 54 weeks in two randomized controlled studies (LIBERTY-CD and LIBERTY-UC).
- Azathioprine plus infliximab IV combination therapy has been shown to result in lower antibodies to infliximab and higher trough levels of infliximab than infliximab monotherapy.
- Post-hoc analysis was performed to compare patients who treated with CT-P13 SC with and without combination immunosuppressants (IS) at baseline.

METHODS

Figure 1. Study design of LIBERTY-CD and LIBERTY-UC



Note. Immunosuppressants (azathioprine, 6-mercaptopurine, or methotrexate) were allowed if patients maintained stable doses at least 8 weeks prior to Week 0, and stable doses were maintained up to Week 54.
[1] Dose adjustment to CT-P13 SC 240mg was allowed in both CT-P13 SC and Placebo groups from Week 22, if patient met loss of response criteria.

Table 1. Summary of Immunosuppressants at baseline (CT-P13 SC group)

	LIBERTY-CD (N=231)	LIBERTY-UC (N=294)
Number of patients who received immunosuppressants at baseline, n (%)		
Azathioprine	63 (27.3%)	63 (21.4%)
6-Mercaptopurine	4 (1.7%)	2 (0.7%)
Methotrexate	4 (1.7%)	0
Dose of immunosuppressants at baseline, mean (SD)		
Azathioprine (mg/kg/day)	1.9 (0.70)	1.8 (0.49)
6-Mercaptopurine (mg/kg/day)	1.3 (0.23)	1.3 (0.43)
Methotrexate (mg/week)	18.8 (5.95)	N/A

Table 2. Baseline characteristics (CD + UC)

		Monotherapy (N=389)	Combination therapy (N=136)
Age, median (IQR)	Years	37.0 (29.0 - 47.0)	35.0 (25.0 - 40.5)
Sex, n(%)	Male	214 (55.0%)	83 (61.0%)
Race, n(%)	White	374 (96.1%)	125 (91.9%)
Weight, median (IQR)	kg	68.5 (58.3 - 82.0)	67.4 (59.2 - 79.8)
Disease duration, mean (SD)	Years	5.1 (5.7)	5.8 (5.8)
CDAI score, mean (SD) –CD	Score	310.7 (58.8)	314.7 (57.8)
SES-CD score, mean (SD) –CD	Score	11.7 (7.2)	11.0 (6.2)
MMS, mean (SD) –UC	Score	6.6 (1.1)	6.8 (1.1)
CRP at Week 10, median (IQR)	nmol/L	10.5 (3.8 - 32.4)	6.7 (2.9 - 18.1)
FC at Week 10, median (IQR)	mg/kg	185.5 (41.0 - 769.0)	177.0 (39.0 - 986.0)
Biologics or JAK inhibitors history, n (%)	Used	38 (9.8%)	17 (12.5%)
Oral corticosteroids at Wk 0, n (%)	Used	170 (43.7%)	49 (36.0%)
Clinical remission at Wk 10*, n (%)	Remitter	223 (57.3%)	94 (69.1%)

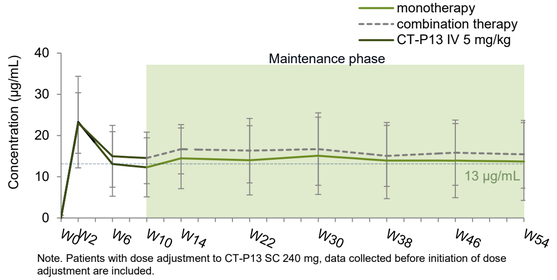
CD, Crohn's disease; CDAI, Crohn's disease activity Index; CRP, C-reactive protein; FC, Fecal calprotectin; IQR, Interquartile range; JAK, Janus kinase; MMS; Modified Mayo Score; SC, subcutaneous; SD, standard deviation; SES-CD, Simplified endoscopic activity score; UC, ulcerative colitis; Wk, week
* P-value = 0.0190

RESULTS

Pharmacokinetics

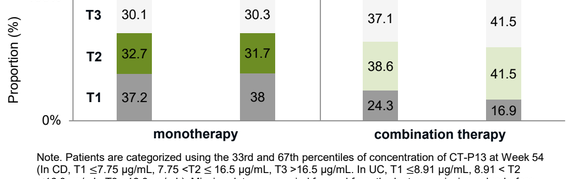
- Monotherapy shows slightly lower concentration of CT-P13 than combination therapy, but the concentration level was consistently above 13 μg/mL during the maintenance phase (Figure 2).
- In the monotherapy, there were no difference in proportion by CT-P13 concentration tertiles. The patients with combination therapy had fewer number of patients in Tertile 1 concentration subgroup (Figure 3).

Figure 2. Mean (SD) pre-dose concentration of CT-P13 (CD + UC)



Note. Patients with dose adjustment to CT-P13 SC 240 mg, data collected before initiation of dose adjustment are included.

Figure 3. Proportion of patients by Concentration Tertiles at Week 54

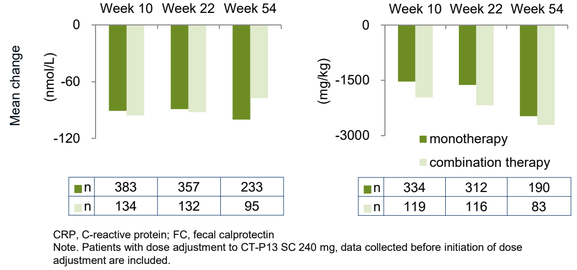


Note. Patients are categorized using the 33rd and 67th percentiles of concentration of CT-P13 at Week 54 (In CD, T1 ≤7.75 μg/mL, 7.75 <T2 ≤ 16.5 μg/mL, T3 >16.5 μg/mL. In UC, T1 ≤8.91 μg/mL, 8.91 < T2 ≤16.0 μg/mL, T3 >16.0 μg/mL). Missing data was carried forward from the last non-missing value before initiation of dose adjustment.

Biomarkers

- The mean change from baseline in biomarkers (CRP and FC) were generally comparable between monotherapy and combination therapy in maintenance phase (Figure 4).

Figure 4. Change from baseline of biomarkers (CD + UC)

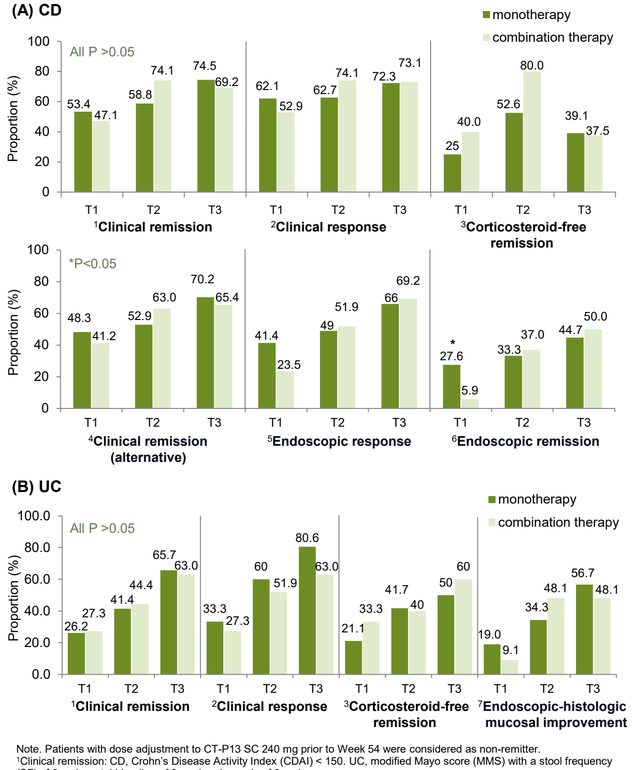


CRP, C-reactive protein; FC, fecal calprotectin
Note. Patients with dose adjustment to CT-P13 SC 240 mg, data collected before initiation of dose adjustment are included.

Efficacy

- There were no meaningful difference in efficacy outcomes at Week 54 by concentration tertiles at Week 54 between monotherapy and combination therapy.
- Efficacy outcomes at Week 54 were associated with concentration of CT-P13 regardless of monotherapy or combination therapy (Figure 5).

Figure 5. Efficacy endpoints at Week 54 by Concentration Tertiles at Week 54



Note. Patients with dose adjustment to CT-P13 SC 240 mg prior to Week 54 were considered as non-remitter.
[1]Clinical remission: CD, Crohn's Disease Activity Index (CDAI) < 150. UC, modified Mayo score (MMS) with a stool frequency (SF) of 0 or 1, rectal bleeding of 0, and endoscopic of 0 or 1.
[2]Clinical response: CD, CDAI-100 response. UC, decrease in MMS from baseline of at least 2 points and at least 30%, with an accompanying decrease in the rectal bleeding of at least 1 point or an absolute rectal bleeding of 0 or 1 point.
[3]Corticosteroid-free remission: Clinical remission in addition to not receiving any corticosteroids for at least 8 weeks prior to Week 54, among the patients who used oral corticosteroids at baseline.
[4]Clinical remission (alternative): average worst daily abdominal pain score of ≤1 (using 4-point scale) and average daily loose/watery SF score of ≤3 (of Type 6 or Type 7 on Bristol Stool Form Scale) with no worsening in either average score compared with baseline.
[5]Endoscopic response: 50% decrease in Simplified endoscopic activity score for Crohn's disease (SES-CD) from baseline.
[6]Endoscopic remission: SES-CD score of ≤4 and at least 2-point reduction from baseline with no sub-score of >1.
[7]Endoscopic-histologic mucosal improvement: endoscopic subscore of 0 or 1 point from MMS and Robarts Histopathology Index score ≤3 with an accompanying lamina propria neutrophils and neutrophils in epithelium of 0 point.

Safety

- No statistically significant difference was seen in safety profile between monotherapy and combination therapy except for infection rate (Table 3).
- The ADA positive conversion rate was higher, and increase in proportion of ADA positive patients started earlier in monotherapy than in combination therapy. The proportion of ADA positive patients tended to be lower in the combination therapy than monotherapy over the entire period in both CD and UC, but the proportion at Week 54 was comparable between two groups in CD (Table 4, Figure 6).

Table 3. Safety results in maintenance phase (CD + UC)

Number of Patients (%)		Monotherapy (N=394)	Combination therapy (N=140)
TEAEs	Total	268 (68.0%)	104 (74.3%)
TESAEs	Total	29 (7.4%)	6 (4.3%)
Systemic injection reaction	Total	13 (3.3%)	2 (1.4%)
Delayed hypersensitivity	Total	0	0
Localized injection site reaction	Total	19 (4.8%)	5 (3.6%)
Infection	Total	106 (26.9%)[$]	51 (36.4%)[$]
Serious infection	Total	10 (2.5%)	3 (2.1%)
Malignancy	Total	1 (0.3%)	0
Death	Total	1 (0.3%)	0

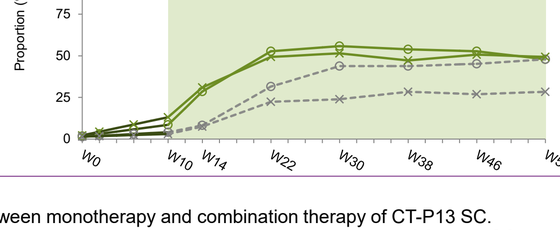
TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event
Note. All data are included regardless of dose adjustment in both monotherapy and combination therapy group.
[$] P-value = 0.0400

Table 4. Immunogenicity results in treatment period (CD + UC)

Number of Patients (%)	Monotherapy (N=394)	Combination therapy (N=140)
Positive Conversion in ADA, n*/N#(%)	269/383 (70.2%)	65/136 (47.8%)

ADA, anti-drug antibody
Note. All data are included regardless of dose adjustment in both monotherapy and combination therapy group.
* Patients who reported at least one ADA positive after Week 0 study drug administration.
# Patients who have at least one immunogenicity result after Week 0 and have not any ADA positive result before Week 0.

Figure 6. Proportion of ADA positive patients



CONCLUSIONS

- No meaningful differences in efficacy outcomes at W54 were observed between monotherapy and combination therapy of CT-P13 SC.
- ADA and pharmacokinetic features were associated with combination therapy, but due to high and persistent concentration of CT-P13 SC, addition of immunosuppressants did not have influence on clinical efficacy.
- The overall safety profile and biomarkers during maintenance phase were comparable between monotherapy and combination therapy.

Disclosure: S. Schreiber: Consultancy and personal fees from AbbVie, Arena, BMS, Biogen, Celltrion, Celgene, Falk, Ferring, Fresenius, Gilead, HIKMA, IMAB, Janssen, MSD, Morphic, Pfizer, Protagonist, Provention Bio, Sandoz, Takeda, and Theravance. J.F. Colombel: Receiving research grants from AbbVie, Janssen Pharmaceuticals and Takeda. Receiving payment for lectures from AbbVie, Amgen, Allergan, Inc. Ferring Pharmaceuticals, Shire, and Takeda. Receiving consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, BMS, Celgene Corporation, Eli Lilly, Ferring Pharmaceuticals, Galmed Research, Genentech, Glaxo Smith Kline, Janssen Pharmaceuticals, Kaleido Biosciences, Imedex, Immunic, Iterative Scopes, Merck, Microbia, Novartis, PBM Capital, Pfizer, Protagonist Therapeutics, Sanofi,Takeda, TiGenix, Vifor. Hold stock options in Intestinal Biotech Development. S.B. Hanauer: Consultant: Abbvie, Amgen, Boehringer-Ingelheim, BMS, Celltrion, Fresnius-Kabi, Genentech, Gilead, GSK, Immunic, Intercept Pharmaceuticals, Janssen, Lilly, Merck, Novartis, Organon, Pfizer, Progenity, Prometheus, Protagonist, Receptos, Salix, Samsung Bioepis, Seres Therapeutics, Takeda, UCB, VHsquared. Clinical Research (Institution): Abbvie, Amgen, Genentech, Gilead, GSK, Janssen, Lilly, Novartis, Pfizer, Prometheus, Receptos, Seres Therapeutics, Takeda, UCB, Speaker: Abbvie, Janssen, Pfizer, Takeda. DSMB: Boehringer-Ingelheim, BMS, Gossamer, Protagonist, Ventyx. W. Sandborn: research grants from Abbvie, Abivax, Arena Pharmaceuticals, Boehringer Ingelheim, Celgene, Genentech, Gilead Sciences, Glaxo Smith Kline, Janssen, Lilly, Pfizer, Prometheus Laboratories, Seres Therapeutics, Shire Pharmaceuticals, Takeda, Theravance Biopharma; consulting fees from Abbvie, Abivax, Admirx, Alfasigma, Alimentiv, Alivio Therapeutics, Allakos, Amgen, Arena Pharmaceuticals, AstraZeneca, Atlantic Pharmaceuticals, Bausch Health (Salix), Beigene, Bellatrix Pharmaceuticals, Biora (Progenity), Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Meyers Squibb, Celgene, Celltrion, Clostrabio, Codexis, Equillium, Forbion, Galapagos, Genentech, Gilead Sciences, GlaxoSmithKline, Gossamer Bio, Immunic (Vital Therapies), Index Pharmaceuticals, Inotrem, Intact Therapeutics, Iota Biosciences, Janssen, Kiniksa Pharmaceuticals, Kyverna Therapeutics, Landos Biopharma, Lilly, Morphic Therapeutics, Novartis, Ono Pharmaceuticals, Oppilan Pharma (now Ventyx Biosciences), Otsuka, Pandion Therapeutics, Pfizer, Pharm Olam, Polpharm, Prometheus Biosciences, Protagonist Therapeutics, PTM Therapeutics, Quell Therapeutics, Reistone Biopharma, Seres Therapeutics, Shanghai Pharma Biotherapeutics, Storeline Biosciences, Sublimity Therapeutics, Surrozen, Takeda, Theravance Biopharma, Thetis Pharmaceuticals, Tillotts Pharma, Vedanta Biosciences, Ventyx Biosciences, Vimalan Biosciences, Vivelix Pharmaceuticals, Vividion Therapeutics, Vivreon Gastrosciences, Xencor, Zealand Pharma; stock or stock options from Allakos, BeiGene, Biora (Progenity), Gossamer Bio, Oppilan Pharma (now Ventyx Biosciences), Prometheus Biosciences, Prometheus Laboratories, Protagonists Therapeutics, Shoreline Biosciences, Ventyx Biosciences, Vimalan Biosciences, Vivreon Gastrosciences; and employee at Shoreline Biosciences and Ventyx Biosciences. Spouse: Iveric Bio - consultant, stock options; Progenity - stock; Oppilan Pharma (now Ventyx Biosciences) - stock; Prometheus Biosciences - employee, stock, stock options; Prometheus Laboratories – stock, stock options, consultant, Ventyx Biosciences –stock, stock options; Vimalan Biosciences – stock. B.E. Sands: consulting fees from Abbvie, Alimentiv , Amgen, Arena Pharmaceuticals, Artugen Therapeutics, Astra Zeneca, Boehringer Ingelheim, Boston Pharmaceuticals, Calibr, Celgene, Celltrion, CiostraBio, Equillium, Enthera, Evommune, Fresenius Kabi, Galapagos, Genentech (Roche), Gilead Sciences, GlaxoSmithKline, Gossamer Bio, Index Pharmaceuticals, Innovation Pharmaceuticals, Inotrem, Kaleido, Kallyope, Merck, Morphic Therapeutics, MRM Health, Progenity, Prometheus Biosciences, Prometheus Laboratories, Protagonist Therapeutics, Q32 Bio, Sun Pharma, Surrozen, Target RWE,Teva, TLL Pharmaceutical , Ventyx Biosciences; consulting and speaking fees from Abivax; consulting and speaking fees and other support from Bristol Myers Squibb, Janssen, Pfizer, Takeda; research grants and consulting fees from Theravance Biopharma; and stock options from Ventyx Biopharma S. Danese: Consultancy fees from AbbVie, Alimentiv, Allergan, Amgen, Applied Molecular Transport, AstraZeneca, Athos Therapeutics, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Dr Falk Pharma, Eli Lilly, Enthera, Ferring Pharmaceuticals Inc, Gilead, Hospira, Inotrem, Janssen, Johnson & Johnson, Morphic, MSD, Mundipharma, Mylan, Pfizer, Roche, Sandoz, Sublimity Therapeutics, Takeda, Teladoc Health, TiGenix, UCB Inc., Vial, Vifor. Reports lecture fees from Abbvie, Amgen, Ferring Pharmaceuticals Inc., Gilead, Janssen, Mylan, Pfizer, Takeda. S.J. Lee, S.H. Kim, Y. Bae, S. Lee, S.G. Lee, J.H. Lee, J.M. Kim, S. Yang, J.M. Lee, G.H. Park, J. Lee: Employee of Celltrion, Inc.