MP362

Subcutaneous Infliximab (CT-P13 SC) dose escalation as an option for managing the loss of response in Inflammatory Bowel Disease from LIBERTY-UC study and LIBERTY-CD study

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Background and Methods

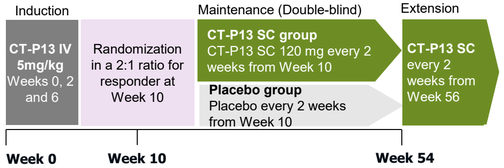
- Dose escalation (DE) of IV infliximab is an option for inflammatory bowel disease patients who lose response.
- Post-hoc subgroup analysis performed to evaluate efficacy, Pharmacokinetics, biomarkers, and safety including immunogenicity for patients with dose escalation (DE) from CT-P13 SC 120 mg to 240 mg in ulcerative colitis (UC) and Crohn's disease (CD)

Table 1. Summary of Dose escalation rate

	UC (N=294)	CD (N=231)
Rate of DE prior to Week 54	27.6% (81/294)	16.9% (39/231)
Rate of DE at Week 22	74.1% (60/81)	51.3% (20/39)
Time to DE [Mean(SD), weeks]	25.6 (6.05)	29.8 (8.38)

DE, dose escalation; SD, standard deviation; Note: Time (week) is calculated as (Datetime of initiation of dose adjustment – Datetime of first study drug administration)

Figure 1. Study design



- From Week 22, patients who initially responded but then had loss of response received escalated dose of CT-P13 SC 240 mg.

Loss of response was defined as

- UC: Modified Mayo score (MMS) increased by ≥ 2 points and ≥ 30% from the Week 10 MMS with actual value of ≥ 5 points, and endoscopic subscore of ≥ 2 points.
- CD: An increase in Crohn's disease activity index (CDAI) of ≥ 100 points from the Week 10 CDAI score with a total score ≥ 220.

Baseline characteristics

- Baseline characteristics were generally comparable between patients with and without DE, except below categories.
  - ✓ In UC, patients with DE had a higher proportion of patients with use of oral corticosteroids at week 0 and biologic/JAK inhibitor history than patients without DE, while clinical remission at week 10 was lower.
  - ✓ In CD, patients with DE had a higher proportion of patients with use of oral corticosteroids at week 0 than patients without DE.

Table 2. Baseline characteristics of patients		Ulcerative colitis (N=294)		Crohn's disease (N=231)	
		with DE (N=81)	w/o DE (N=213)	with DE (N=39)	w/o DE (N=192)
Age, Median (IQR)	years	38.0 (31.0-50.0)	37.0 (28.0-46.0)	36.0 (29.0-42.0)	36.0 (24.5-43.0)
Sex, n (%)	Male	44 (54.3%)	119 (55.9%)	23 (59.0%)	111 (57.8%)
Race, n (%)	White	80 (98.8%)	208 (97.7%)	34 (87.2%)	177 (92.2%)
Baseline Weight, Median (IQR)	kg	73.0 (63.0 - 84.9)	70.0 (59.0 - 82.0)	67.5 (55.0 - 86.2)	65.7 (57.6 - 78.0)
Disease duration, Mean (SD)	years	6.7 (5.4)	5.9 (6.2)	4.6 (4.5)	4.3 (5.3)
Baseline MMS/CDAI score, Mean (SD)	-	6.8 (1.0)	6.5 (1.1)	318.4 (59.0)	310.7 (58.4)
Baseline SES-CD score, Mean (SD)	-	-	-	11.7 (6.0)	11.4 (7.1)
Immunosuppressant use at Week 0	Used	21 (25.9%)	44 (20.7%)	13 (33.3%)	58 (30.2%)
Biologics or JAK inhibitors history, n (%)	Used	14 (17.3%)	15 (7.0%)	3 (7.7%)	23 (12.0%)
Oral corticosteroids at Week 0, n (%)	Used	43 (53.1%)	77 (36.2%)	22 (56.4%)	77 (40.1%)
Clinical remission at Week 10, n (%)	Remitter	20 (24.7%)	123 (57.7%)	31 (79.5%)	143 (74.5%)

CDAI, Crohn's disease activity index; DE, dose escalation; IQR, Inter quartile range; JAK, Janus kinase; MMS, Modified Mayo score; SC, subcutaneous; SD, standard deviation; SES-CD: Simple endoscopic score for Crohn's disease; w/o, without. N` = number of patients with/without dose adjustment to CT-P13 SC 240 mg prior to Week 54 in CT-P13 SC 120 mg group.

Pharmacokinetics and biomarkers

- Concentrations of CT-P13 SC before DE were lower in patients with DE compared to those without DE (Table 3).
- PD parameters before DE were higher in patients with DE compared to patients without DE (Table 4).

Table 3. Concentration of CT-P13 SC before dose escalation

Mean (SD), µg/mL		with DE	w/o DE
UC	Week 10	11.5 (6.9)	13.9 (6.5)
	Week 22	10.2 (6.3)	16.5 (7.7)
	Prior to DE*	9.9 (6.6)	N/A
CD	Week 10	10.8 (5.8)	12.9 (7.6)
	Week 22	10.9 (8.6)	15.4 (8.7)
	Prior to DE*	9.2 (8.4)	N/A

DE, dose escalation; SD, standard deviation; w/o, without
*The latest result before initiation of dose adjustment was used.

Table 4. Biomarker Parameters before dose escalation

Mean (SD) at Week 22		with DE	w/o DE
UC	CRP(nmol/L)	58.4(106.3)	23.8 (60.0)
	FC (mg/kg)	1749.1 (3602.0)	808.1 (2236.3)
CD	CRP(nmol/L)	60.2 (143.04)	31.0(61.7)
	FC (mg/kg)	742.8(1012.7)	509.2(1311.3)

CRP, C-reactive protein; DE, dose escalation; FC, Fecal calprotectin; SD, standard deviation; w/o, without

Efficacy

- For both UC and CD, patients showed improvement of efficacy outcomes after DE.(Table 5, Table 6).
- Including DE patients, clinical remission rates are 50% and 71.4% for LIBERTY-UC and LIBERTY-CD, respectively (Figure 2).
- Among patients with DE, higher serum concentrations of CT-P13 SC at Week 54 are associated with higher rates of efficacy outcomes (Figure 3).

Table 5. Change in MMS, CDAI, SES-CD of dose escalated patients

	UC	CD	
	MMS (n=38)	CDAI (n=28)	SES-CD (n=16)
Prior to first dose escalation	5.8	256.4	7.8
Week 54	3.4	105.4	6.5
Mean change, p-value	-2.3, <0.0001	-150.9, <0.0001	-1.3, 0.1237

CDAI, Crohn's disease activity index; SES-CD, simplified endoscopic activity score for Crohn's disease; MMS, Modified Mayo score; SES-CD, simplified endoscopic activity; n=The patients with dose escalation prior to Week 54 who had efficacy outcomes at both dose escalation visit and Week 54

Figure 2. Efficacy endpoints at Week 54

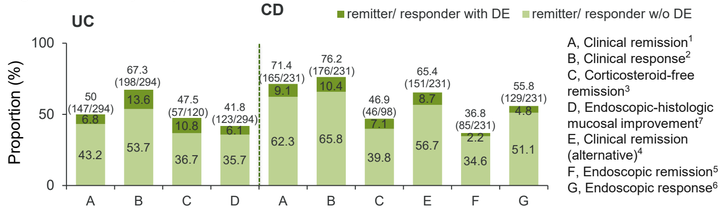
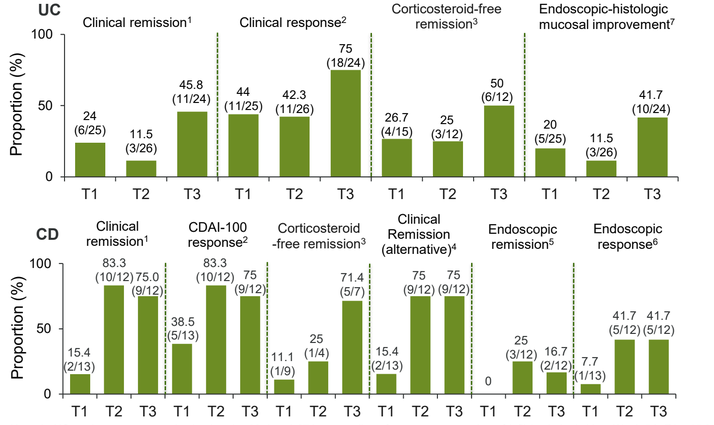


Figure 3. Efficacy endpoints at Week 54 by Concentration Tertiles at Week 54 for patients with dose escalation



Note. In UC, patients are categorized using the 33rd and 67th percentiles of serum concentration of infliximab (ng/mL) at Week 54. T1 ≤15.3 µg/mL, 15.3 <T2 ≤ 26.4 µg/mL, T3 >26.4 µg/mL. In CD, patients are categorized using the 33rd and 67th percentiles of serum concentration of infliximab (ng/mL) at Week 54. T1 ≤11.2 µg/mL, 11.2 <T2 ≤ 24.2 µg/mL, T3 >24.2 µg/mL. Missing data was imputed using Last Observation Carried Forward (LOCF) method for data after dose escalation only.

For figure 2,3 and Table 6; [1]In CD, Clinical remission: Crohn's Disease Activity Index (CDAI) < 150. In UC, Clinical remission: modified Mayo score (MMS) with a stool frequency (SF) of 0 or 1, rectal bleeding of 0, and endoscopic of 0 or 1. [2]In CD, Clinical response: CDAI-100. In UC, Clinical response: decrease in MMS from baseline of at least 2 points and at 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 definition): 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 remission: SES-CD score of ≤4 and at least 2-point reduction from baseline with no sub-score of >1. [6]Endoscopic response: 50% decrease in Simplified endoscopic activity score for Crohn's disease (SES-CD) from baseline. [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.

Table 6. Efficacy endpoints at Week 54 of dose escalated patients, n'/N' (%)

	UC	CD
Clinical remission[1]	20/81 (24.7%)	21/39 (53.8%)
Clinical response[2]	40/81 (49.4%)	24/39 (61.5%)
Corticosteroid-free remission[3]	13/43 (30.2%)	7/22 (31.8%)
Clinical remission (alternative)[4]	N/A	20/39 (51.3%)
Endoscopic remission[5]	N/A	5/39 (12.8%)
Endoscopic response[6]	N/A	11/39 (28.2%)
Endoscopic-histologic mucosal improvement[7]	18/81 (22.2%)	N/A

CDAI, Crohn's disease activity index; N'= Number of patients with dose escalation to CT-P13 SC 240 mg prior to Week 54 in CT-P13 SC 120 mg group; n' = Number of patients achieving each endpoint among dose-escalated patients

Safety and Immunogenicity

- In the pooled data of UC and CD, no noticeable difference was observed between the subgroups in the safety profile including anti-drug antibody (ADA).
- Dose escalation from CT-P13 SC 120mg to 240 mg had no significant effect on the safety profile of CT-P13 SC.

Table 7. Safety and Immunogenicity

	with DE (N'=137, PY=108.52)	w/o DE (N'=397, PY=313.76)
Safety results: maintenance phase, Pooled population (UC, CD) Number of Patients at least 1 event (%, PY)		
TEAE	72.3, 91.23	68.8, 87.01
TESAE	5.8, 7.37	6.8, 8.61
SIR/Delayed hypersensitivity	3.6, 4.61	2.5, 3.19
Localized injection site reaction	5.1, 6.45	4.3, 5.42
Infections	29.9, 37.78	29.2, 36.97
Malignancy	0	0.3, 0.32
Immunogenicity: Treatment period, Pooled population (UC, CD) Number of Patients (%)		
Positive Conversion in ADA	79/132 (59.8)	255/387 (65.9)

ADA, Anti-drug antibody; DE, dose escalation; SC, subcutaneous; SIR, systemic injection reaction; TEAE, Treatment-emergent adverse event; TESAE, Treatment-emergent serious adverse event; PY, Person Year; w/o, without; N', number of patients with/without dose escalation to CT-P13 SC 240 mg during Maintenance Phase in CT-P13 SC 120 mg groups.
Note: For conversion in ADA, number of patients who reported at least one ADA positive after Week 0 study drug administration are used as the numerator, and the number of patients who have at least one immunogenicity result (including NRR) after Week 0 study drug administration and have not any ADA positive result before Week 0 study drug administration are used as the denominator.

Conclusion

- Dose escalation of CT-P13 SC from 120 mg to 240 mg every 2 weeks shown to be effective in restoring efficacy.
- Dose escalated patient with higher concentration of CT-P13 SC at Week 54 showed higher likelihood of achieving clinical response/remission at Week 54.
- Safety profiles including immunogenicity results were generally comparable between patients with or without dose escalation and no new safety concerns were found after dose escalation.

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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, P&M 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 Pharmaceiticals, 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. 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Spouse: Iveric Bio - consultant, stock options; Progenity - stock; Opplan 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, ClostraBio, 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. 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.S.J. Lee, S.H. Kim, Y. Bae, S. Lee, S.G. Lee, J.H. Lee, J.M. Kim, S. Yang, J. Lee, G.H. Park, J.H. Lee: Employee of Celltrion, Inc.