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Network meta-analysis to evaluate the comparative efficacy of biologics for maintenance treatment of adult patients with Crohn's disease

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Introduction

- While the therapeutic armamentarium for Crohn's disease (CD) is rapidly expanding, direct evidence on comparative efficacy of biologic treatments is lacking.[1]
- CT-P13 subcutaneous (SC), a SC formulation of the infliximab (IFX) biosimilar CT-P13, provides patients with a new option for maintenance treatment of their disease.[2] Currently, the use of CT-P13 SC is approved in 53 countries, including European Medicines Agency (EMA) member countries.[2]
- Recent results from LIBERTY-CD, a Phase 3 clinical trial of IFX SC,[3] may provide new and important insights into comparative efficacy within the biologic treatment landscape.
- We conducted a network meta-analysis (NMA) to compare the efficacy of biologic agents licensed by the EMA or United Stated Food and Drug Administration (FDA) for the first-line treatment of patients with CD following an inadequate response or intolerance to conventional therapy.[4,5]

Methodology

NMA study characteristics and patients

- The NMA protocol was registered with PROSPERO (PROSPERO number: CRD42023413752).
- Studies were identified through systematic literature searches of PubMed and Embase up to 31 March 2023.
- Briefly, Phase 3 randomised controlled trials (RCTs) that evaluated EMA/FDA-licensed biologics (i.e. IFX intravenous [IV]/SC, adalimumab [ADL] SC, vedolizumab [VDZ] IV/SC, ustekinumab [UST] SC, or risankizumab [RZB] SC) for maintenance treatment of adults aged >16 years with moderate-to-severe CD were included.
  - Studies could be controlled with placebo (PBO) or an active comparator.
  - Head-to-head studies of licensed biologics were also eligible for inclusion.
- Eligible studies evaluated the efficacy of maintenance treatment with 52–64 weeks' follow-up for patients who responded during the induction phase (except for SEAVUE, which used a treat-through study design).
- Most studies enrolled biologic- and/or Janus kinase inhibitor-exposed and -naïve patients; ACCENT I and SEAVUE enrolled only anti-tumour necrosis factor-naïve and biologic-naïve patients, respectively.

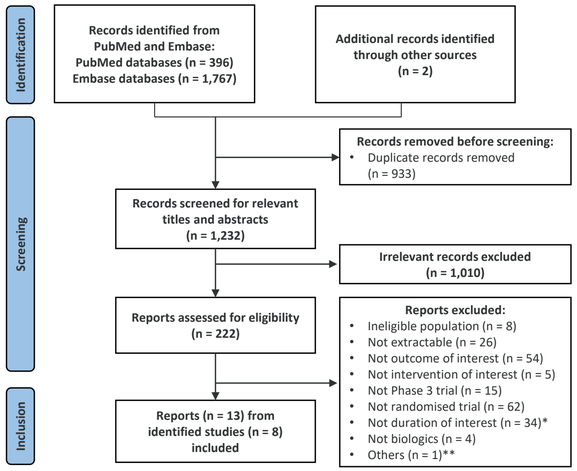
Statistical analysis

- Clinical remission (defined as a Crohn's Disease Activity Index [CDAI] score <150) was analysed in a Bayesian NMA fixed-effect model, using data from patients treated with recommended dosing regimens on the label of each biologic.
- Rank probabilities of each comparator arm were summarised with surface under the cumulative ranking curve (SUCRA) values.
- Analyses were not stratified by previous tumour necrosis factor inhibitor or biologic exposure owing to the scarcity of subgroup data in some studies.

Results

- Overall, 8 RCTs were identified and included in the analysis (**Figure 1**).
- The RCTs were generally consistent in terms of study design, despite the number of randomisation varying among studies (**Table 1**).

Figure 1. PRISMA flow chart



*Certolizumab pegol excluded owing to lack of 1-year data.
**Natalizumab excluded owing to limited use in clinical environment.

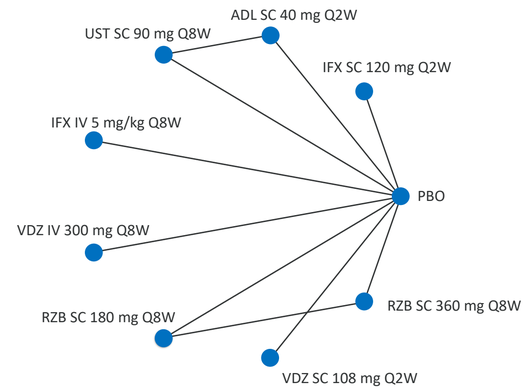
Table 1. Characteristics of the included studies

Drug (study)	Intervention during maintenance phase (n patients)	Study design	Follow-up week	Disease duration
IFX SC (LIBERTY-CD / NCT03945019)[3]	IFX SC 120 mg Q2W (231) PBO (112)	Double-blind / Randomised / Induction responders / PBO induced with active drug* / Blinded during maintenance	54	≥3 months
IFX IV (ACCENT I / NCT00207662)[6]	IFX IV 5 mg/kg Q8W (113) IFX IV 10 mg/kg Q8W (112) PBO (110)	Double-blind / Randomised / Induction responders** / PBO induced with active drug* / Blinded during maintenance	54	≥3 months
VDZ IV (GEMINI 2 / NCT00783692)[7]	VDZ IV 300 mg Q8W (154) VDZ IV 300 mg Q4W (154) PBO (153)	Double-blind / Re-randomised / Induction responders† / PBO induced with active drug* / Blinded during maintenance	52	≥3 months
VDZ SC (VISIBLE 2 / NCT02611817)[8]	VDZ SC 108 mg Q2W (275) PBO (134)	Double-blind / Randomised / Induction responders / PBO induced with active drug* / Blinded during maintenance	52	≥3 months
UST SC (IM-UNITI / NCT01369355)[9]	UST SC 90 mg Q12W (129) UST SC 90 mg Q8W (128) PBO (131)	Double-blind / Re-randomised / Induction responders / PBO induced with active drug* / Blinded during maintenance	52‡	≥3 months
ADL SC (CHARM / NCT00077779)[10]	ADL SC 40 mg Q2W (172) ADL SC 40 mg QW (157) PBO (170)	Double-blind / Randomised / Induction responders** / PBO induced with active drug* / Blinded during maintenance	56	≥4 months
RZB SC (FORTIFY / NCT03105102)[11]	RZB SC 180 mg Q8W (157) RZB SC 360 mg Q8W (141) PBO (164)	Double-blind / Re-randomised / Induction responders§ / PBO induced with active drug* / Blinded during maintenance	64‡	≥3 months
UST SC / ADL SC (SEAVUE / NCT03464136)[12]	UST SC 90 mg Q8W (191) ADL SC 40 mg Q2W (195)	Double-blind / Randomised / Treat-through / Active comparator (parallel-group) / Blinded during maintenance	52	≥3 months

*Patients in the PBO group during maintenance period were treated with active drug during the induction period; **Efficacy assessment was conducted for induction responders only; †Induction responders from both cohort 1 (PBO controlled) and cohort 2 (open-label induction); ‡Including weeks from previous induction studies; §Patients who showed clinical response to PBO in the induction phase were included in safety analyses but excluded from efficacy analyses.
ADL, adalimumab; IFX, infliximab; IV, intravenous; PBO, placebo; Q*n*W, every *n* weeks; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

- The evidence network map was constructed as depicted in **Figure 2**, enabling direct and indirect comparisons to evaluate relative efficacy of each comparator arm.

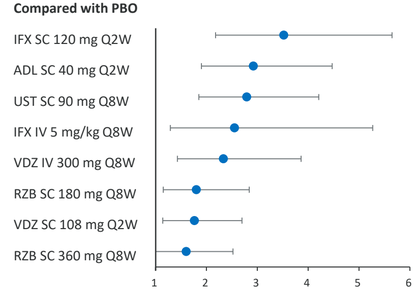
Figure 2. Network evidence map



ADL, adalimumab; IFX, infliximab; IV, intravenous; PBO, placebo; Q*n*W; every *n* weeks; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

- All biologics were superior to placebo (the 95% credible intervals [CrIs] of odds ratio [OR] did not cross 1).
- IFX SC 120 mg Q2W had the highest OR for clinical remission (CDAI score <150) during the maintenance phase (OR: 3.52; 95% CrIs: 2.18, 5.65; **Figure 3**), although the data should be interpreted with caution as the 95% CrIs overlapped.

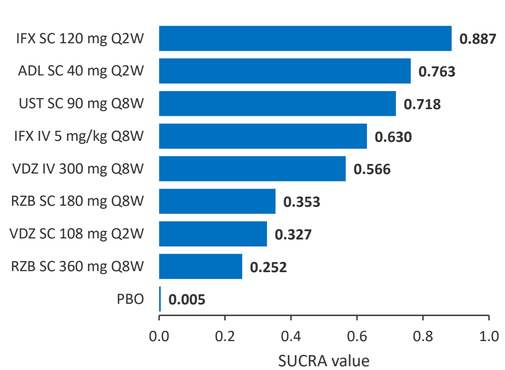
Figure 3. Clinical remission (CDAI score <150) rates in patients with moderate-to-severe CD



ADL, adalimumab; CDAI, Crohn's Disease Activity Index; CrI, credible interval; IFX, infliximab; IV, intravenous; PBO, placebo; Q*n*W, every *n* weeks; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab; VDZ, vedolizumab.

- IFX SC 120 mg showed the largest SUCRA values for clinical remission among the biologic regimens tested (**Figure 4**).

Figure 4. SUCRA values for clinical remission during maintenance therapy



ADL, adalimumab; IFX, infliximab; IV, intravenous; PBO, placebo; Q*n*W, every *n* weeks; RZB, risankizumab; SC, subcutaneous; SUCRA, surface under the cumulative ranking curve; UST, ustekinumab; VDZ, vedolizumab.

Summary and Conclusions

- **In the current Bayesian NMA model, IFX SC showed favourable efficacy in terms of clinical remission during maintenance treatment of 52–64 weeks' duration in patients with moderate-to-severe CD.**
- **The current findings should be interpreted cautiously, given potential bias from between-study heterogeneity in design and patient populations.**

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