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Network meta-analysis to evaluate the comparative efficacy of advanced therapies as first-line for maintenance treatment of adult patients with moderate-to-severe Crohn's disease

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BACKGROUND

- Subcutaneous (SC) CT-P13 (SC infliximab [IFX]) provides patients and physicians with a new opportunity for maintenance treatment of Crohn's disease (CD).[1]
- Given the rapidly expanding therapeutic armamentarium for CD and a lack of direct comparative evidence,[2] an updated network meta-analysis (NMA) of data from Phase III randomised controlled trials (RCTs) was performed to evaluate the comparative efficacy of advanced CD therapies licensed in Europe or the US.

METHODS

- Eligible parallel-group Phase III RCTs with 52–64 weeks of follow-up were identified by systematic literature review (PROSPERO number: CRD42023413752).[3]
  - ***Patients***: Biologic-naïve and/or Janus kinase inhibitor (JAKi)-naïve adults (aged ≥18 years) with moderate-to-severe CD (duration ≥3 months), who received advanced medication as first-line therapy.
  - ***Interventions***: Intravenous (IV) IFX or SC IFX; SC adalimumab; IV or SC vedolizumab; SC ustekinumab; SC risankizumab; or oral upadacitinib.
  - ***Comparators***: Placebo or active comparator.
  - ***Outcomes***: Clinical remission (Crohn's Disease Activity Index [CDAI] score <150) and endoscopic response (≥50% decrease in Simple Endoscopic Score for Crohn's Disease [SES-CD] from baseline) achieved with maintenance treatment.
- Data were synthesised in a frequentist NMA random-effects model that included all evaluated dosing regimens, and compared by using risk difference and P score.[4]

RESULTS

- Sixteen reports from nine RCTs were identified and included in the NMA; characteristics of the included studies are shown in **Table 1**.

Table 1. Characteristics of the included studies

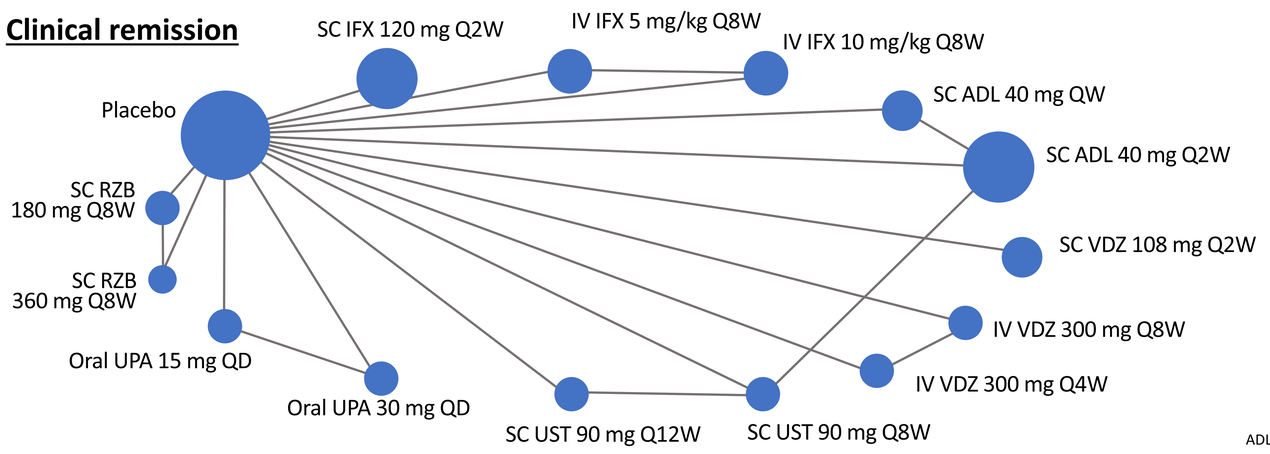
Drug (study)	Intervention during maintenance phase	Total pts, N (pts with first-line use, n)	Study design: Double-blind	Rando-mised	Induction responders	PBO group induced with active drug	Maintenance treatment blinded	F/U week	Disease duration, months	Included in network for: CRem	ERes
SC IFX (LIBERTY-CD / NCT03945019)	SC IFX 120 mg Q2W PBO	231 (205) 112 (103)	●	●	●	●*	●	54	≥3	●	●
IV IFX (ACCENT I / NCT00207662)	IV IFX 5 mg/kg Q8W IV IFX 10 mg/kg Q8W PBO	113 (113) 112 (112) 110 (110)	●	●	●**	●*	●	54	≥3	●	–#
IV VDZ (GEMINI 2 / NCT00783692)	IV VDZ 300 mg Q8W IV VDZ 300 mg Q4W PBO	154 (66) 154 (71) 153 (71)	●	●¶	●†	●*	●	52	≥3	●	–
SC VDZ (VISIBLE 2 / NCT02611817)	SC VDZ 108 mg Q2W PBO	275 (107) 134 (63)	●	●	●	●*	●	52	≥3	●	–#
SC UST (IM-UNITI / NCT01369355)	SC UST 90 mg Q12W SC UST 90 mg Q8W PBO	129 (53) 128 (52) 131 (51)	●	●¶	●	●*	●	52‡	≥3	●	–#
SC ADL (CHARM / NCT00077779)	SC ADL 40 mg Q2W SC ADL 40 mg QW PBO	172 (87) 157 (86) 170 (89)	●	●	●**	●*	●	56	≥4	●	–
SC RZB (FORTIFY / NCT03105102)	SC RZB 180 mg Q8W SC RZB 360 mg Q8W PBO	157 (44) 141 (39) 164 (41)	●	●¶	●§	●*	●	64‡	≥3	●	●
Oral UPA (U-ENDURE / NCT03345823)	Oral UPA 15 mg QD Oral UPA 30 mg QD PBO	169 (45) 168 (41) 165 (39)	●	●¶	●	●*	●	64‡	≥3	●	●
SC UST / SC ADL (SEAVUE / NCT03464136)	SC UST 90 mg Q8W SC ADL 40 mg Q2W	191 (191) 195 (195)	●	●	Treat-through	Active comparator (parallel-group)	●	52	≥3	●	–#

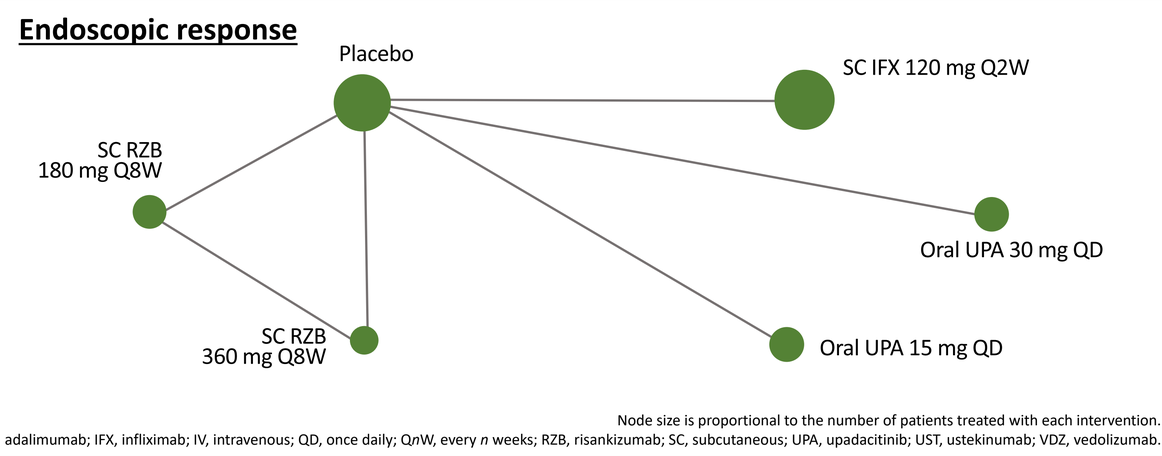
*Patients in the PBO group during the maintenance period were treated with the active drug during the induction period. **Efficacy assessment was conducted for induction responders only. †Induction responders from both cohort 1 (placebo-controlled) and cohort 2 (open-label induction). ‡Including weeks 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. ¶Patients were first randomised at the start of the induction study, then induction responders were re-randomised to each intervention during the maintenance phase. #Endoscopic data were available but could not be compared due to differences in definition or inability to form a network with the PBO.
ADL, adalimumab; CRem, clinical remission; ERes, endoscopic response; F/U, follow-up; IFX, infliximab; IV, intravenous; PBO, placebo; pts, patients; QD, once daily; Q*n*W, every *n* weeks; RZB, risankizumab; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

RESULTS

- Evidence network diagrams are presented for clinical remission and endoscopic response outcomes (**Figure 1**).

Figure 1. Evidence network diagrams for patients receiving first-line treatment

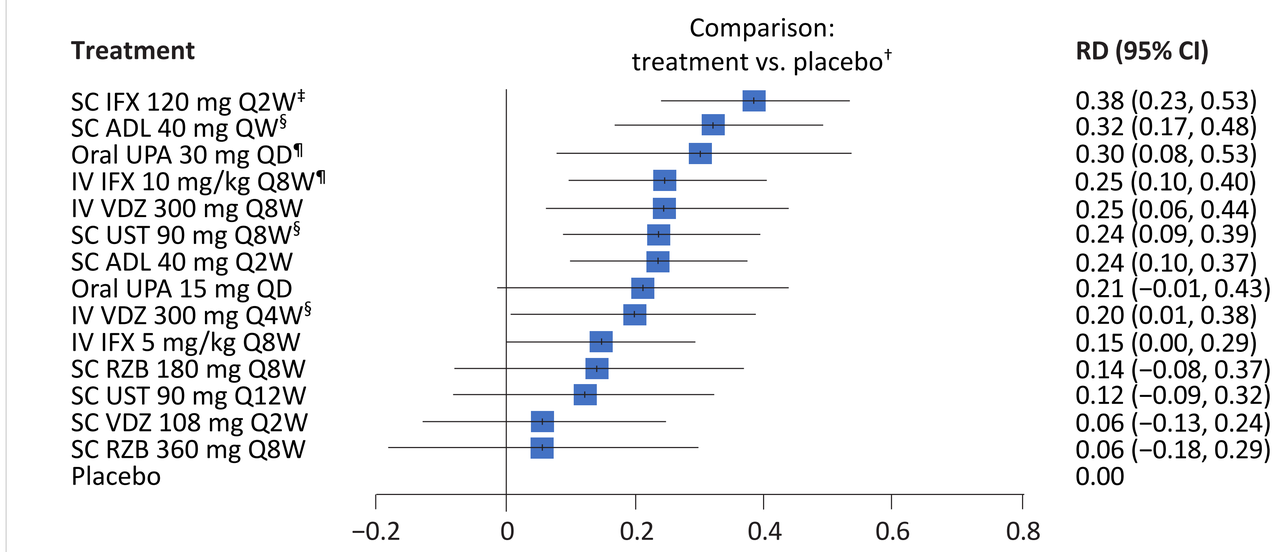


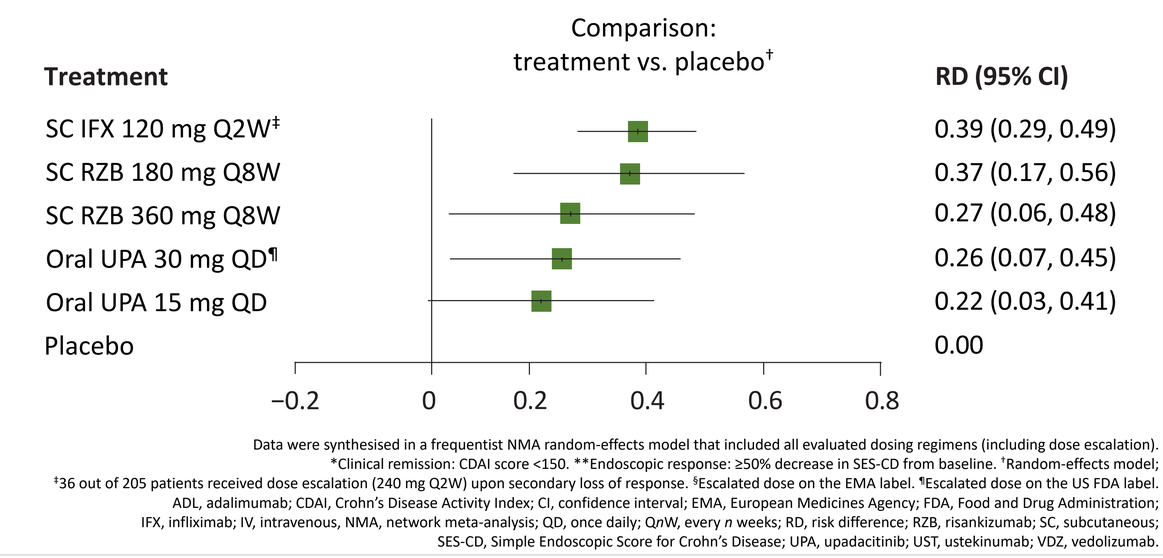


Node size is proportional to the number of patients treated with each intervention.
ADL, adalimumab; IFX, infliximab; IV, intravenous; QD, once daily; Q*n*W, every *n* weeks; RZB, risankizumab; SC, subcutaneous; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

- SC IFX 120 mg every 2 weeks (Q2W) showed the highest risk difference for achieving clinical remission (0.38 [95% confidence interval 0.23–0.53]) and endoscopic response (0.39 [0.29–0.49]) during the maintenance phase (**Figure 2**).

Figure 2. Risk difference (95% CI) for achievement of efficacy endpoints

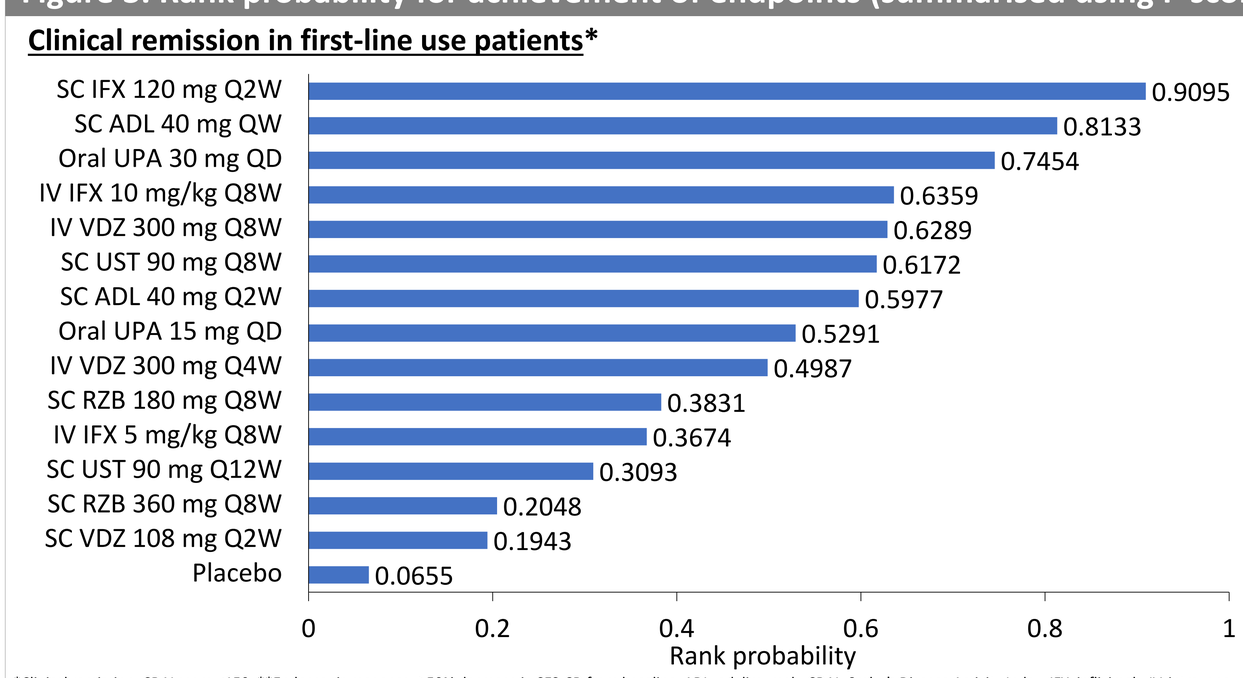


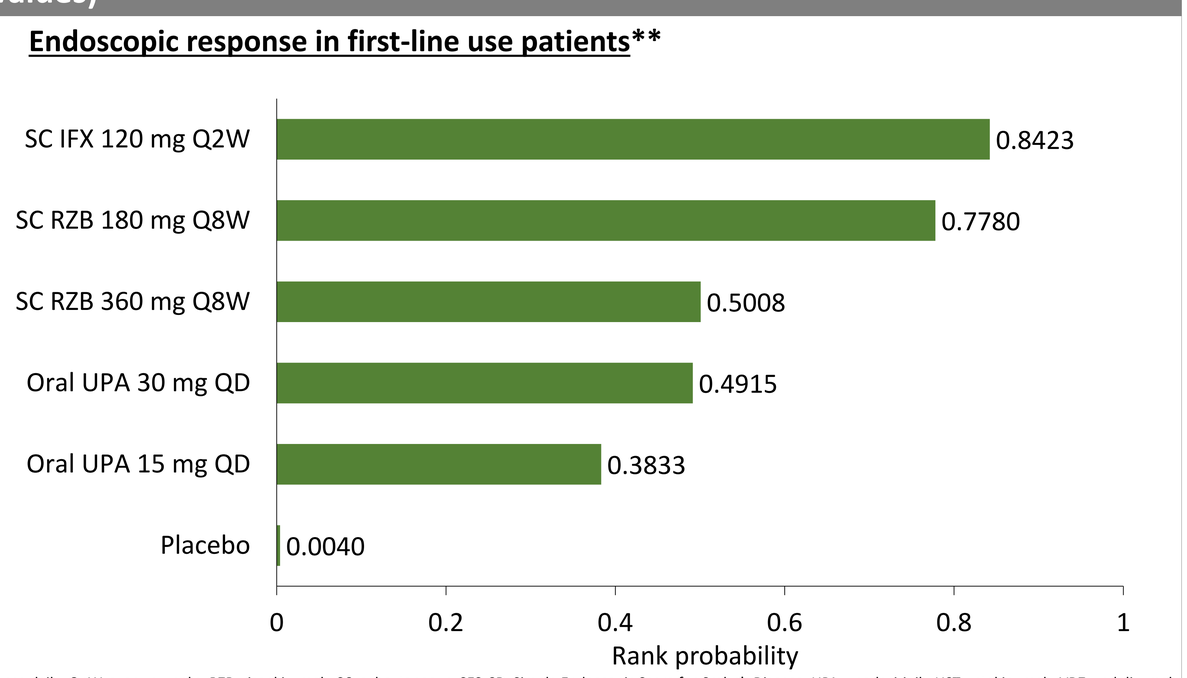


Data were synthesised in a frequentist NMA random-effects model that included all evaluated dosing regimens (including dose escalation).
*Clinical remission: CDAI score <150. **Endoscopic response: ≥50% decrease in SES-CD from baseline. †Random-effects model; ‡36 out of 205 patients received dose escalation (240 mg Q2W) upon secondary loss of response. §Escalated dose on the EMA label. ¶Escalated dose on the US FDA label.
ADL, adalimumab; CDAI, Crohn's Disease Activity Index; CI, confidence interval; EMA, European Medicines Agency; FDA, Food and Drug Administration; IFX, infliximab; IV, intravenous, NMA, network meta-analysis; QD, once daily; Q*n*W, every *n* weeks; RD, risk difference; RZB, risankizumab; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

- Among all tested regimens, SC IFX 120 mg Q2W ranked first (i.e. demonstrated the highest P score) for both clinical remission and endoscopic response (**Figure 3**).

Figure 3. Rank probability for achievement of endpoints (summarised using P score values)





*Clinical remission: CDAI score <150. **Endoscopic response: ≥50% decrease in SES-CD from baseline. ADL, adalimumab; CDAI, Crohn's Disease Activity Index; IFX, infliximab; IV, intravenous, QD, once daily; Q*n*W, every *n* weeks; RZB, risankizumab; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

CONCLUSIONS

- **In this analysis, SC IFX 120 mg Q2W showed a favourable efficacy profile in achieving clinical remission and endoscopic response when used as first-line advanced therapy for maintenance treatment of biologic- and/or JAKi-naïve patients with moderate-to-severe CD.**
- **These findings should be interpreted with caution given potential bias due to heterogeneity in study design and pharmacokinetic characteristics such as half-life across tested drugs as well as the influence of re-randomisation designs.**

Abbreviations: ADL, adalimumab; CDAI, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CRem, clinical remission; EMA, European Medicines Agency; ERes, endoscopic response; FDA, Food and Drug Administration; F/U, follow-up; JAKi, Janus kinase inhibitor; IFX, infliximab; IV, intravenous; NMA, network meta-analysis; PBO, placebo; pts, patients; QD, once daily; Q*n*W, every *n* weeks; RCT, randomised controlled trial; RD, risk difference; RZB, risankizumab; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab.

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