LOW REMISSION RECAPTURE AFTER USTEKINUMAB DOSE OPTIMIZATION IN CROHN'S DISEASE: RESULTS OF THE RANDOMIZED PLACEBO-CONTROLLED DOUBLE-BLIND **REScUE STUDY**.

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Conflict of interest

- Study was supported by an unrestricted research grant by JANSSEN PHARMACEUTICA NV. JANSSEN PHARMACEUTICA NV did not interfere with the study design, data collection and data interpretation.
- PB: Financial support for research: AbbVie, EG. Lecture fees: AbbVie, AMC ICP, Amgen, Bristol Myers Squibb, Celltrion, Dr Falk Benelux, EG, Galapagos, Globalport, Lilly, Medtalks, Materia Prima, Pentax, Springer Media. Advisory board: AbbVie, Bristol Meyers Squibb, CIRC, Galapagos, Janssen, Lilly, Pentax, PSI-CRO, Roche, Takeda, Tetrameros.

Introduction

- The retrospective SUCCESS and SUSTAIN cohorts demonstrate 20-30% loss of response to ustekinumab over 1 year. [1,2]
- Observational and retrospective studies show variable recapture of response in patients with secondary loss of response to ustekinumab. [3,4]
- Different dose optimization schemes have been proposed including IV reinduction or reducing the interval SC to 4 weekly.
- Prospective data on recapture of response after secondary loss of response to ustekinumab are not available.

1 Am J Gastroenterol. 2023 Feb 1;118(2):317-328; 2 Inflamm Bowel Dis. 2022 Nov 2;28(11):1725-1736; 3 Aliment Pharmacol Ther. 2022 Apr;55(7):764-777; 4 Clin Gastroenterol Hepatol. 2022 Dec;20(12):2728-2740.

Aim

- The **REScUE** study investigated the effect of **two different** re-induction regimens with ustekinumab on clinical, endoscopic, biological and pharmacological outcomes in patients with Crohn's disease who experienced **secondary loss of response** to ustekinumab.

BIRD
BELGIAN INFLAMMATORY BOWEL DISEASE RESEARCH AND DEVELOPMENT

Study Design

- A prospective randomized double-blind placebo-controlled multicenter study
- Belgian IBD research and development group (BIRD)
- 17 (academic and non-academic) sites in Belgium

Patient population

- **Primary** response to ustekinumab (≤ week 16) demonstrated by
  - Clinical response (PGA) **AND** biomarker OR endoscopic response

- **Secondary loss of response** to ustekinumab (any time > week 16) demonstrated by
  - Clinical relapse PRO-2 (AP > 1 AND SF > 3)

AND either

  - Biomarker increase (CRP >5 mg/L OR FCP > 250 µg/mg) or
  - Endoscopic relapse (SES-CD ≥6 , for patients with isolated ileitis SES-CD ≥4)

PGA: physician glabal assessment; PRO: patient reported outcome; AP: abdominal pain; SF: stool frequency; CRP: C-reactive protein; FCP: fecal calprotectin; SES-CD: simple endoscopic score for Crohn's disease

≈ 6mg/kg UST

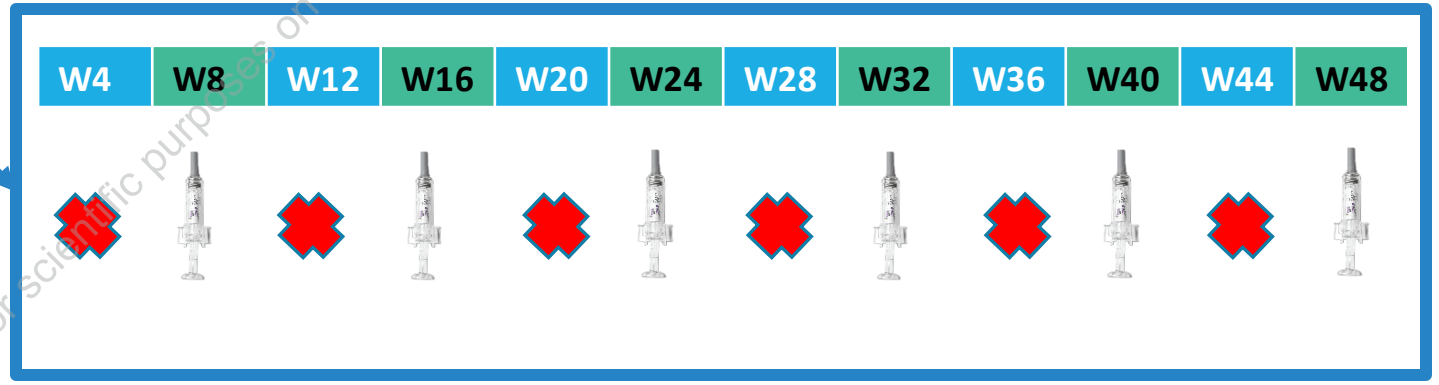
screening

1:1

Baseline
8weeks after last UST dosing

≈ 6mg/kg UST

IV re-induction + q4w 90 mg UST



IV re-induction + q8w 90 mg UST

Endpoints

- **Primary endpoint:**
  - **Steroid free clinical remission**: PRO2 (AP ≤ 1 AND SF ≤ 3) AND FCP <250µg/g AND no steroids for 90 days prior to week 48

- **Secondary endpoints:**
  - Endoscopic remission: SES-CD <3 at week 48
  - Endoscopic response: 50% decrease in SES-CD compared to baseline at week 48
  - Biomarker remission: CRP <5 mg/L and FCP <250 µg/g at week 48

- **Sample size**
  - 80% power to detect an assumed 30% difference with a two-sided alpha of 5%
  - 20% attrition
  - 108 patients with 54 patients per treatment arm

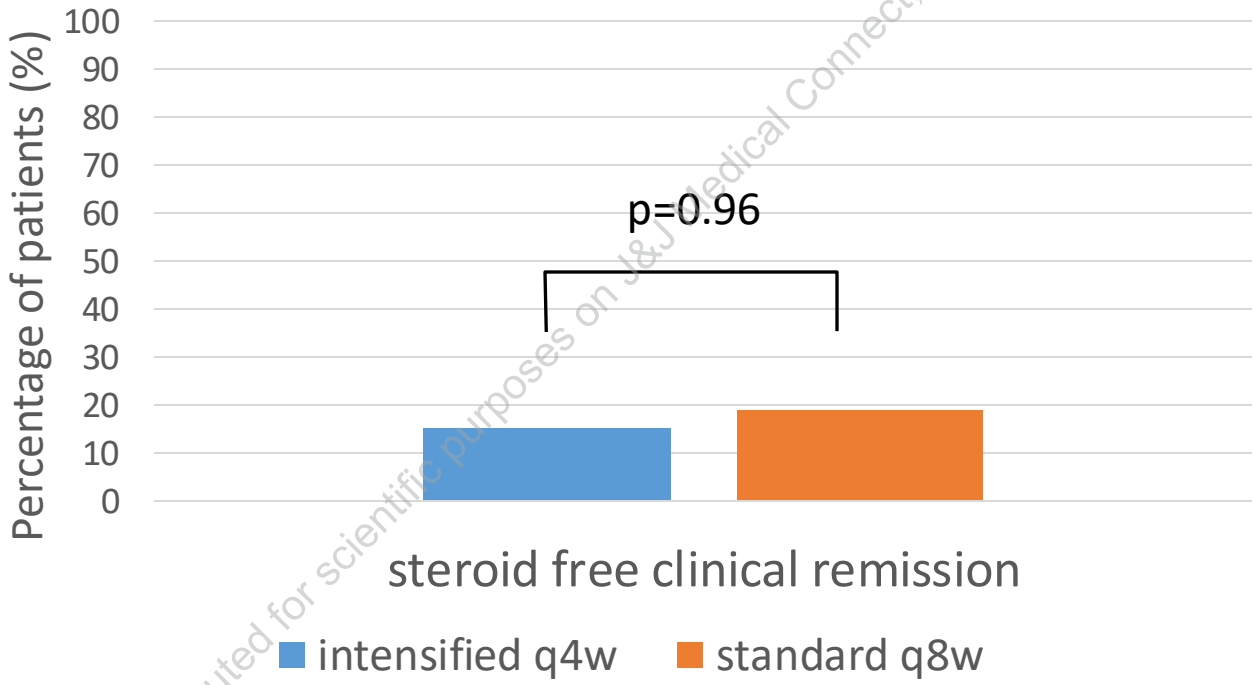
SES-CD: simple endoscopic score for Crohn's disease; CRP: C-reactive protein; FCP: fecal calprotectin; PRO: patient reported outcome; AP: abdominal pain; SF: stool frequency;

Results: baseline characteristics

	Q4 UST group, N = 54	Q8 UST group, N = 54
Age (years; median (IQR))	40 (32, 57)	41 (32, 53)
Disease duration (years; median (IQR))	14 (8, 23)	12 (7, 21)
Sex (female)	35 (65%)	32 (59%)
Weight (kg; median (IQR))	69 (62, 82)	69 (60, 81)
Active smoking (n; %)	12 (26%)	13 (24%)
CD Montreal location		
L1 Ileal (n; %)	16 (30%)	12 (22%)
L2 Colonic (n; %)	9 (17%)	6 (11%)
L3 Ileocolonic (n; %)	29 (54%)	36 (67%)
Peri-anal involvement (n; %)	11 (20%)	12 (22%)
Previous resective surgery (n; %)	30 (56%)	28 (52%)
Previous anti-TNF exposure (n; %)	49 (91%)	50 (93%)
CRP (mg/L; median (IQR))	7 (3, 16)	4 (2, 7)
FCP (µg/g; median (IQR))	293 (124, 719)	341 (69, 828)
Steroids at baseline (n; %)	6 (11%)	6 (11%)

IQR: inter quartile range; CD: Crohn's disease; TNF: tumor necrosis factor; CRP: C-reactive protein; FCP: fecal calprotectin

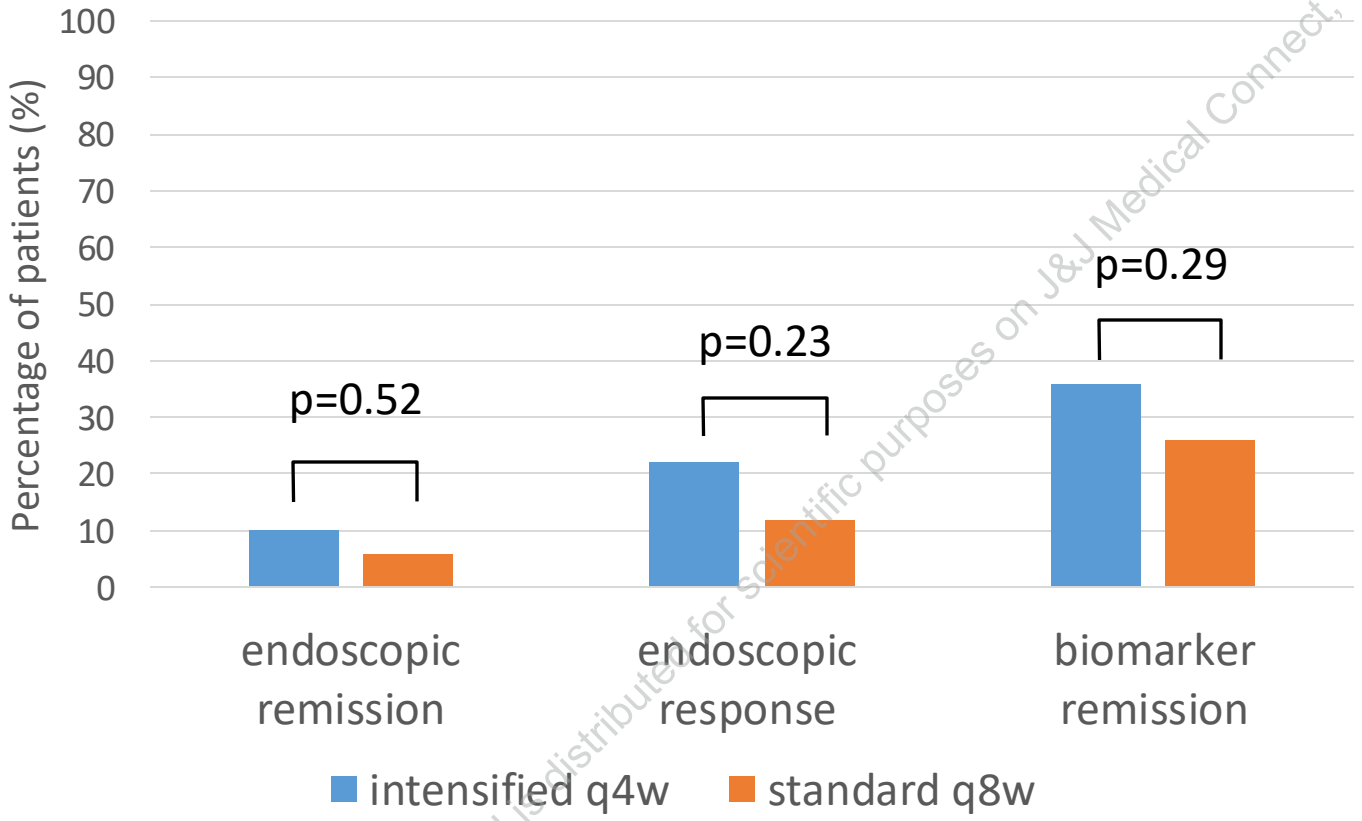
Results: primary endpoint at week 48



Steroid free clinical remission: PRO2 (AP ≤ 1 AND SF ≤ 3) and FCP <250µg/g and no steroids for 90 days prior to week 48

PRO: patient reported outcome; AP: abdominal pain; SF: stool frequency; FCP: fecal calprotectin

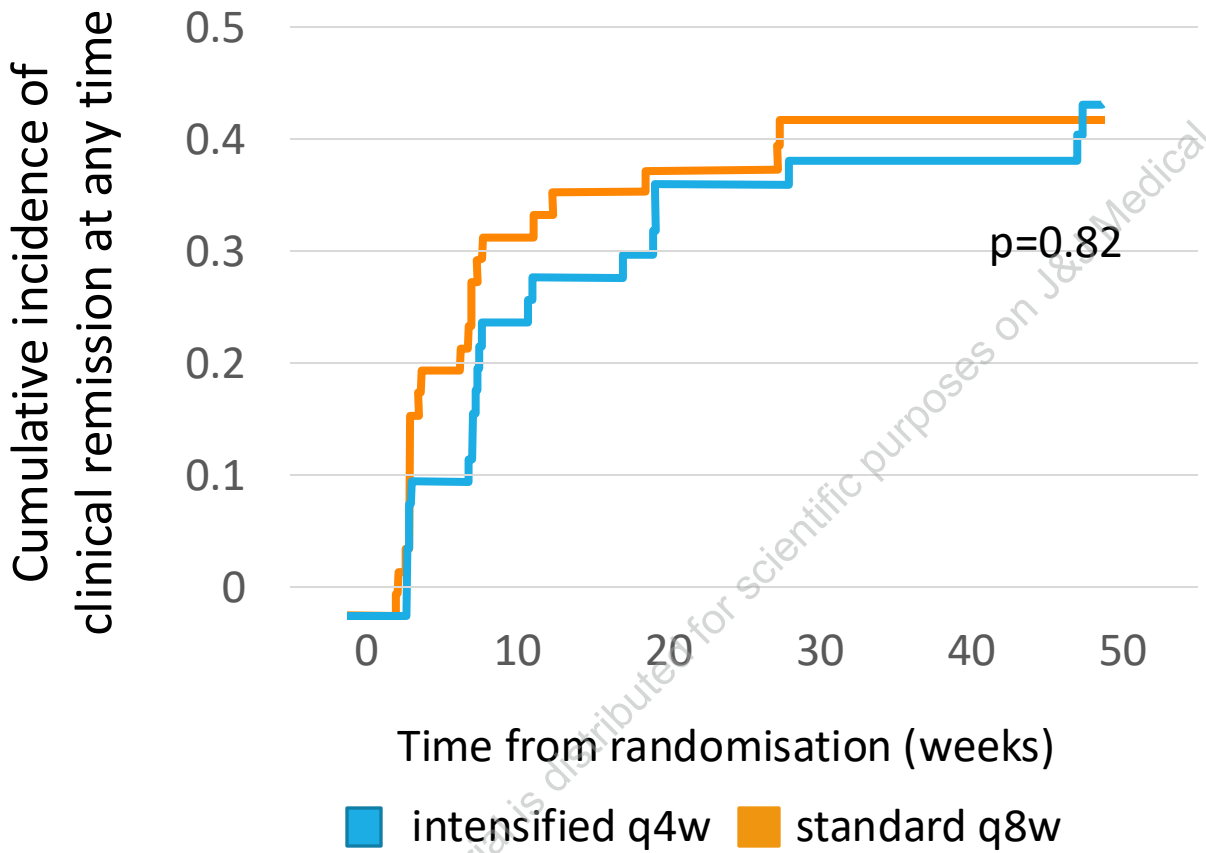
Results: secondary endpoints at week 48



- **Endoscopic remission**: SES-CD <3 at week 48
- **Endoscopic response**: 50% decrease in SES-CD compared to baseline at week 48
- **Biomarker remission**: CRP <5 mg/L and FCP <250 µg/g at week 48

SES-CD: simple endoscopic score for Crohn's disease; CRP: C-reactive protein; FCP: fecal calprotectin

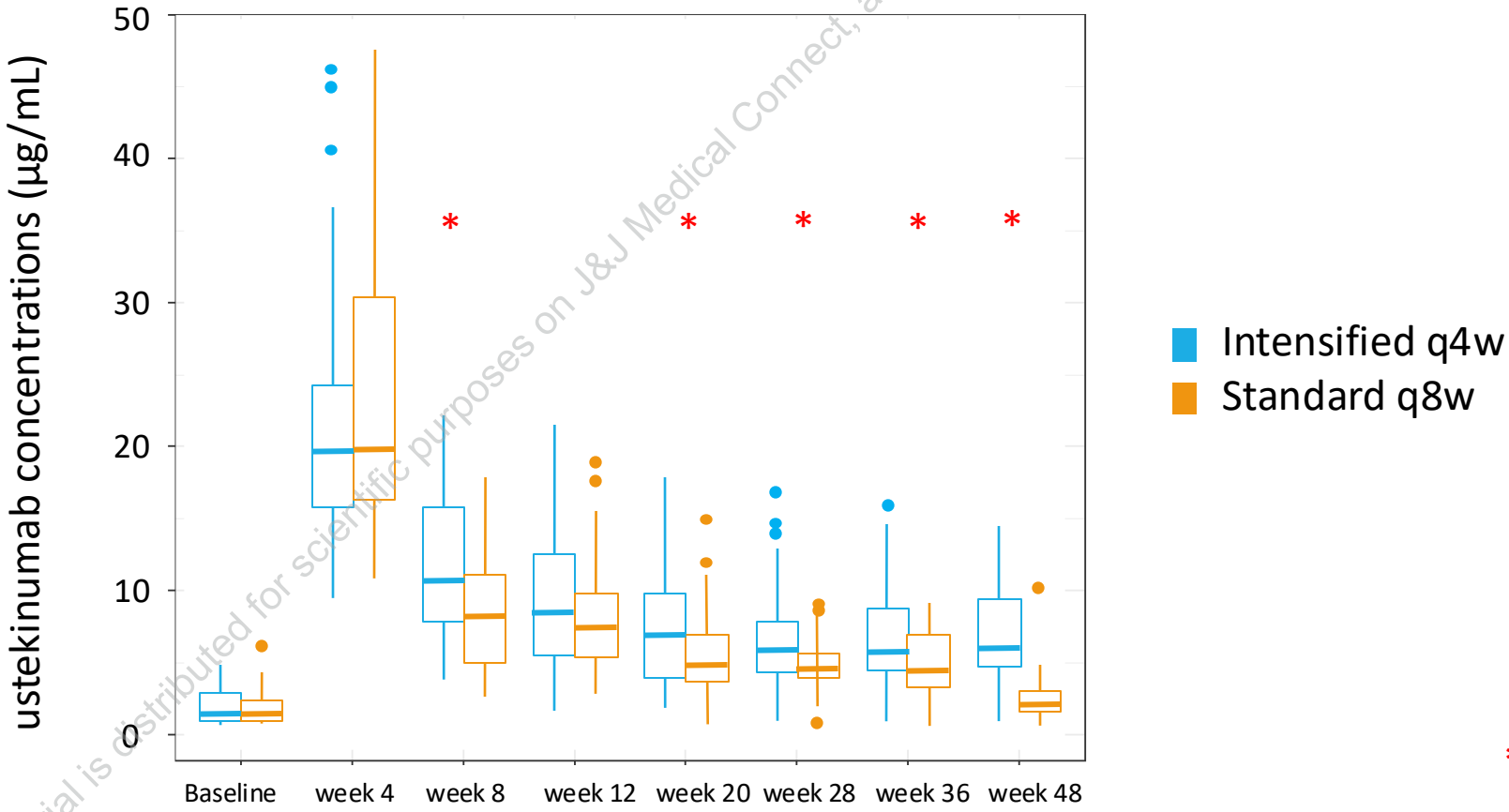
Results: time to clinical remission



- **Clinical remission**: PRO2 (AP ≤ 1 AND SF ≤ 3) and FCP <250µg/g

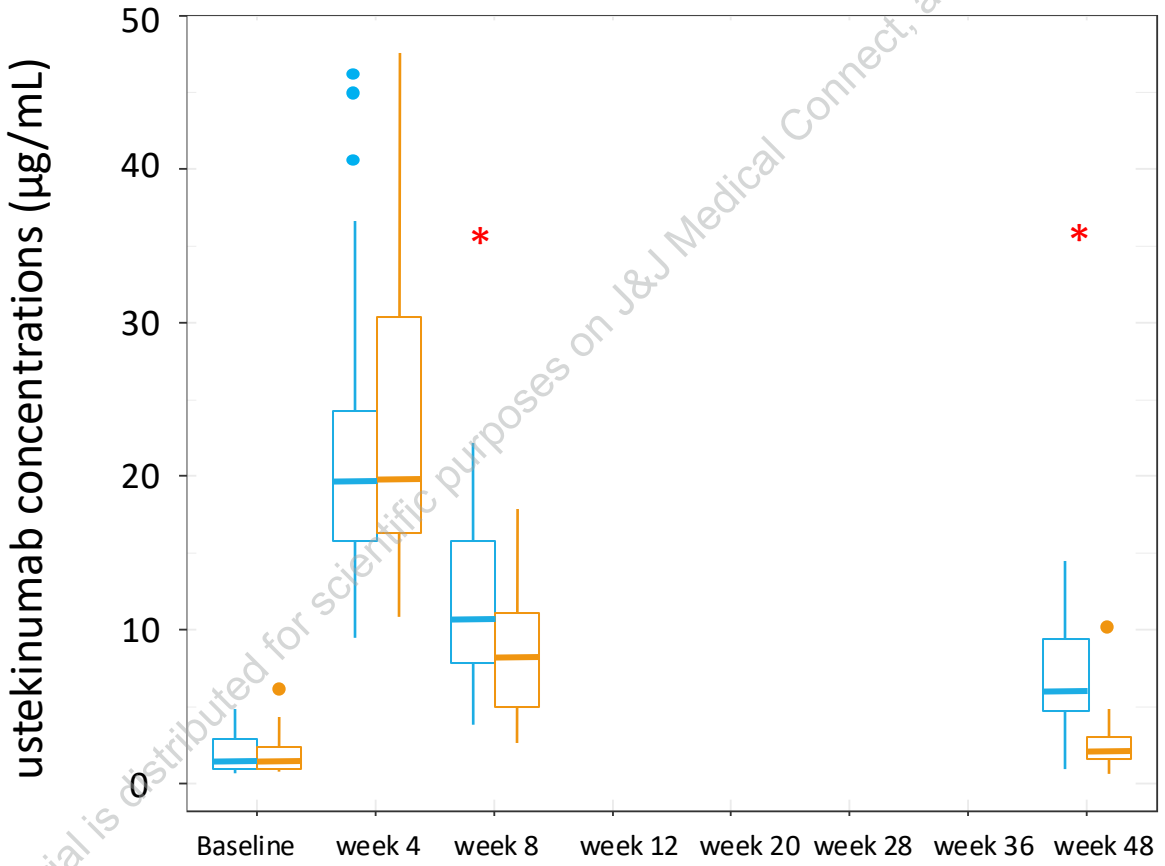
PRO: patient reported outcome; AP: abdominal pain; SF: stool frequency; FCP: fecal calprotectin

Results: ustekinumab serum concentrations



* p< 0.05

Results: ustekinumab serum concentrations



Intensified q4w
Standard q8w

* p< 0.05

Conclusion

- Following secondary loss of response to ustekinumab, dose optimisation recaptures remission in only a minority of patients (<20 %).
- **No significant difference** was seen **comparing two optimisation regimens** although one IV-reinduction infusion with ustekinumab followed by q4 weekly SC dosing was numerically better compared to one IV reinduction infusion followed by q8 weekly SC dosing.
- Although **ustekinumab serum levels significantly increased** after IV reinduction, this did not correlate with better outcomes.

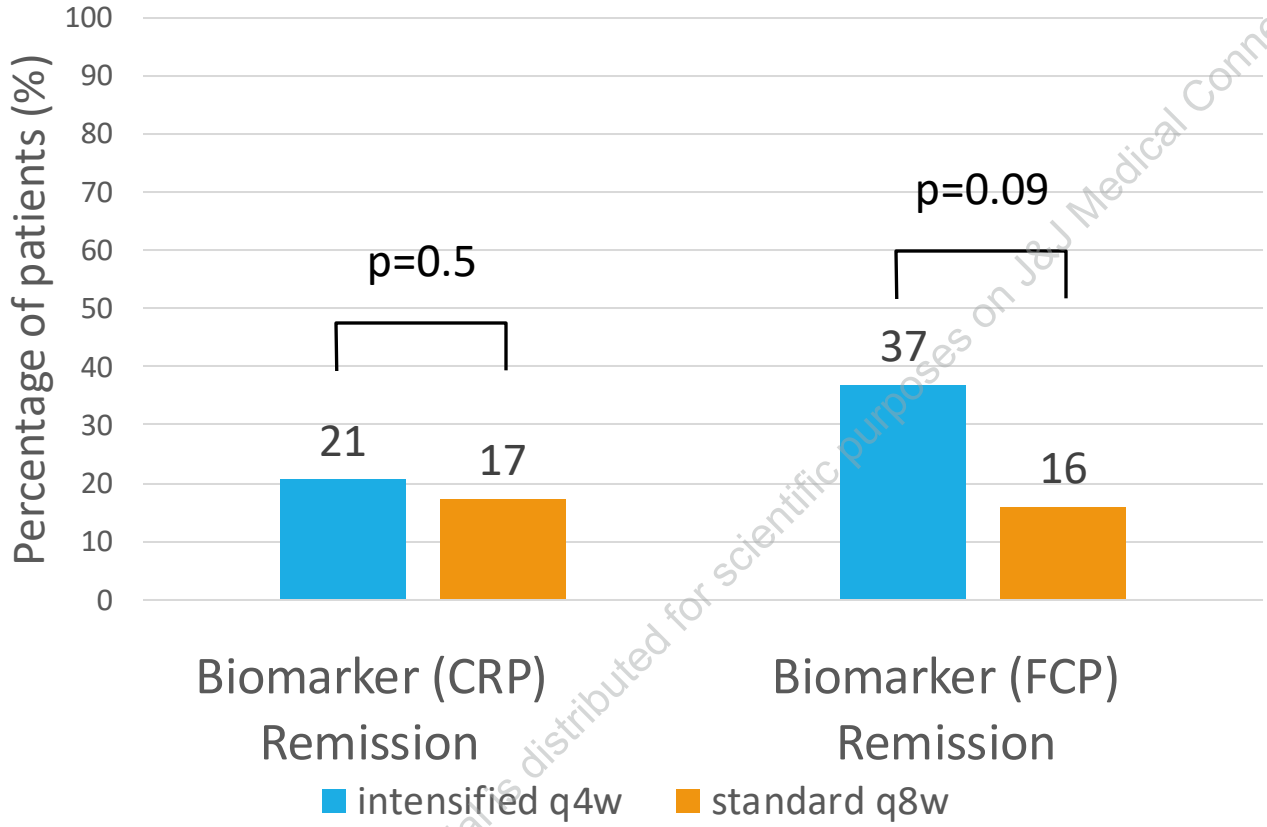
Rescue team

- Participating sites
  - Imelda General Hospital, Bonheiden
  - CHU Namur, Yvoir
  - AZ Delta, Roeselare
  - CHU University Hospital, Liège
  - University Hospital Antwerp, Antwerp
  - Ghent University Hospital, Ghent
  - AZ Sint-Lucas, Brugge
  - AZ St-Lucas, Ghent
  - AZ Maria Middelares, Ghent
  - Erasme University Hospital, Brussels
  - ZNA Jan Palfijn, Merksem
  - AZ Sint Jan, Brugge
  - AZ Turnhout, Turnhout
  - St. Luc University Hospital, Brussels
  - University Hospitals Leuven, Leuven

- BIRD office
  - Laura Vansteenkiste
  - Ingrid Arijs
  - Jolien De Rechter
- Statistics (StatGent)
  - Dries Reynders
- Grant support
  - Janssen Pharmaceutical NV

Backup slides

Results: secondary endpoints at week 48



- **Biomarker remission**: CRP <5 mg/L and FCP <250 µg/g at week 48 in patients with increased CRP or FCP at baseline respectively

CRP: C-reactive protein; FCP: fecal calprotectin

Results: ustekinumab serum concentrations and week 48 outcomes

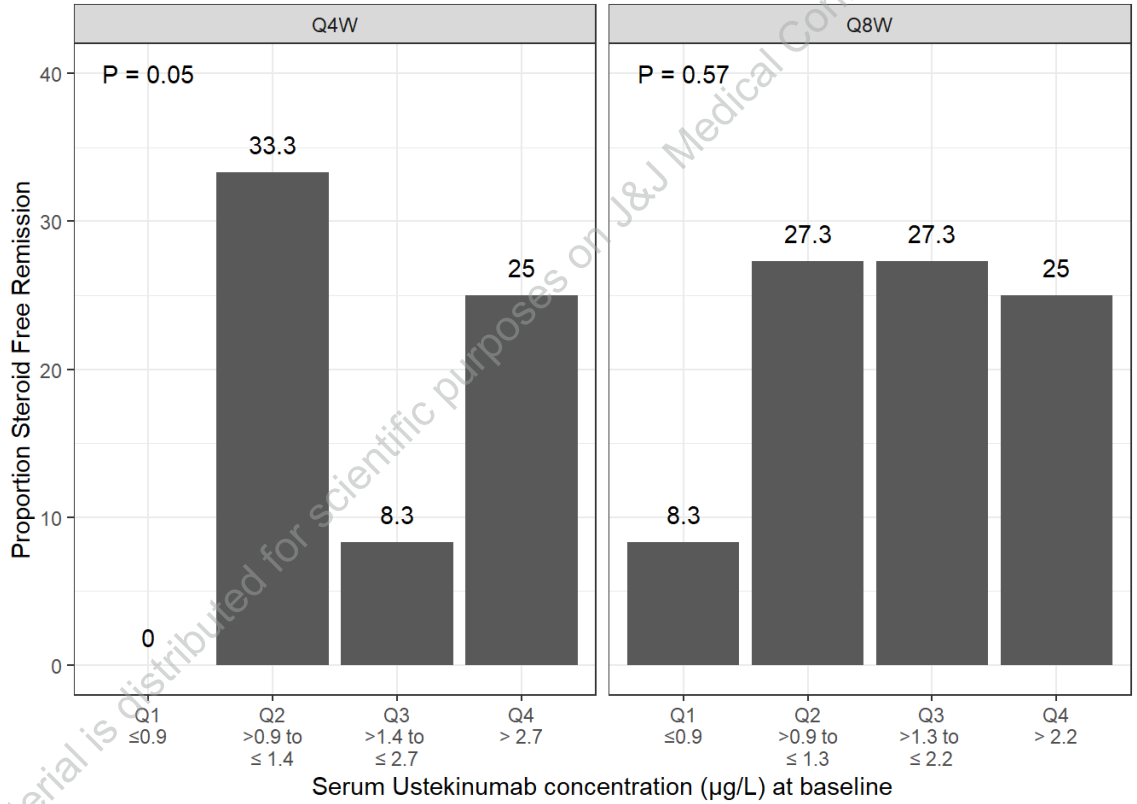
Characteristic	Steroid Free Clinical Remission OR (95% CI)	Endoscopic Remission OR (95% CI)	Clinical Remission OR (95% CI)	Biomarker Remission OR (95% CI)
Baseline Trough Levels	1.30 (0.84, 2.00)	1.53 (0.86, 2.66)	1.30 (0.84, 2.00)	2.98 (1.85, 5.23) *
No. Obs.	95	96	95	95
Week 8 Trough Levels	1.00 (0.94, 1.07)	1.05 (0.96, 1.14)	1.00 (0.94, 1.07)	1.12 (1.06, 1.19) *
No. Obs.	***	***	***	***
Week 48 Trough Levels	0.99 (0.83, 1.17)	1.09 (0.85, 1.36)	0.99 (0.83, 1.17)	1.35 (1.13, 1.66) *
No. Obs.	64	65	64	64

* $p < 0.003$

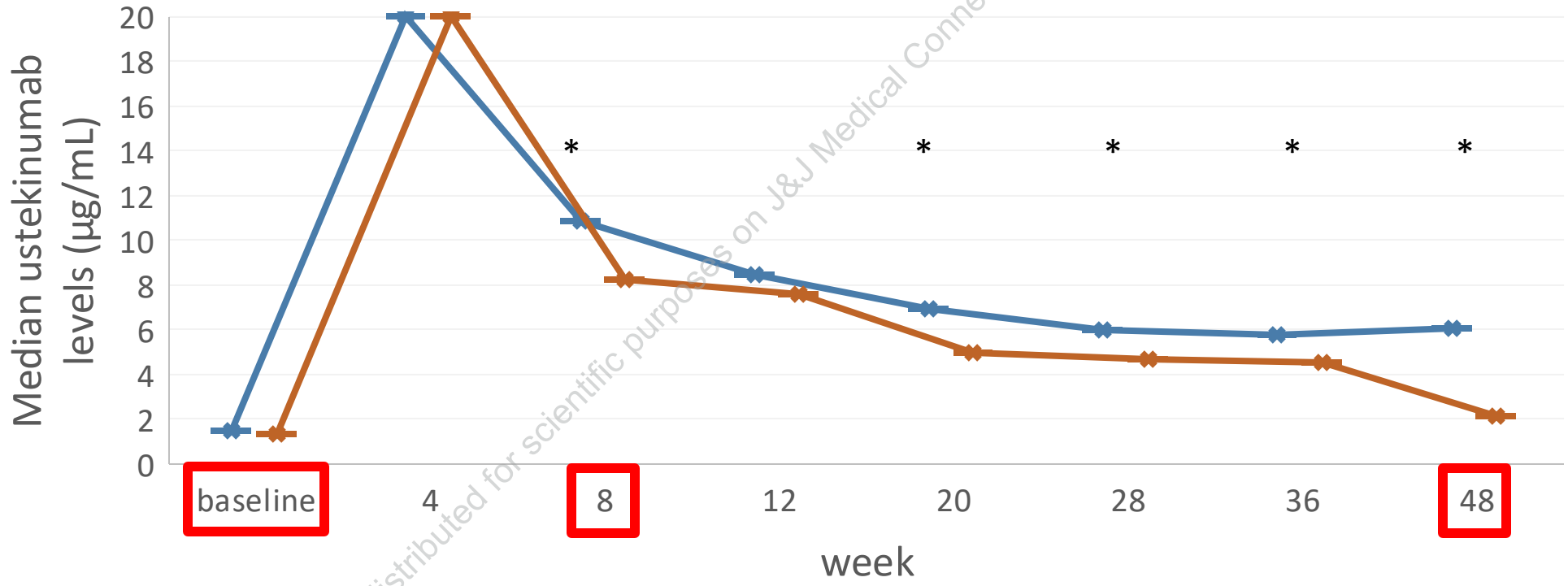
OR: Odd's ratio; CI: confidence interval; No. Obs.: numbers observed

Results: ustekinumab serum concentrations at week 48

- **Quartile analysis per treatment group**



Results: ustekinumab serum concentrations



* p< 0.05

Trough levels

Results: association between baseline variables and primary endpoint

- univariate analysis

Baseline variable	p-value
Baseline Trough Levels	0.754
Age	0.321
Disease duration	0.512
Sex	0.450
Weight	0.953
Smoking status	**0.008**
CD Montreal location	0.541
Previous surgery	0.934
CRP at screening	0.387
Previous anti-TNF exposure	0.278

CI: confidence interval; CD: Crohn's disease; CRP: C-reactive protein; TNF: tumor necrosing factor