SUPPLEMENTARY MATERIAL FOR:

Symptom Response Dynamics for Personalised Therapy with Subcutaneous Infliximab in Crohn's Disease: Insights from the Randomised, Placebo-Controlled, Phase 3 LIBERTY-CD Trial

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Supplementary Table 1. Summary of statistical indicator results for model evaluation

Polynomial degrees	*N* groups	Log-likelihood	AIC	BIC	Posterior probabilities of group membership (mean)	Minimum N of allocated to group (%)
2	3	-4253.186	8564.372	8730.977	0.9296	61 (26.4)
	4	-4193.431	8464.861	8688.916	0.9088	51 (22.1)
	5	-4145.966	8389.931	8671.436	0.9083	27 (11.7)
3	3	-3950.867	7971.734	8172.809	0.9397	67 (29.0)
	4	-3876.332	7846.664	8116.679	0.9203	52 (22.5)
	5	-3822.187	7762.373	8101.328	0.9007	29 (12.6)

AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; N, number.

Supplementary Table 2. Univariable and multivariable logistic regression analyses for being Super-responder versus Limited responder

Characteristic	Univariable		Multivariable	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Sex				
Female	1.00 (Reference)	-		
Male	1.90 (0.90–4.07)	0.095	2.08 (0.80–5.59)	0.136
Prior biologic or JAK inhibitor use	9.80 (1.78–183.25)	**0.033**	13.60 (1.14–896.32)	0.103
Oral corticosteroid use	0.50 (0.23–1.07)	0.075	0.32 (0.11–0.87)	**0.031**
Disease location				
- Ileal (vs Colonic)	1.13 (0.37–3.52)	0.835		
- Ileal-colonic (vs Colonic)	1.09 (0.48–2.53)	0.832		
CD duration, years	1.04 (0.96–1.13)	0.381		
History of surgery	0.20 (0.01–1.38)	0.151	0.09 (0–1.00)	0.082
History of anal disease	0.82 (0.24–2.78)	0.743		
Age, years	0.97 (0.94–1.00)	0.065	1.01 (0.97–1.05)	0.790
Weight, kg	1.00 (0.98–1.03)	0.903		
BMI, kg/m²	0.96 (0.87–1.04)	0.304		
SES-CD	1.05 (0.99–1.12)	0.100	1.04 (0.96–1.12)	0.345
CDAI score	1.01 (1.01–1.02)	**0.0004**	1.01 (1.00–1.02)	**0.005**
FC, mg/kg	1.00 (1.00–1.00)	0.822		
CRP, nmol/L	1.00 (1.00–1.00)	0.372		
Lymphocytes, 10^9 cells/L	1.16 (0.71–1.91)	0.558		
Neutrophils, 10^9 cells/L	1.15 (0.99–1.37)	0.082	1.16 (0.94–1.47)	0.177
Albumin, g/L	1.02 (0.94–1.10)	0.658		
W14 IFX serum level ≥12 µg/mL	3.55 (1.58–8.28)	**0.003**	4.26 (1.56–12.70)	**0.006**

BMI, Body mass index; CD, Crohn's Disease; CDAI, Crohn's Disease Activity Index; CDC, Comprehensive Disease Control; CI, confidence interval; CRP, C-reactive protein; FC, faecal calprotectin; IFX, infliximab; JAK, Janus kinase; OR, Odds ratio; SES-CD, Simple Endoscopic Score for Crohn's Disease; W, week.

Supplementary Table 3. Univariable and multivariable logistic regression analyses for being Fast responder versus Slow responder.

Characteristic	Univariable		Multivariable	
	OR (95% CI)	**P-value**	**OR (95% CI)**	**P-value**
Sex				
Female	1.00 (Reference)			
Male	1.39 (0.66–2.98)	0.393		
Prior biologic or JAK inhibitor use	1.33 (0.45–4.06)	0.603		
Oral corticosteroid use	1.62 (0.78–3.40)	0.198	1.60 (0.75–3.42)	0.225
Disease location				
- Ileal (vs Colonic)	0.38 (0.11–1.15)	0.099	0.37 (0.11–1.16)	0.101
- Ileal-colonic (vs Colonic)	0.78 (0.34–1.74)	0.537	0.79 (0.34–1.82)	0.587
CD duration, years	1.01 (0.94–1.08)	0.852		
History of surgery	0.83 (0.16–3.95)	0.819		
History of anal disease	1.82 (0.61–5.77)	0.288		
Age, years	0.99 (0.96–1.02)	0.599		
Weight, kg	1.01 (0.98–1.03)	0.511		
BMI, kg/m²	1.02 (0.94–1.11)	0.624		
SES-CD	1.02 (0.97–1.07)	0.529		
CDAI score	1.00 (0.99–1.01)	0.838		
FC, mg/kg	1.00 (1.00–1.00)	0.284		
CRP, nmol/L	1.00 (1.00–1.00)	0.584		
Lymphocytes, 10^9 cells/L	1.13 (0.69–1.84)	0.628		
Neutrophils, 10^9 cells/L	1.00 (0.87–1.15)	0.987		
Albumin, g/L	0.97 (0.90–1.04)	0.389		
W14 IFX serum level ≥10 µg/mL	0.45 (0.18–1.04)	0.066	0.44 (0.18-1.05)	0.069

BMI, Body mass index; CD, Crohn's Disease; CDAI, Crohn's Disease Activity Index; CDC, Comprehensive Disease Control; CI, confidence interval; CRP, C-reactive protein; FC, faecal calprotectin; IFX, infliximab; JAK, Janus kinase; OR, Odds ratio; SES-CD, Simple Endoscopic Score for Crohn's Disease; W, week.

Supplementary Table 4. Comprehensive disease control by response trajectories

	Super-responders (n=61)	**Fast responders (n=56)**	**Slow responders (n=63)**	**Limited responders (n=51)**
Number of endpoints achieved, n (%)				
4 (CDC)*	17 (27.9)	9 (16.1)	16 (25.4)	3 (5.9)
3	16 (26.2)	16 (28.6)	18 (28.6)	14 (27.5)
2	16 (26.2)	13 (23.2)	19 (30.2)	7 (13.7)
1	1 (1.6)	8 (14.3)	3 (4.8)	6 (11.8)
0	11 (18.0)	10 (17.9)	7 (11.1)	21 (41.2)

*CDC was defined as achieving clinical remission, endoscopic remission, faecal calprotectin normalisation and remission by health-related quality of life, simultaneously.
The definitions of each component: Clinical remission, an absolute CDAI score <150; Endoscopic remission, SES-CD of ≤4 and ≥2-point reduction from the baseline value with no segment sub-score of >1; Faecal calprotectin normalisation, ≤250 μg/g; Remission by health-related quality of life, SIBDQ score ≥50. Rates of clinical remission, endoscopic remission, FC normalization, HRQoL remission and CDC included data for patients who received dose-adjustment.
Patients with missing data were classed as a non-responder/non-remitter.
CDAI, Crohn's disease activity index; CDC, comprehensive disease control; FC, faecal calprotectin; HRQoL, health-related quality of life; SES-CD, Simple Endoscopic Score for Crohn's Disease; SIBDQ, Short Inflammatory Bowel Disease Questionnaire.

Supplementary Table 5. Proportion of ADA-positive patients by response trajectories

	Super-responders (n=61)	**Fast responders (n=56)**	**Slow responders (n=63)**	**Limited responders (n=51)**
Visit, % (n/N)				
W0	0 (0/60)	1.8 (1/56)	3.2 (2/62)	2.0 (1/51)
W10	3.3 (2/61)	7.1 (4/56)	9.5 (6/63)	9.8 (5/51)
W14	16.9 (10/59)	19.6 (11/56)	27.9 (17/61)	28.6 (14/49)
W22	39.0 (23/59)	48.1 (25/52)	48.4 (30/62)	55.1 (27/49)
W30	49.1 (28/57)	56.0 (28/50)	55.7 (34/61)	58.3 (28/48)
W38	57.4 (31/54)	58.3 (28/48)	58.6 (34/58)	53.7 (22/41)
W46	55.6 (30/54)	62.0 (31/50)	55.9 (33/59)	51.3 (20/39)
W54	45.1 (23/51)	63.3 (31/49)	56.9 (33/58)	58.3 (21/36)

ADA, anti-drug antibody; W, week.

Supplementary Table 6. Distribution of ADA titer levels across response trajectories.

	Super-responders (n=61)	**Fast responders (n=56)**	**Slow responders (n=63)**	**Limited responders (n=51)**
Visit, % (n/N)				
W0				
Low	0 (0/60)	0 (0/56)	1.6 (1/62)	2.0 (1/51)
Moderate	0 (0/60)	1.8 (1/56)	1.6 (1/62)	0 (0/51)
High	0 (0/60)	0 (0/56)	0 (0/62)	0 (0/51)
W10				
Low	1.6 (1/61)	3.6 (2/56)	6.3 (4/63)	7.8 (4/51)
Moderate	1.6 (1/61)	1.8 (1/56)	1.6 (1/63)	2.0 (1/51)
High	0 (0/61)	1.8 (1/56)	1.6 (1/63)	0 (0/51)
W14				
Low	10.2 (6/59)	12.5 (7/56)	23.0 (14/61)	22.4 (11/49)
Moderate	5.1 (3/59)	5.4 (3/56)	1.6 (1/61)	4.1 (2/49)
High	1.7 (1/59)	1.8 (1/56)	3.3 (2/61)	2.0 (1/49)
W22				
Low	23.7 (14/59)	34.6 (18/52)	27.4 (17/62)	26.5 (13/49)
Moderate	13.6 (8/59)	9.6 (5/52)	17.7 (11/62)	24.5 (12/49)
High	1.7 (1/59)	3.8 (2/52)	3.2 (2/62)	4.1 (2/49)
W30				
Low	21.1 (12/57)	30.0 (15/50)	26.2 (16/61_	31.3 (15/48)
Moderate	22.8 (13/57)	20.0 (10/50)	24.6 (15/61)	14.6 (7/48)
High	5.3 (3/57)	6.0 (3/50)	4.9 (3/61)	12.5 (6/48)
W38				
Low	24.1 (13/54)	18.8 (9/48)	20.7 (12/58)	26.8 (11/41)
Moderate	20.4 (11/54)	29.2 (14/48)	31.0 (18/58)	19.5 (8/41)
High	13.0 (7/54)	10.4 (5/48)	6.9 (4/58)	7.3 (3/41)
W46				
Low	22.2 (12/54)	28.0 (14/50)	18.6 (11/59)	25.6 (10/39)
Moderate	20.4 (11/54)	24.0 (12/50)	30.5 (18/59)	15.4 (6/39)
High	13.0 (7/54)	10.0 (5/50)	6.8 (4/59)	10.3 (4/39)
W54				
Low	11.8 (6/51)	30.6 (15/49)	22.4 (13/58)	27.8 (10/36)
Moderate	23.5 (12/51)	24.5 (12/49)	25.9 (15/58)	19.4 (7/36)
High	9.8 (5/51)	8.2 (4/49)	8.6 (5/58)	11.1 (4/36)

ADA-positive patients were further stratified according to the maximum serum dilution factor (ADA titer) used for ADA testing during the study: low (<100), moderate (≥100 to <1000) and high (≥1000).

ADA, anti-drug antibody; W, week.

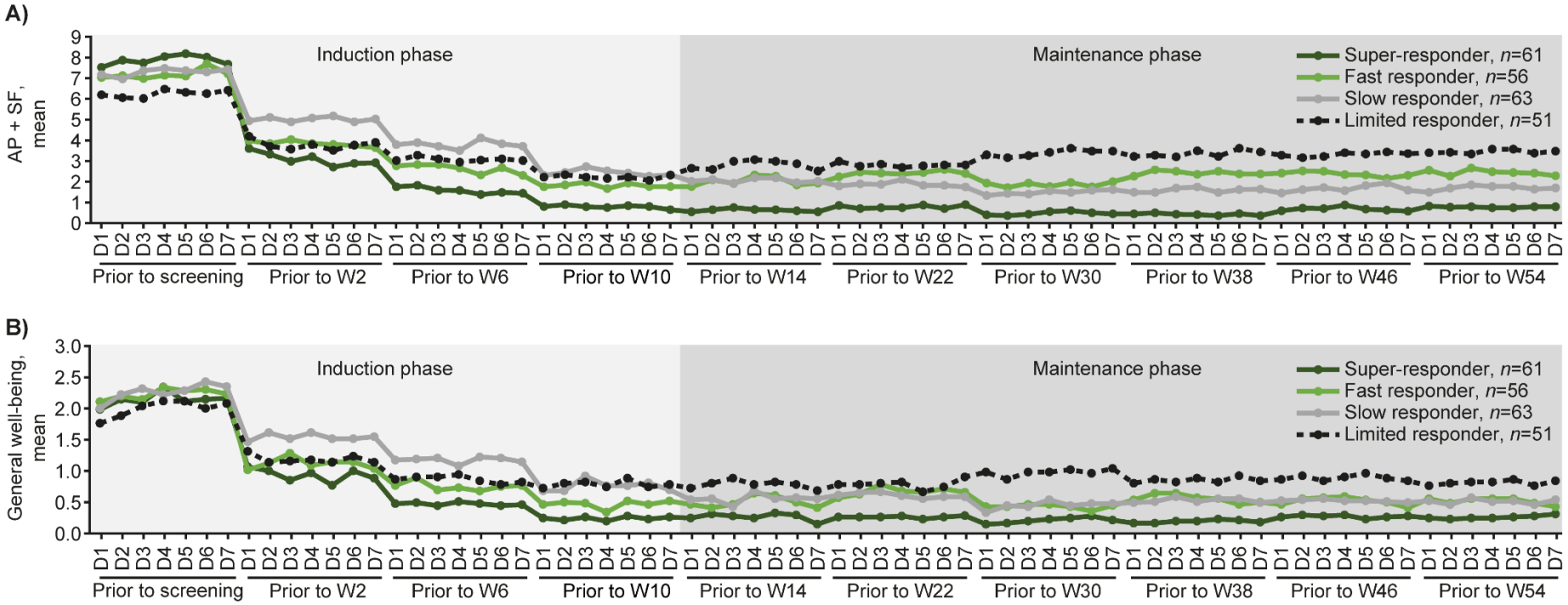
Supplementary Table 7. Comparison of patients with pre-dose serum infliximab levels at week 10 and week 14 by trajectories.

Trajectories	Pre-dose infliximab levels ≥ 14 µg/mL at week 10			Pre-dose infliximab levels ≥ 12 µg/mL at week 14		
		p-value†			p-value†	
	Achieved patient n / Total patient n (%)	SR vs others	SR vs LR or FR vs Sl.R	Achieved patient n / Total patient n (%)	SR vs others	SR vs LR or FR vs Sl.R
Super responders (SR)	32/60 (53.3)	0.024	0.085	48/58 (82.8)	0.002	0.002
Limited responders (LR)	18/49 (36.7)			26/48 (54.2)		
Fast responders (FR)	21/56 (37.5)		0.821	33/55 (60.0)		0.616
Slow responders (Sl. R)	22/62 (35.5)			40/62 (64.5)		

†Statistical comparisons were analysed by chi-square test.

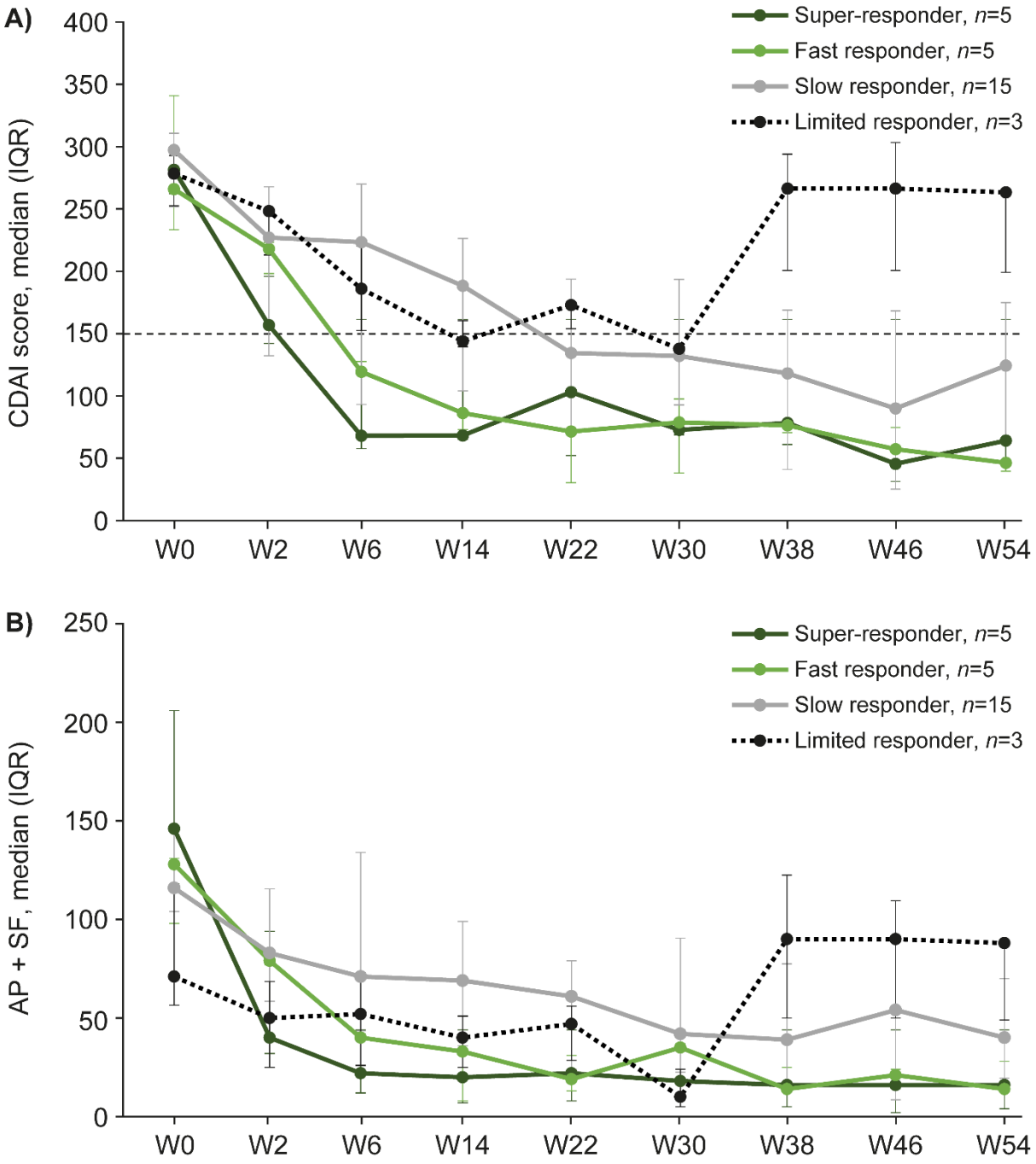
FR, Fast responders; LR, Limited responders; n, number; Sl. R, Slow responders; SR, Super-responders.

Supplementary Figure 1. Onset of symptomatic response based on patient-reported AP and SF (A) and general well-being (B) scores, by response trajectories.



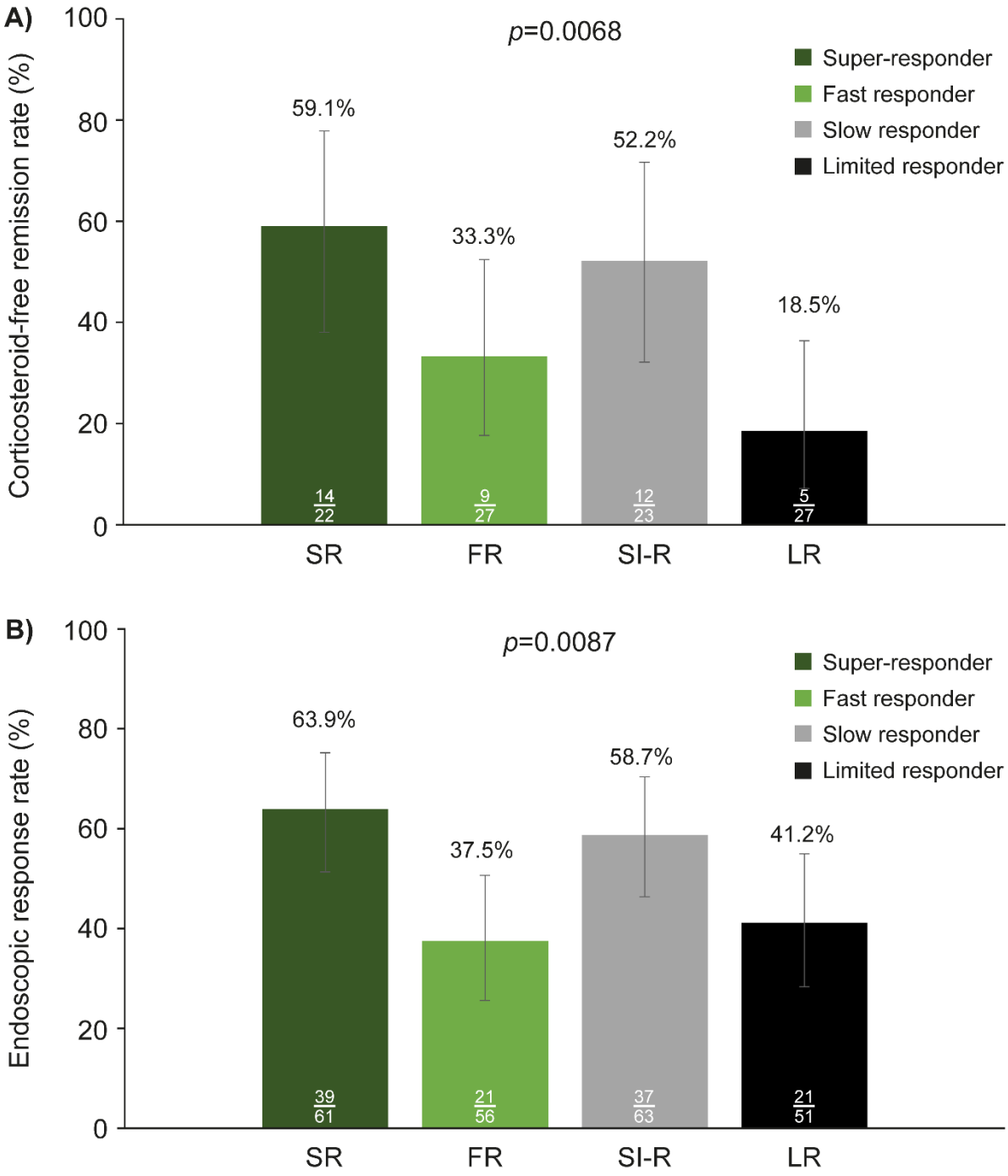
AP, abdominal pain; D, day; SF, stool frequency; W, week

Supplementary Figure 2. Replication test with data from the European registration study (1.6 study). CDAI score (A) or AP and SF (B) according to response trajectory in patients treated with SC infliximab.



The horizontal dashed line indicates the threshold for clinical remission (CDAI score <150 points).
AP, abdominal pain; CDAI, Crohn's Disease Activity Index; IQR, interquartile range; SC, subcutaneous; SF, stool frequency.

Supplementary Figure 3. Additional clinical outcomes by response trajectories including (A) corticosteroid-free remission and (B) endoscopic response rates at week 54.



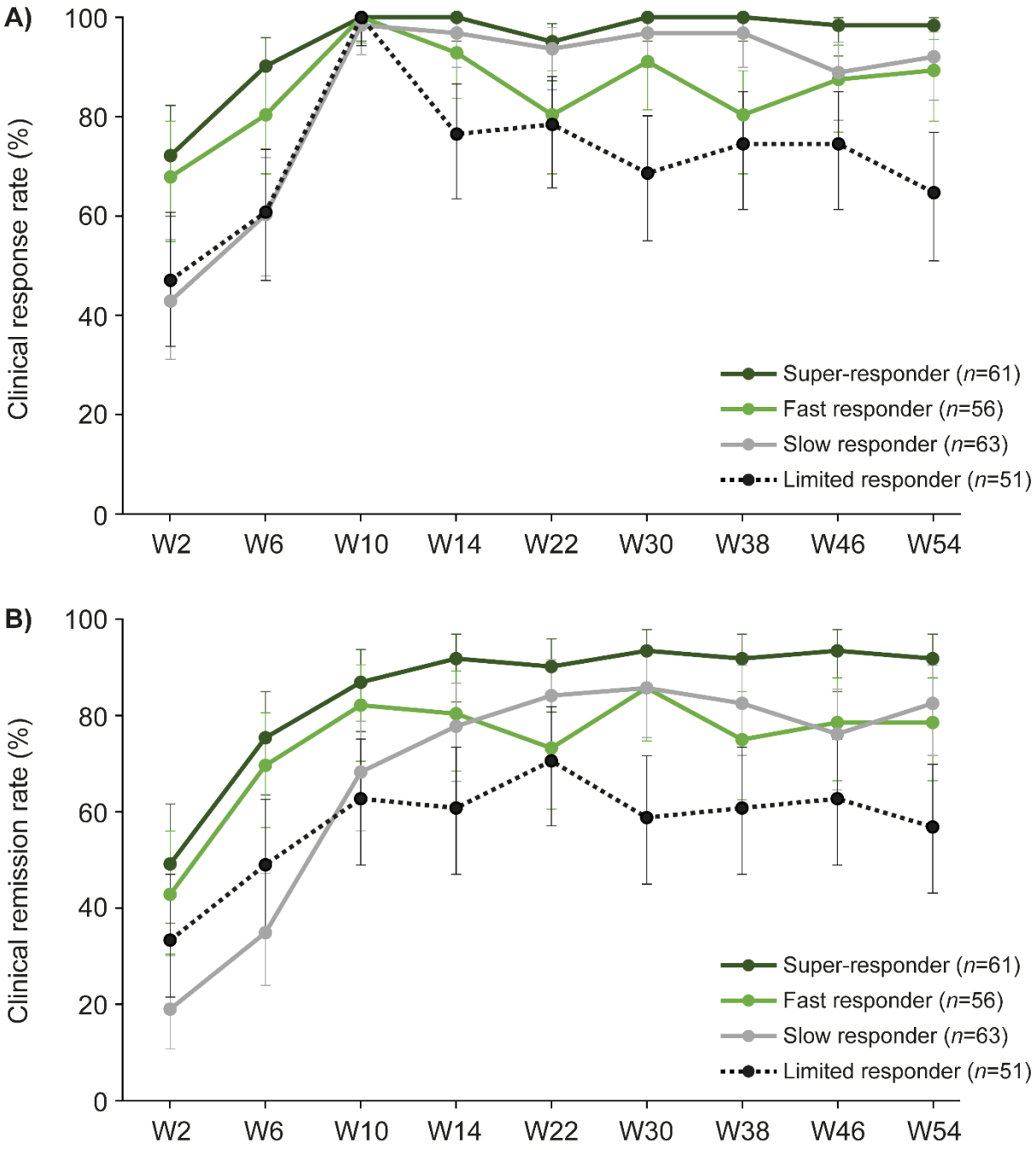
Corticosteroid-free remission at Week 54, as being in clinical remission in addition to not receiving corticosteroids for ≥8 weeks prior to Week 54, among patients who used oral corticosteroids at baseline; Endoscopic response, ≥ 50% decrease in SES-CD from baseline.

Patients with dose adjustment to infliximab SC 240 mg were considered as non-remitter/non-responder.

Statistical comparisons were analysed by chi-square test.

FR, Fast responder; LR, Limited responder; SC, subcutaneous; SES-CD, Simple Endoscopic Score for Crohn's Disease; SR, Super-responder; Sl-R, Slow responder; W, week.

Supplementary Figure 4. Clinical response (A) and clinical remission (B) rates by response trajectories.



Clinical response, decrease in CDAI score of 100 points or more from the baseline value; clinical remission, CDAI score of < 150 points including patients with dose adjustment to infliximab SC 240 mg. Missing data were imputed using the last observation carried forward (LOCF) method to complete the longitudinal dataset.

CDAI, Crohn's Disease Activity Index; SC, subcutaneous; W, week.