Supplementary Materials

Real-World Safety and Effectiveness of Infliximab in 255 Patients with Intestinal, Neurological, and Vascular Behçet's Disease: A Post-Marketing Surveillance

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Supplementary Methods

Observation Period and Final Evaluation Date

The observation period for safety was 2 years (or until the last observation day for patients who discontinued the observation). The observation period for effectiveness was up to the day of the last administration of infliximab (IFX) for patients who continued treatment (maximum of 2 years). For patients who discontinued treatment, the observation period was either “the day of the last administration + 56 days” or “the day of the most recent global improvement assessment after the latest administration day”, whichever was longer.

For patients who discontinued treatment, the final evaluation date was the date after the last administration and the date closest to the last administration date; for patients who continued treatment, the final evaluation date was the last date of treatment.

Patient Demographics and Background

The following patient demographics and background data were collected: sex; age; intestinal Behçet's disease (BD), neurological BD (NBD), or vascular BD (VBD) duration; body mass index; history of tuberculosis infection, allergies, malignancy, respiratory disease, and adverse drug reactions (ADRs); major and minor symptoms of BD; comorbidities; and treatment history. Concomitant treatment and combination therapy used at least once during the observation period were recorded.

Definitions of ADR

ADRs were defined as adverse events determined by the investigator or sponsor to have a causal relationship to IFX and were categorized using the Medical Dictionary for Regulatory Activities, Japanese edition, version 25.0.

Assessment Criteria of Effectiveness

The largest diameter of the main intestinal ulcer:

The change in size compared with the largest diameter prior to the first IFX dose was rated on a 4-point scale (resolved, reduced, unchanged, or worsened).

Brain MRI:

The change in high-signal areas and brainstem atrophy compared prior to the first IFX dose was rated on a 4-pont scale (disappeared, reduced, unchanged, or worsened) and a 2-point scale (unchanged or worsened), respectively.

Vascular imaging:

The degree of improvement from scans prior to IFX administration was rated on a 3-point scale (improved, unchanged, or worsened).

Statistical Analyses

Continuous data were summarized using summary statistics (mean, standard deviation, median, interquartile range, and range), and categorical and frequency data were summarized by number and percentage.

ADR and effectiveness by patient background:

The incidence of ADRs in patients with intestinal BD, NBD, and VBD and global improvement in patients, except those with ANBD, were stratified by patient background factors and evaluated. A chi-square test was conducted to examine background factors associated with ADRs and effectiveness (global improvement), and Fisher's exact test was used for categorical factors with two levels. For ADRs and effectiveness, risk ratios and ratios were calculated with their 95% confidence intervals between categories, respectively.

Factors with differences in ADRs and effectiveness were defined as those with a statistically significant difference or ratios of < 0.50 or > 2.00 in ≥ 5 patients among the factor categories (excluding unknown or not described). Factors with a difference in ADRs by system organ class were defined as those with ratios of < 0.50 or > 2.00 in ≥ 5 patients of ADRs in the category (excluding unknown or not described) paired with reference.

Post hoc analyses:

For patients with data at the final evaluation, the time from the start of treatment to the final evaluation was tabulated as a post hoc analysis. The percentage of patients with acute NBD (ANBD) who had no new acute attacks was calculated post hoc with reference to the 2018 update of the EULAR recommendations for the management of Behçet's syndrome [1]. The Kaplan–Meier method was used to evaluate treatment persistence rate as a post hoc analysis.

Reference

1. Hatemi G, Christensen R, Bang D, et al. 2018 update of the EULAR recommendations for the management of Behçet's syndrome. Ann Rheum Dis. 2018; 77:808–18.

Supplementary Figures

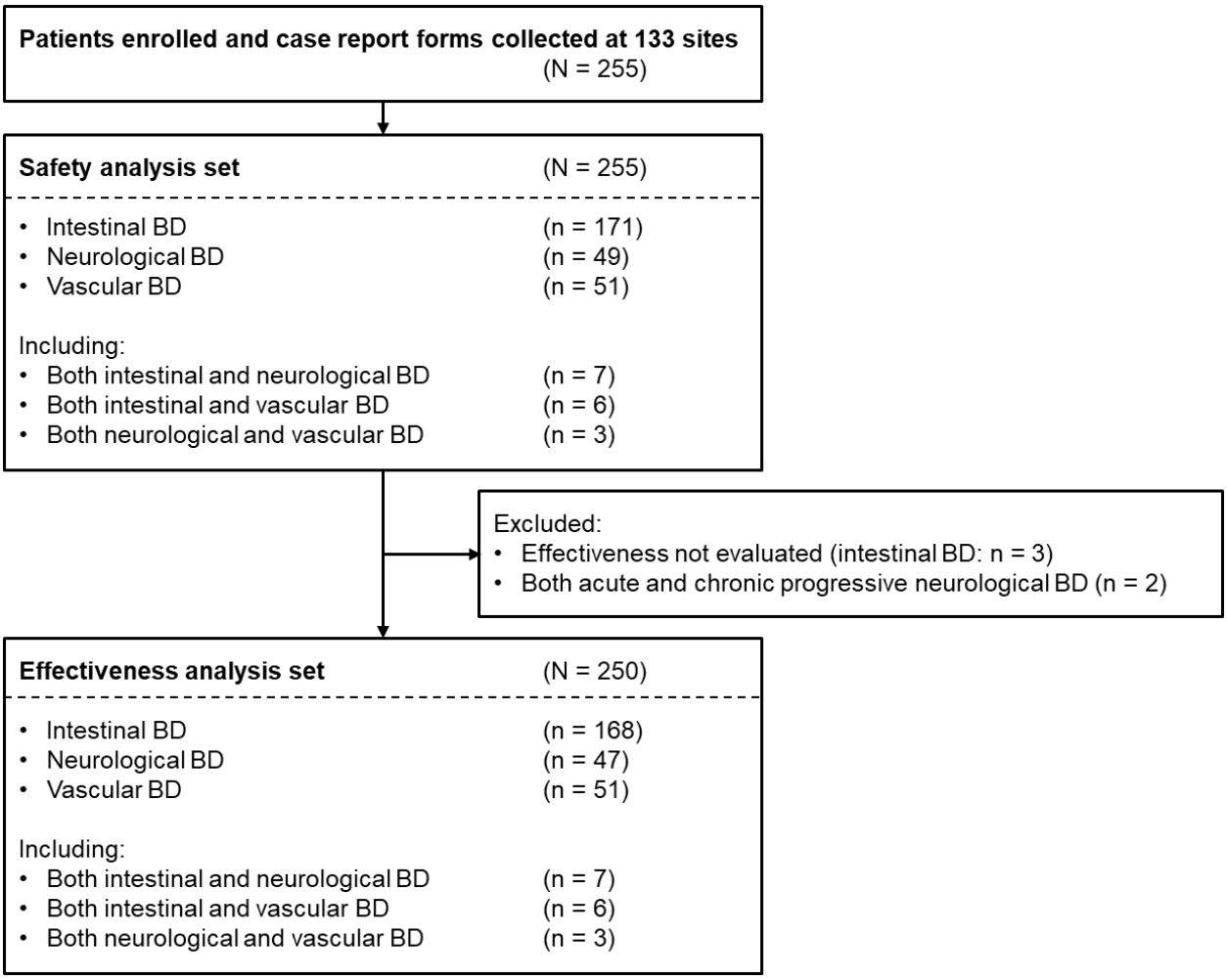
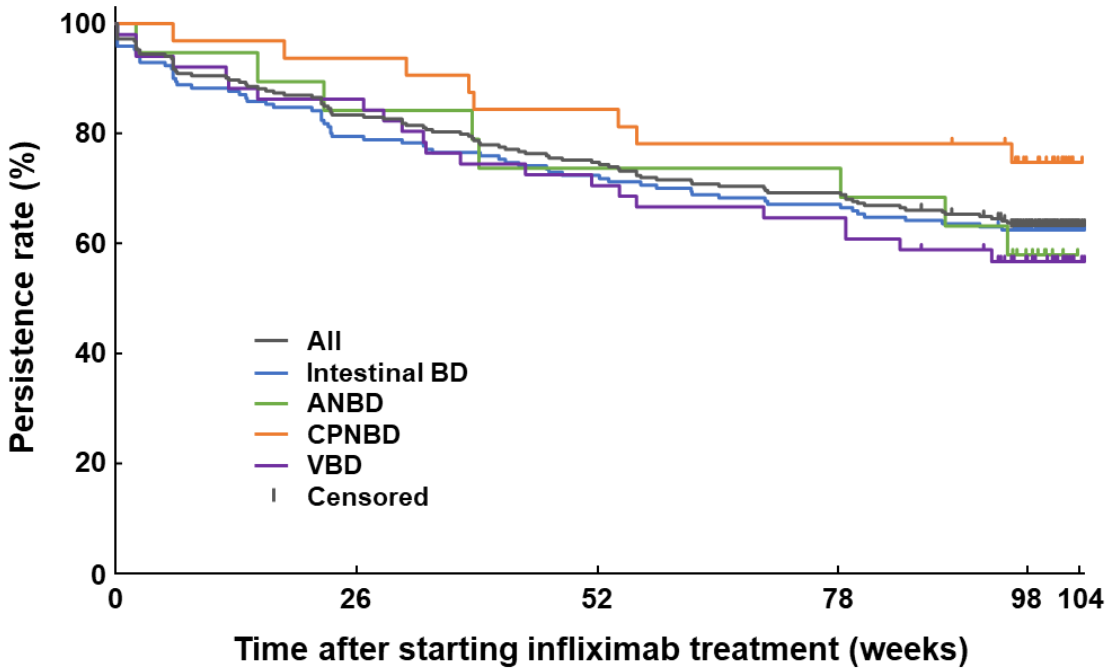


Fig. S1. Study flow diagram.

The number of patients enrolled at 133 sites was one patient at 76 (57.1%) sites, two patients at 26 (19.5%) sites, three patients at 18 (13.5%) sites, four patients at 4 (3.0%) sites, five patients at 4 (3.0%) sites, six patients at 1 (0.8%) site, seven patients at 1 (0.8%) site, and eight patients at 3 (2.3%) sites.

BD Behçet's disease.



No. at risk					
All	255[a]	212	190	176	134
Intestinal BD	171	135	123	114	94
ANBD	19[b]	16	14	14	8
CPNBD	32[b]	30	27	25	18
VBD	51	44	36	33	22

Fig. S2. Treatment persistence rate (Kaplan–Meier method).

Dose escalation of IFX was regarded as treatment persistence. The IFX dose was increased in 80 patients (intestinal BD: n = 61; NBD: n = 16; and VBD: n = 10).

[a]Including seven patients with both intestinal and neurological BD, six patients with both intestinal and vascular BD, and three patients with both neurological and vascular BD.

[b]Including two patients with both ANBD and CPNBD.

ANBD acute neurological Behçet's disease, *BD* Behçet's disease, *CPNBD* chronic progressive neurological Behçet's disease, *VBD* vascular Behçet's disease.

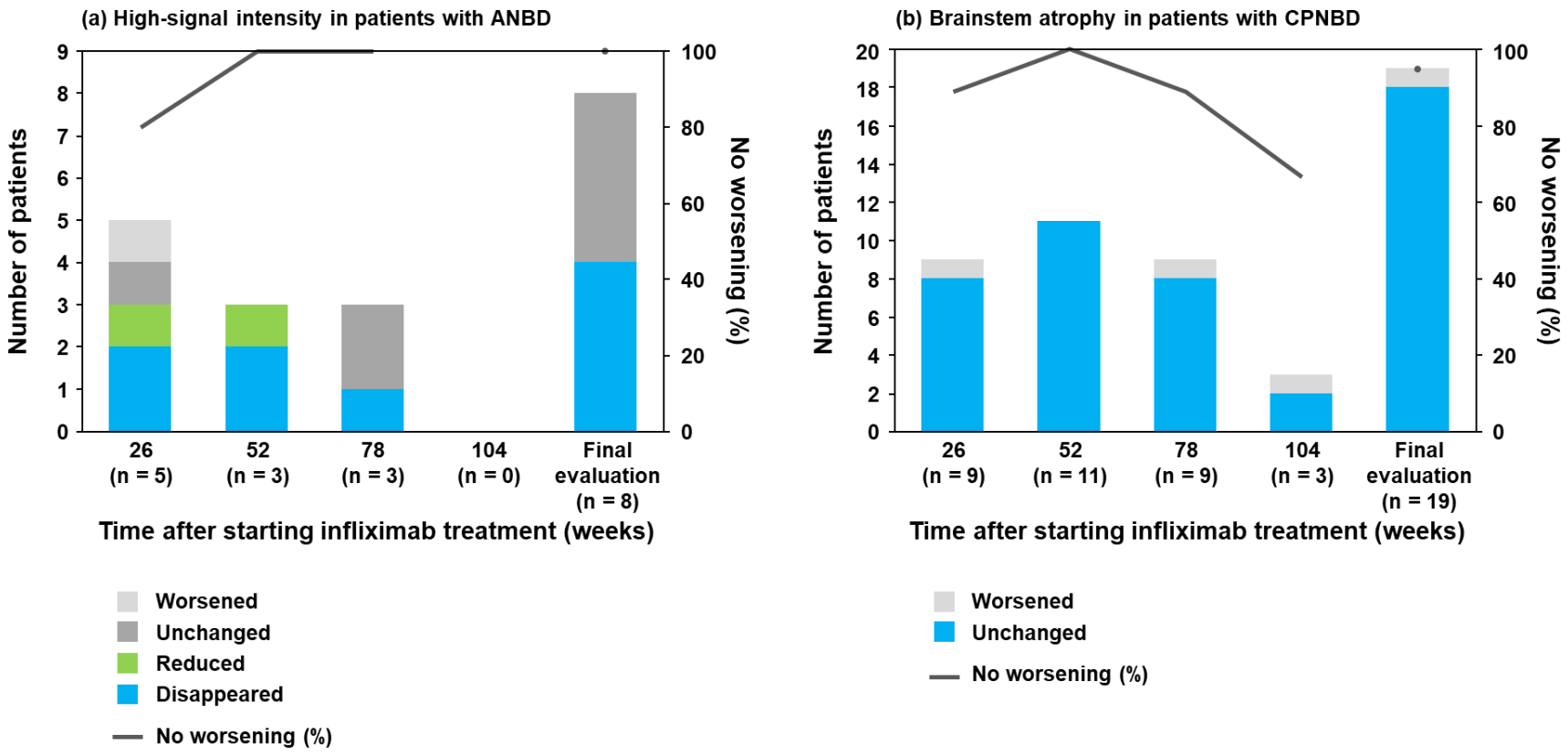


Fig.S3. Brain magnetic resonance imaging scan results of patients with NBD.

(a) High-signal intensity areas on T2-weighted images of magnetic resonance imaging scans of patients with ANBD. The number of patients with ANBD categorized as disappeared, reduced, unchanged, or worsened (multicolored bar graph, left axis) and the percentage of patients with ANBD and no worsening symptoms (line graph, right axis), as determined by high-signal intensity changes on brain magnetic resonance imaging scans. The median (IQR) final evaluation was 47.7 (32.2–67.3) weeks. **(b)** Brainstem atrophy on magnetic resonance imaging scans of patients with CPNBD. The number of patients with CPNBD and unchanged or

worsened symptoms (multiple-colored bar graph, left axis) and the percentage of patients with CPNBD and no worsening symptoms (line graph, right axis), as determined by brainstem atrophy measurements. The median (IQR) final evaluation was 68.7 (55.3–87.9) weeks.

ANBD acute neurological Behçet's disease, *CPNBD* chronic progressive neurological Behçet's disease, *IQR* interquartile range.

Supplementary Tables

Table S1. Adverse drug reactions of interest.

Adverse drug reactions of interest	Definition
Serious infections	Infections of any SOC that are serious
Tuberculosis	PT: tuberculosis, disseminated tuberculosis
Pneumocystis pneumonia	PT: *Pneumocystis jirovecii* pneumonia
Cytomegalovirus infections	PT: cytomegalovirus infection
Interstitial pneumonia	PT: interstitial lung disease, pneumonitis, allergic alveolitis, organizing pneumonia
Malignant tumors	SOC: neoplasms benign, malignant, and unspecified (including cysts and polyps) PT: phagocytic histiocytosis Any one of the above neoplasms suspected to be malignant by a medical specialist
Infusion reactions	Any adverse drug reaction occurring during or within 2 hours of the drug infusion
Demyelinating disease	PT: demyelination (SMQ narrow search), Guillain-Barré syndrome (SMQ narrow search)
Cardiac failure	PT: cardiac failure (SMQ narrow search)
Lupus-like syndromes associated with positive anti-dsDNA antibodies	PT: systemic lupus erythematosus (SMQ narrow search)
Cytopenia	Any serious event that may lead to cytopenia

dsDNA double-stranded deoxyribonucleic acid, *MedDRA* Medical Dictionary for Regulatory Activities, *PT* preferred term, *SMQ* standardized MedDRA query, *SOC* system organ class.

Table S2. Patient baseline characteristics, and concomitant treatment and combination therapy used at least once during the observation period (effectiveness analysis set).

Characteristic	All N = 250[a]	Intestinal BD n = 168	NBD Total n = 47	NBD ANBD n = 17	NBD CPNBD n = 30	VBD n = 51
Sex, female	125 (50.0)	93 (55.4)	22 (46.8)	9 (52.9)	13 (43.3)	17 (33.3)
Age, years	47.1 ± 16.3 [10–86]	48.4 ± 17.1 [10–86]	44.2 ± 12.5 [15–71]	37.8 ± 11.2 [15–56]	47.9 ± 11.9 [22–71]	45.0 ± 16.1 [16–79]
Disease duration[b], years	4.5 ± 5.8 [0–32]	4.6 ± 5.8 [0–32]	4.3 ± 5.1 [0–19]	2.6 ± 4.8 [0–19]	5.3 ± 5.0 [0–15]	4.7 ± 7.0 [0–31]
Body mass index[c], kg/m^2	21.76 ± 3.96 [11.9–31.8]	21.56 ± 4.01 [11.9–31.8]	22.70 ± 4.08 [16.7-31.8]	22.99 ± 4.54 [16.7–31.6]	22.52 ± 3.85 [16.9–31.8]	22.14 ± 3.90 [15.9–31.6]
History of tuberculosis infection	3 (1.2)	2 (1.2)	0	0	0	1 (2.0)
Tuberculosis prophylaxis	22 (8.8)	12 (7.1)	6 (12.8)	2 (11.8)	4 (13.3)	5 (9.8)
ADR history	38 (15.2)	28 (16.7)	5 (10.6)	1 (5.9)	4 (13.3)	8 (15.7)
Allergy history	24 (9.6)	15 (8.9)	3 (6.4)	2 (11.8)	1 (3.3)	8 (15.7)
Malignancy history	6 (2.4)	4 (2.4)	1 (2.1)	0	1 (3.3)	1 (2.0)
Respiratory disease history	10 (4.0)	7 (4.2)	2 (4.3)	1 (5.9)	1 (3.3)	2 (3.9)
Major BD symptoms						
Recurrent oral aphthous ulcers	242 (96.8)	165 (98.2)	44 (93.6)	16 (94.1)	28 (93.3)	49 (96.1)
Skin symptoms	197 (78.8)	132 (78.6)	33 (70.2)	14 (82.4)	19 (63.3)	44 (86.3)
Ocular symptoms	65 (26.0)	29 (17.3)	23 (48.9)	5 (29.4)	18 (60.0)	15 (29.4)
Genital ulcer	160 (64.0)	110 (65.5)	25 (53.2)	12 (70.6)	13 (43.3)	34 (66.7)
Minor BD symptoms						
Arthritis[d]	134 (53.6)	105 (62.5)	16 (34.0)	7 (41.2)	9 (30.0)	19 (37.3)
Epididymal inflammation	8 (3.2)	3 (1.8)	2 (4.3)	1 (5.9)	1 (3.3)	5 (9.8)
Gastrointestinal Lesions/ileocecal ulcers	176 (70.4)	168 (100.0)	11 (23.4)	2 (11.8)	9 (30.0)	10 (19.6)
Vascular lesions	56 (22.4)	10 (6.0)	4 (8.5)	3 (17.6)	1 (3.3)	51 (100.0)
CNS lesions	48 (19.2)	8 (4.8)	47 (100.0)	17 (100.0)	30 (100.0)	4 (7.8)
History of adalimumab use	46 (18.4)	46 (27.4)	1 (2.1)	0	1 (3.3)	1 (2.0)
Prior BD treatment within the previous 26 weeks	237 (94.8)	159 (94.6)	47 (100.0)	17 (100.0)	30 (100.0)	47 (92.2)
Immunosuppressants or immunomodulators	121 (48.4)	76 (45.2)	31 (66.0)	9 (52.9)	22 (73.3)	26 (51.0)
Glucocorticoids	180 (72.0)	113 (67.3)	39 (83.0)	15 (88.2)	24 (80.0)	40 (78.4)
Other medications	182 (72.8)	130 (77.4)	26 (55.3)	12 (70.6)	14 (46.7)	38 (74.5)
Comorbidities	155 (62.0)	99 (58.9)	34 (72.3)	11 (64.7)	23 (76.7)	34 (66.7)
Respiratory disease	5 (2.0)	2 (1.2)	1 (2.1)	0	1 (3.3)	3 (5.9)
Hepatic dysfunction	10 (4.0)	6 (3.6)	5 (10.6)	2 (11.8)	3 (10.0)	0
Cardiac disorders	16 (6.4)	6 (3.6)	1 (2.1)	1 (5.9)	0	10 (19.6)
Renal impairment	4 (1.6)	2 (1.2)	0	0	0	2 (3.9)
Diabetes mellitus	23 (9.2)	14 (8.3)	5 (10.6)	1 (5.9)	4 (13.3)	4 (7.8)
Other	138 (55.2)	90 (53.6)	29 (61.7)	10 (58.8)	19 (63.3)	29 (56.9)
Concomitant treatment	247 (98.8)	165 (98.2)	47 (100.0)	17 (100.0)	30 (100.0)	51 (100.0)
Glucocorticoids	181 (72.4)	114 (67.9)	34 (72.3)	14 (82.4)	20 (66.7)	44 (86.3)
Colchicine	146 (58.4)	95 (56.5)	28 (59.6)	10 (58.8)	18 (60.0)	33 (64.7)
5-aminosalicylic acid	95 (38.0)	91 (54.2)	8 (17.0)	2 (11.8)	6 (20.0)	4 (7.8)
Methotrexate	71 (28.4)	35 (20.8)	33 (70.2)	9 (52.9)	24 (80.0)	15 (29.4)

Azathioprine or mercaptopurine	55 (22.0)	46 (27.4)	2 (4.3)	1 (5.9)	1 (3.3)	8 (15.7)
Cyclosporine	11 (4.4)	9 (5.4)	0	0	0	2 (3.9)
Tacrolimus	5 (2.0)	3 (1.8)	0	0	0	2 (3.9)
Metronidazole	3 (1.2)	2 (1.2)	0	0	0	1 (2.0)
Cyclophosphamide	1 (0.4)	0	0	0	0	1 (2.0)
Other immunosuppressants or immunomodulators	1 (0.4)	0	1 (2.1)	1 (5.9)	0	0
Antiplatelet agents	32 (12.8)	14 (8.3)	7 (14.9)	5 (29.4)	2 (6.7)	16 (31.4)
Anticoagulants	39 (15.6)	16 (9.5)	5 (10.6)	2 (11.8)	3 (10.0)	23 (45.1)
Antimycobacterial drug	26 (10.4)	13 (7.7)	8 (17.0)	2 (11.8)	6 (20.0)	6 (11.8)
Other drugs	212 (84.8)	140 (83.3)	42 (89.4)	15 (88.2)	27 (90.0)	46 (90.2)
Combination therapy	36 (14.4)	33 (19.6)	0	0	0	6 (11.8)
Surgical treatment	19 (7.6)	17 (10.1)	0	0	0	3 (5.9)
Endovascular treatment	1 (0.4)	1 (0.6)	0	0	0	0
Total parenteral nutrition	12 (4.8)	12 (7.1)	0	0	0	2 (3.9)
Enteral nutrition	10 (4.0)	10 (6.0)	0	0	0	0
Other	3 (1.2)	2 (1.2)	0	0	0	1 (2.0)

Data are shown as n (%) or mean ± SD [range].

[a]Including two patients with both intestinal BD and ANBD, five patients with both intestinal BD and CPNBD, six patients with both intestinal BD and VBD, and three patients with both ANBD and VBD.

[b]N = 231 in all patients, n = 156 in patients with intestinal BD, n = 46 in patients with total NBD, n = 17 in patients with ANBD, n = 29 in patients with CPNBD, and n = 44 in patients with VBD.

[c]N = 238 in all patients, n = 160 in patients with intestinal BD, n = 46 in patients with total NBD, n = 17 in patients with ANBD, n = 29 in patients with CPNBD, and n = 47 in patients with VBD.

[d]Without deformity or stiffness.

ADR adverse drug reaction, *ANBD* acute neurological Behçet's disease, *BD* Behçet's disease, *CNS* central nervous system, *CPNBD* chronic progressive neurological Behçet's disease, *NBD* neurological Behçet's disease, *VBD* vascular Behçet's disease.

Table S3. All adverse drug reactions.

	ADRs						Serious ADRs					
			NBD						NBD			
	All N = 255[a]	Intestinal BD n = 171	Total n = 49	ANBD n = 19[b]	CPNBD n = 32[b]	VBD n = 51	All N = 255[a]	Intestinal BD n = 171	Total n = 49	ANBD n = 19[b]	CPNBD n = 32[b]	VBD n = 51
Patients with ADRs	72 (28.2)	51 (29.8)	14 (28.6)	5 (26.3)	9 (28.1)	12 (23.5)	38 (14.9)	24 (14.0)	9 (18.4)	2 (10.5)	7 (21.9)	8 (15.7)
ADRs	129	88	25	6	19	24	58	33	15	3	12	16
ADR by SOC and PT												
Infections and infestations	39 (15.3)	22 (12.9)	10 (20.4)	2 (10.5)	8 (25.0)	10 (19.6)	24 (9.4)	13 (7.6)	7 (14.3)	1 (5.3)	6 (18.8)	6 (11.8)
Actinomycotic pulmonary infection	1 (0.4)	0	0	0	0	1 (2.0)	1 (0.4)	0	0	0	0	1 (2.0)
Bronchitis	2 (0.8)	2 (1.2)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Bronchopulmonary aspergillosis	2 (0.8)	2 (1.2)	0	0	0	1 (2.0)	2 (0.8)	2 (1.2)	0	0	0	1 (2.0)
Cellulitis	1 (0.4)	1 (0.6)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Cystitis	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Cytomegalovirus infection	1 (0.4)	1 (0.6)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Disseminated tuberculosis	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0
Endocarditis	1 (0.4)	1 (0.6)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Herpes simplex	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Herpes zoster	6 (2.4)	3 (1.8)	1 (2.0)	0	1 (3.1)	2 (3.9)	3 (1.2)	0	1 (2.0)	0	1 (3.1)	2 (3.9)
Infection	2 (0.8)	0	2 (4.1)	0	2 (6.3)	0	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0
Influenza	1 (0.4)	1 (0.6)	1 (2.0)	1 (5.3)	0	0	0	0	0	0	0	0
Meningitis cryptococcal	1 (0.4)	1 (0.6)	0	0	0	1 (2.0)	1 (0.4)	1 (0.6)	0	0	0	1 (2.0)
Mucormycosis	1 (0.4)	1 (0.6)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Nasopharyngitis	5	3	1	0	1	1	0	0	0	0	0	0

	(2.0)	(1.8)	(2.0)		(3.1)	(2.0)						
Oesophageal candidiasis	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Periodontitis	1 (0.4)	0	0	0	0	1 (2.0)	0	0	0	0	0	0
Peritonitis	1 (0.4)	1 (0.6)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Pharyngitis	2 (0.8)	2 (1.2)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Pneumonia	5 (2.0)	2 (1.2)	3 (6.1)	1 (5.3)	2 (6.3)	1 (2.0)	5 (2.0)	2 (1.2)	3 (6.1)	1 (5.3)	2 (6.3)	1 (2.0)
Pneumonia aspiration	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0	0	0	0	0	0	0
Pyelonephritis	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0
Pyoderma	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Sinusitis	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Systemic candida	1 (0.4)	1 (0.6)	0	0	0	1 (2.0)	1 (0.4)	1 (0.6)	0	0	0	1 (2.0)
Tooth abscess	1 (0.4)	0	0	0	0	1 (2.0)	0	0	0	0	0	0
Tuberculosis	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0
Upper respiratory tract infection	3 (1.2)	0	1 (2.0)	0	1 (3.1)	2 (3.9)	0	0	0	0	0	0
Urinary tract infection	2 (0.8)	1 (0.6)	1 (2.0)	0	1 (3.1)	0	0	0	0	0	0	0
Viral infection	1 (0.4)	1 (0.6)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Perineal abscess	1 (0.4)	0	0	0	0	1 (2.0)	1 (0.4)	0	0	0	0	1 (2.0)
Tinea infection	1 (0.4)	0	0	0	0	1 (2.0)	1 (0.4)	0	0	0	0	1 (2.0)
Post procedural infection	1 (0.4)	0	1 (2.0)	1 (5.3)	0	0	1 (0.4)	0	1 (2.0)	1 (5.3)	0	0
Gastroenteritis norovirus	1 (0.4)	1 (0.6)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Pneumocystis jirovecii pneumonia	2 (0.8)	2 (1.2)	0	0	0	0	2 (0.8)	2 (1.2)	0	0	0	0
Candida infection	1 (0.4)	0	0	0	0	1 (2.0)	1 (0.4)	0	0	0	0	1 (2.0)

Neoplasms benign, malignant and unspecified (including cysts and polyps)	3 (1.2)	3 (1.8)	0	0	0	0	3 (1.2)	3 (1.8)	0	0	0	0
Gastric cancer	1 (0.4)	1 (0.6)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Pancreatic carcinoma	1 (0.4)	1 (0.6)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Lung neoplasm malignant	1 (0.4)	1 (0.6)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Blood and lymphatic system disorders	2 (0.8)	2 (1.2)	0	0	0	0	0	0	0	0	0	0
Eosinophilia	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Lymphadenopathy	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Immune system disorder	1 (0.4)	1 (0.6)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Anaphylactic reaction	1 (0.4)	1 (0.6)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Nervous system disorder	5 (2.0)	4 (2.3)	1 (2.0)	1 (5.3)	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Facial paralysis	1 (0.4)	1 (0.6)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Headache	2 (0.8)	2 (1.2)	0	0	0	0	0	0	0	0	0	0
Neuropathy peripheral	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Restless legs syndrome	1 (0.4)	0	1 (2.0)	1 (5.3)	0	0	0	0	0	0	0	0
Angiopathy	1 (0.4)	0	0	0	0	1 (2.0)	0	0	0	0	0	0
Hypertension	1 (0.4)	0	0	0	0	1 (2.0)	0	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	9 (3.5)	5 (2.9)	1 (2.0)	0	1 (3.1)	3 (5.9)	5 (2.0)	2 (1.2)	1 (2.0)	0	1 (3.1)	2 (3.9)
Asthma	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Cough	3 (1.2)	2 (1.2)	0	0	0	1 (2.0)	0	0	0	0	0	0
Interstitial lung disease	3 (1.2)	2 (1.2)	0	0	0	1 (2.0)	3 (1.2)	2 (1.2)	0	0	0	1 (2.0)

Pulmonary embolism	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0
Organizing pneumonia	1 (0.4)	0	0	0	0	1 (2.0)	1 (0.4)	0	0	0	0	1 (2.0)
Oropharyngeal pain	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Gastrointestinal disorder	8 (3.1)	7 (4.1)	1 (2.0)	1 (5.3)	0	1 (2.0)	5 (2.0)	4 (2.3)	1 (2.0)	1 (5.3)	0	1 (2.0)
Diarrhoea	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Gastrointestinal perforation	1 (0.4)	0	1 (2.0)	1 (5.3)	0	0	1 (0.4)	0	1 (2.0)	1 (5.3)	0	0
Intestinal obstruction	1 (0.4)	1 (0.6)	0	0	0	1 (2.0)	1 (0.4)	1 (0.6)	0	0	0	1 (2.0)
Intestinal perforation	2 (0.8)	2 (1.2)	0	0	0	0	2 (0.8)	2 (1.2)	0	0	0	0
Nausea	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Oral mucosal blistering	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Small intestinal perforation	1 (0.4)	1 (0.6)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Lip blister	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Hepatobiliary disorders	2 (0.8)	1 (0.6)	1 (2.0)	0	1 (3.1)	0	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0
Hepatic function abnormal	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0
Liver disorder	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Skin and subcutaneous tissue disorders	7 (2.7)	5 (2.9)	1 (2.0)	0	1 (3.1)	1 (2.0)	1 (0.4)	0	0	0	0	1 (2.0)
Alopecia	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Dermatitis contact	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Erythema	2 (0.8)	1 (0.6)	0	0	0	1 (2.0)	1 (0.4)	0	0	0	0	1 (2.0)
Prurigo	1 (0.4)	0	0	0	0	1 (2.0)	0	0	0	0	0	0
Pruritus	2 (0.8)	2 (1.2)	0	0	0	0	0	0	0	0	0	0
Psoriasis	1	1	0	0	0	0	0	0	0	0	0	0

	(0.4)	(0.6)										
Rash	2 (0.8)	0	1 (2.0)	0	1 (3.1)	1 (2.0)	1 (0.4)	0	0	0	0	1 (2.0)
Palmoplantar pustulosis	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	3 (1.2)	3 (1.8)	0	0	0	1 (2.0)	1 (0.4)	1 (0.6)	0	0	0	1 (2.0)
Arthralgia	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Fasciitis	1 (0.4)	1 (0.6)	0	0	0	1 (2.0)	1 (0.4)	1 (0.6)	0	0	0	1 (2.0)
Neck pain	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Renal and urinary disorders	2 (0.8)	2 (1.2)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Neurogenic bladder	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Renal infarct	1 (0.4)	1 (0.6)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
General disorders and administration site conditions	7 (2.7)	5 (2.9)	2 (4.1)	0	2 (6.3)	0	3 (1.2)	1 (0.6)	2 (4.1)	0	2 (6.3)	0
Cyst	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0
Death	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0
Malaise	2 (0.8)	2 (1.2)	0	0	0	0	0	0	0	0	0	0
Pyrexia	3 (1.2)	3 (1.8)	0	0	0	0	1 (0.4)	1 (0.6)	0	0	0	0
Peripheral swelling	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Laboratory test	4 (1.6)	2 (1.2)	2 (4.1)	0	2 (6.3)	0	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0
Blood creatine phosphokinase increased	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
C-reactive protein increased	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0
Platelet count decreased	1 (0.4)	0	1 (2.0)	0	1 (3.1)	0	0	0	0	0	0	0

DNA antibody positive	1 (0.4)	1 (0.6)	0	0	0	0	0	0	0	0	0	0
Injury, poisoning and procedural complications	11 (4.3)	11 (6.4)	1 (2.0)	1 (5.3)	0	0	2 (0.8)	2 (1.2)	0	0	0	0
Infusion related reaction	11 (4.3)	11 (6.4)	1 (2.0)	1 (5.3)	0	0	2 (0.8)	2 (1.2)	0	0	0	0

Data are shown as n or n (%).

[a]Including seven patients with both intestinal BD and NBD, six patients with both intestinal BD and VBD, and three patients with both NBD and VBD.

[b]Including two patients with both ANBD and CPNBD.

ADR adverse drug reaction, *ANBD* acute neurological Behçet's disease, *BD* Behçet's disease, *CPNBD* chronic progressive neurological Behçet's disease, *NBD* neurological Behçet's disease, *PT* preferred term, *SOC* system organ class, *VBD* vascular Behçet's disease.

Table S4. Adverse drug reactions after infliximab dose-escalation.

	ADRs						Serious ADRs					
			NBD						NBD			
	All N = 80[a]	Intestinal BD n = 61	Total n = 16	ANBD n = 7	CPNBD n = 9	VBD n = 10	All N = 80[a]	Intestinal BD n = 61	Total n = 16	ANBD n = 7	CPNBD n = 9	VBD n = 10
Patients with ADRs	14 (17.5)	11 (18.0)	5 (31.3)	3 (42.9)	2 (22.2)	0	6 (7.5)	4 (6.6)	2 (12.5)	1 (14.3)	1 (11.1)	0
ADRs	23	19	6	3	3		6	4	2	1	1	
ADR by SOC and PT												
Infections and infestations	10 (12.5)	7 (11.5)	4 (25.0)	2 (28.6)	2 (22.2)	0	5 (6.3)	3 (4.9)	2 (12.5)	1 (14.3)	1 (11.1)	0
Cellulitis	1 (1.3)	1 (1.6)	0	0	0	0	1 (1.3)	1 (1.6)	0	0	0	0
Cystitis	1 (1.3)	1 (1.6)	0	0	0	0	0	0	0	0	0	0
Herpes zoster	2 (2.5)	1 (1.6)	1 (6.3)	0	1 (11.1)	0	1 (1.3)	0	1 (6.3)	0	1 (11.1)	0
Infection	1 (1.3)	0	1 (6.3)	0	1 (11.1)	0	0	0	0	0	0	0
Influenza	1 (1.3)	1 (1.6)	1 (6.3)	1 (14.3)	0	0	0	0	0	0	0	0
Nasopharyngitis	1 (1.3)	1 (1.6)	0	0	0	0	0	0	0	0	0	0
Oesophageal candidiasis	1 (1.3)	1 (1.6)	0	0	0	0	0	0	0	0	0	0
Pharyngitis	1 (1.3)	1 (1.6)	0	0	0	0	0	0	0	0	0	0
Upper respiratory tract infection	1 (1.3)	0	1 (6.3)	0	1 (11.1)	0	0	0	0	0	0	0
Viral infection	1 (1.3)	1 (1.6)	0	0	0	0	1 (1.3)	1 (1.6)	0	0	0	0
Post procedural infection	1 (1.3)	0	1 (6.3)	1 (14.3)	0	0	1 (1.3)	0	1 (6.3)	1 (14.3)	0	0
Pneumocystis jirovecii pneumonia	1 (1.3)	1 (1.6)	0	0	0	0	1 (1.3)	1 (1.6)	0	0	0	0
Nervous system disorder	1 (1.3)	1 (1.6)	0	0	0	0	0	0	0	0	0	0
Headache	1 (1.3)	1 (1.6)	0	0	0	0	0	0	0	0	0	0

Respiratory, thoracic and mediastinal disorders	1 (1.3)	1 (1.6)	0	0	0	0	0	0	0	0	0	0
Asthma	1 (1.3)	1 (1.6)	0	0	0	0	0	0	0	0	0	0
Gastrointestinal disorder	2 (2.5)	2 (3.3)	0	0	0	0	0	0	0	0	0	0
Diarrhoea	1 (1.3)	1 (1.6)	0	0	0	0	0	0	0	0	0	0
Oral mucosal blistering	1 (1.3)	1 (1.6)	0	0	0	0	0	0	0	0	0	0
Lip blister	1 (1.3)	1 (1.6)	0	0	0	0	0	0	0	0	0	0
Renal and urinary disorders	1 (1.3)	1 (1.6)	0	0	0	0	0	0	0	0	0	0
Neurogenic bladder	1 (1.3)	1 (1.6)	0	0	0	0	0	0	0	0	0	0
Laboratory test	1 (1.3)	1 (1.6)	0	0	0	0	0	0	0	0	0	0
Blood creatine phosphokinase increased	1 (1.3)	1 (1.6)	0	0	0	0	0	0	0	0	0	0
Injury, poisoning and procedural complications	3 (3.8)	3 (4.9)	1 (6.3)	1 (14.3)	0	0	1 (1.3)	1 (1.6)	0	0	0	0
Infusion related reaction	3 (3.8)	3 (4.9)	1 (6.3)	1 (14.3)	0	0	1 (1.3)	1 (1.6)	0	0	0	0

Data are shown as n or n (%).

[a]Including four patients with both intestinal BD and NBD, two patients with both intestinal BD and VBD, and one patient with both NBD and VBD.

ADR adverse drug reaction, *ANBD* acute neurological Behçet's disease, *BD* Behçet's disease, *CPNBD* chronic progressive neurological Behçet's disease, *NBD* neurological Behçet's disease, *PT* preferred term, *SOC* system organ class, *VBD* vascular Behçet's disease.

Table S5. Infections and infestations in patients with intestinal Behçet's disease by background factors and concomitant treatment and combination therapy used at least once during the observation period.

		Patients	Patients with infection and infestation ADRs	*P*-value[b]	Risk ratio [95% CI]
All patients		171[a]	22 (12.9)		
Sex					
Male		76 (44.4)	14 (18.4)	0.066	Reference
Female		95 (55.6)	8 (8.4)		0.46 [0.20–1.03]
Age, years					
< 65		136 (79.5)	17 (12.5)	0.780	Reference
≥ 65		35 (20.5)	5 (14.3)		1.14 [0.45–2.88]
Disease duration, years					
< 3		91 (53.2)	13 (14.3)	NC	Reference
3 to < 5		13 (7.6)	3 (23.1)		1.62 [0.53–4.92]
5 to < 10		26 (15.2)	3 (11.5)		0.81 [0.25–2.62]
10 to < 15		18 (10.5)	0 (0.0)		NC
≥ 15		11 (6.4)	3 (27.3)		1.91 [0.64–5.67]
Body mass index, kg/m^2					
< 25		131 (76.6)	17 (13.0)	NC	Reference
25 to < 30		26 (15.2)	3 (11.5)		0.89 [0.28–2.82]
≥ 30		6 (3.5)	1 (16.7)		1.28 [0.20–8.11]
ADR history					
None		142 (83.0)	15 (10.6)	0.059	Reference
Yes		28 (16.4)	7 (25.0)		2.37 [1.06–5.27]
Allergy history					
None		152 (88.9)	18 (11.8)	NC	Reference
Yes		15 (8.8)	3 (20.0)		1.69 [0.56–5.08]
Malignancy history					
None		167 (97.7)	22 (13.2)	NC	Reference
Yes		4 (2.3)	0 (0.0)		NC
Respiratory disease history					
None		164 (95.9)	20 (12.2)	NC	Reference
Yes		7 (4.1)	2 (28.6)		2.34 [0.68–8.11]
Comorbidities					
None		72 (42.1)	3 (4.2)	NC	Reference
Yes		99 (57.9)	19 (19.2)		4.61 [1.42–14.98]
Respiratory disease	None	169 (98.8)	21 (12.4)	NC	Reference
	Yes	2 (1.2)	1 (50.0)		4.02 [0.95–17.03]
Hepatic dysfunction	None	165 (96.5)	22 (13.3)	NC	Reference
	Yes	6 (3.5)	0 (0.0)		NC
Cardiac disorders	None	165 (96.5)	20 (12.1)	NC	Reference

	Yes	6 (3.5)	2 (33.3)		2.75 [0.83–9.17]
Renal impairment	None	169 (98.8)	21 (12.4)	NC	Reference
	Yes	2 (1.2)	1 (50.0)		4.02 [0.95–17.03]
Diabetes mellitus	None	157 (91.8)	19 (12.1)	NC	Reference
	Yes	14 (8.2)	3 (21.4)		1.77 [0.60–5.26]
Concomitant drug					
Glucocorticoids	None	56 (32.7)	5 (8.9)	0.338	Reference
	Yes	115 (67.3)	17 (14.8)		1.66 [0.64–4.26]
Colchicine	None	74 (43.3)	12 (16.2)	0.261	Reference
	Yes	97 (56.7)	10 (10.3)		0.64 [0.29–1.39]
5-aminosalicylic acid	None	78 (45.6)	8 (10.3)	0.371	Reference
	Yes	93 (54.4)	14 (15.1)		1.47 [0.65–3.32]
Metronidazole	None	169 (98.8)	21 (12.4)	NC	Reference
	Yes	2 (1.2)	1 (50.0)		4.02 [0.95–17.03]
Azathioprine and mercaptopurine	None	124 (72.5)	15 (12.1)	0.616	Reference
	Yes	47 (27.5)	7 (14.9)		1.23 [0.54–2.83]
Cyclosporine	None	161 (94.2)	19 (11.8)	NC	Reference
	Yes	10 (5.8)	3 (30.0)		2.54 [0.90–7.17]
Tacrolimus	None	166 (97.1)	21 (12.7)	NC	Reference
	Yes	5 (2.9)	1 (20.0)		1.58 [0.26–9.55]
Methotrexate	None	134 (78.4)	16 (11.9)	0.579	Reference
	Yes	37 (21.6)	6 (16.2)		1.36 [0.57–3.22]
Other immunosuppressive or modulatory agents	None	170 (99.4)	21 (12.4)	NC	Reference
	Yes	1 (0.6)	1 (100.0)		8.10 [5.42–12.08]
Antimycobacterial drugs	None	157 (91.8)	20 (12.7)	NC	Reference
	Yes	13 (7.6)	2 (15.4)		1.21 [0.32–4.61]
Other drugs	None	28 (16.4)	0 (0.00)	NC	Reference
	Yes	143 (83.6)	22 (15.4)		NC
Combination therapy					
Surgical treatment	None	153 (89.5)	18 (11.8)	NC	Reference
	Yes	18 (10.5)	4 (22.2)		1.89 [0.72–4.97]
Total parenteral nutrition	None	159 (93.0)	17 (10.7)	0.010	Reference
	Yes	12 (7.0)	5 (41.7)		3.90 [1.74–8.73]
Enteral nutrition	None	160 (93.6)	18 (11.3)	NC	Reference
	Yes	11 (6.4)	4 (36.4)		3.23 [1.32–7.91]
Other	None	169 (98.8)	20 (11.8)	NC	Reference
	Yes	2 (1.2)	2 (100.0)		8.45 [5.60–12.75]

Data are shown as n or n (%).

Factors with a difference in ADRs in infections and infestations were defined as those with a statistically significant difference ($P < 0.05$) or ratios of < 0.50 or > 2.00 in ≥ 5 patients of ADRs in the category (excluding unknown or not described) paired with reference.

[a]Including seven patients with both intestinal Behçet's disease and neurological Behçet's disease, and six patients with both intestinal Behçet's disease and vascular Behçet's disease.

[b]*P*-values calculated using Fisher's exact test (for categorical factors with two levels) or a chi-square test (for categorical factors with three or more levels) for categories with ≥ 5 patients per group, except where otherwise stated.

ADR adverse drug reaction, *CI* confidence interval, *NC* not calculated.

Table S6. Infections and infestations in patients with neurological Behçet's disease by background factors and concomitant treatment and combination therapy used at least once during the observation period.

		Patients	Patients with infection and infestation ADRs	*P*-value[b]	Risk ratio [95% CI]
All patients		49[a]	10 (20.4)		
Sex					
Male		25 (51.0)	7 (28.0)	NC	Reference
Female		24 (49.0)	3 (12.5)		0.45 [0.13–1.53]
Age, years					
< 65		48 (98.0)	10 (20.8)	NC	Reference
≥ 65		1 (2.0)	0 (0.00)		NC
Disease duration, years					
< 3		28 (57.1)	5 (17.9)	NC	Reference
3 to < 5		5 (10.2)	1 (20.0)		1.12 [0.16–7.68]
5 to < 10		7 (14.3)	1 (14.3)		0.80 [0.11–5.80]
10 to < 15		6 (12.2)	2 (33.3)		1.87 [0.47–7.44]
≥ 15		2 (4.1)	1 (50.0)		2.80 [0.57–13.83]
Body mass index, kg/m^2					
< 25		35 (71.4)	9 (25.7)	NC	Reference
25 to < 30		10 (20.4)	1 (10.0)		0.39 [0.06–2.71]
≥ 30		3 (6.1)	0 (0.0)		NC
ADR history					
None		42 (85.7)	7 (16.7)	NC	Reference
Yes		5 (10.2)	2 (40.0)		2.40 [0.67–8.54]
Allergy history					
None		44 (89.8)	9 (20.5)	NC	Reference
Yes		3 (6.1)	0 (0.0)		NC
Malignancy history					
None		48 (98.0)	10 (20.8)	NC	Reference
Yes		1 (2.0)	0 (0.0)		NC
Respiratory disease history					
None		47 (95.9)	10 (21.3)	NC	Reference
Yes		2 (4.1)	0 (0.0)		NC
Comorbidities					
None		14 (28.6)	1 (7.1)	NC	Reference
Yes		35 (71.4)	9 (25.7)		3.60 [0.50–25.84]
Respiratory disease	None	48 (98.0)	10 (20.8)	NC	Reference
	Yes	1 (2.0)	0 (0.0)		NC
Hepatic dysfunction	None	44 (89.8)	8 (18.2)	NC	Reference
	Yes	5 (10.2)	2 (40.0)		2.20 [0.63–7.63]
Cardiac disorders	None	48 (98.0)	10 (20.8)	NC	Reference

	Yes	1 (2.0)	0 (0.0)		NC
Diabetes mellitus	None	44 (89.8)	10 (22.7)	NC	Reference
	Yes	5 (10.2)	0 (0.0)		NC
Concomitant drug					
Glucocorticoids	None	12 (24.5)	0 (0.0)	NC	Reference
	Yes	36 (73.5)	9 (25.0)		NC
Colchicine	None	19 (38.8)	3 (15.8)	NC	Reference
	Yes	29 (59.2)	6 (20.7)		1.31 [0.37–4.62]
Azathioprine and mercaptopurine	None	47 (95.9)	9 (19.1)	NC	Reference
	Yes	2 (4.1)	1 (50.0)		2.61 [0.58–11.76]
Methotrexate	None	14 (28.6)	3 (21.4)	NC	Reference
	Yes	35 (71.4)	7 (20.0)		0.93 [0.28–3.11]
Other immunosuppressive or modulatory agents	None	48 (98.0)	10 (20.8)	NC	Reference
	Yes	1 (2.0)	0 (0.0)		NC
Antimycobacterial drugs	None	41 (83.7)	6 (14.6)	NC	Reference
	Yes	8 (16.3)	4 (50.0)		3.42 [1.24–9.41]
Other drugs	None	5 (10.2)	0 (0.0)	NC	Reference
	Yes	44 (89.8)	10 (22.7)		NC

Data are shown as n or n (%).

Factors with a difference in ADRs in infections and infestations were defined as those with a statistically significant difference ($P < 0.05$) or ratios of < 0.50 or > 2.00 in ≥ 5 patients of ADRs in the category (excluding unknown or not described) paired with reference.

[a]Including seven patients with both neurological Behçet's disease and intestinal Behçet's disease, and three patients with both neurological Behçet's disease and vascular Behçet's disease.

[b]*P*-values calculated using Fisher's exact test (for categorical factors with two levels) or a chi-square test (for categorical factors with three or more levels) for categories with ≥ 5 patients per group.

ADR adverse drug reaction, *CI* confidence interval, *NC* not calculated.

Table S7. Infections and infestations in patients with vascular Behçet's disease by background factors and concomitant treatment and combination therapy used at least once during the observation period.

		Patients	Patients with infection and infestation ADRs	*P*-value[b]	Risk ratio [95% CI]
All patients		51[a]	10 (19.6)		
Sex					
Male		34 (66.7)	5 (14.7)	0.270	Reference
Female		17 (33.3)	5 (29.4)		2.00 [0.67–5.97]
Age, years					
< 65		42 (82.4)	10 (23.8)	NC	Reference
≥ 65		9 (17.6)	0 (0.0)		NC
Disease duration, years					
< 3		26 (51.0)	7 (26.9)	NC	Reference
3 to < 5		5 (9.8)	1 (20.0)		0.74 [0.12–4.79]
5 to < 10		5 (9.8)	2 (40.0)		1.49 [0.43–5.17]
10 to < 15		3 (5.9)	0 (0.0)		NC
≥ 15		5 (9.8)	0 (0.0)		NC
Body mass index, kg/m^2					
< 25		38 (74.5)	8 (21.1)	NC	Reference
25 to < 30		7 (13.7)	0 (0.0)		NC
≥ 30		2 (3.9)	1 (50.0)		2.38 [0.52–10.82]
ADR history					
None		42 (82.4)	8 (19.0)	NC	Reference
Yes		8 (15.7)	2 (25.0)		1.31 [0.34–5.08]
Allergy history					
None		42 (82.4)	9 (21.4)	NC	Reference
Yes		8 (15.7)	1 (12.5)		0.58 [0.09–3.99]
Malignancy history					
None		50 (98.0)	10 (20.0)	NC	Reference
Yes		1 (2.0)	0 (0.0)		NC
Respiratory disease history					
None		49 (96.1)	8 (16.3)	NC	Reference
Yes		2 (3.9)	2 (100.0)		6.13 [3.25–11.54]
Comorbidities					
None		17 (33.3)	2 (11.8)	NC	Reference
Yes		34 (66.7)	8 (23.5)		2.00 [0.48–8.41]
Respiratory disease	None	48 (94.1)	8 (16.7)	NC	Reference
	Yes	3 (5.9)	2 (66.7)		4.00 [1.44–11.09]
Cardiac disorders	None	41 (80.4)	9 (22.0)	NC	Reference
	Yes	10 (19.6)	1 (10.0)		0.46 [0.07–3.19]
Renal impairment	None	49 (96.1)	10 (20.4)	NC	Reference

	Yes	2 (3.9)	0 (0.0)		NC
Diabetes mellitus	None	47 (92.2)	9 (19.1)	NC	Reference
	Yes	4 (7.8)	1 (25.0)		1.31 [0.22–7.87]
Concomitant drug					
Glucocorticoids	None	7 (13.7)	0 (0.00)	NC	Reference
	Yes	44 (86.3)	10 (22.7)		NC
Colchicine	None	17 (33.3)	2 (11.8)	NC	Reference
	Yes	34 (66.7)	8 (23.5)		2.00 [0.48–8.41]
Azathioprine or mercaptopurine	None	43 (84.3)	7 (16.3)	NC	Reference
	Yes	8 (15.7)	3 (37.5)		2.30 [0.75–7.08]
Methotrexate	None	36 (70.6)	8 (22.2)	NC	Reference
	Yes	15 (29.4)	2 (13.3)		0.60 [0.14–2.50]
Cyclophosphamide	None	50 (98.0)	10 (20.0)	NC	Reference
	Yes	1 (2.0)	0 (0.0)		NC
Antiplatelet drugs	None	35 (68.6)	9 (25.7)	NC	Reference
	Yes	16 (31.4)	1 (6.3)		0.24 [0.03–1.76]
Anticoagulants	None	28 (54.9)	3 (10.7)	NC	Reference
	Yes	23 (45.1)	7 (30.4)		2.84 [0.83–9.77]
Antimycobacterial drugs	None	45 (88.2)	7 (15.6)	NC	Reference
	Yes	6 (11.8)	3 (50.0)		3.21 [1.12–9.19]
Other drugs	None	5 (9.8)	0 (0.0)	NC	Reference
	Yes	46 (90.2)	10 (21.7)		NC
Combination therapy					
Surgical treatment	None	47 (92.2)	10 (21.3)	NC	Reference
	Yes	3 (5.9)	0 (0.0)		NC
Other	None	49 (96.1)	10 (20.4)	NC	Reference
	Yes	1 (2.0)	0 (0.0)		NC

Data are shown as n or n (%).

Factors with a difference in ADRs in infections and infestations were defined as those with a statistically significant difference ($P < 0.05$) or ratios of < 0.50 or > 2.00 in ≥ 5 patients of ADRs in the category (excluding unknown or not described) paired with reference.

[a]Including six patients with both vascular Behçet's disease and intestinal Behçet's disease, and three patients with both vascular Behçet's disease and neurological Behçet's disease.

[b]*P*-values calculated using Fisher's exact test (for categorical factors with two levels) or a chi-square test (for categorical factors with three or more levels) for categories with ≥ 5 patients per group.

ADR adverse drug reaction, *CI* confidence interval, *NC* not calculated.

Table S8. Effectiveness (global improvement) in patients with intestinal Behçet's disease by background factors and concomitant treatment and combination therapy used at least once during the observation period.

		Patients	Patients with symptom improvement at final evaluation	*P*-value[b]	Ratio [95% CI]
All patients		138[a]	95 (68.8)		
Sex					
Male		60 (43.5)	37 (61.7)	0.139	Reference
Female		78 (56.5)	58 (74.4)		1.21 [0.95–1.53]
Age, years					
< 65		113 (81.9)	83 (73.5)	0.017	Reference
≥ 65		25 (18.1)	12 (48.0)		0.65 [0.43–1.00]
Disease duration, years					
< 3		73 (52.9)	49 (67.1)	0.593	Reference
3 to < 5		10 (7.2)	5 (50.0)		0.74 [0.39–1.41]
5 to < 10		22 (15.9)	17 (77.3)		1.15 [0.87–1.52]
10 to < 15		16 (11.6)	11 (68.8)		1.02 [0.71–1.48]
≥ 15		9 (6.5)	7 (77.8)		1.16 [0.79–1.70]
Body mass index, kg/m^2					
< 25		105 (76.1)	68 (64.8)	0.077	Reference
25 kg/m^2 to < 30		23 (16.7)	19 (82.6)		1.28 [1.01–1.61]
≥ 30		5 (3.6)	5 (100.0)		1.54 [1.34–1.78]
ADR history					
None		115 (83.3)	80 (69.6)	0.620	Reference
Yes		22 (15.9)	14 (63.6)		0.91 [0.65–1.28]
Allergy history					
None		124 (89.9)	84 (67.7)	0.752	Reference
Yes		12 (8.7)	9 (75.0)		1.11 [0.78–1.57]
Malignancy history					
None		136 (98.6)	94 (69.1)	NC	Reference
Yes		2 (1.4)	1 (50.0)		0.72 [0.18–2.91]
Respiratory disease history					
None		135 (97.8)	93 (68.9)	NC	Reference
Yes		3 (2.2)	2 (66.7)		0.97 [0.43–2.17]
Prior adalimumab treatment					
None		97 (70.3)	76 (78.4)	<0.001	Reference
Yes		41 (29.7)	19 (46.3)		0.59 [0.42–0.84]
Comorbidities					
None		57 (41.3)	44 (77.2)	0.094	Reference
Yes		81 (58.7)	51 (63.0)		0.82 [0.66–1.02]
Respiratory disease	None	136 (98.6)	93 (68.4)	NC	Reference
	Yes	2 (1.4)	2 (100.0)		1.46 [1.30–1.64]

Hepatic dysfunction	None	132 (95.7)	92 (69.7)	NC	Reference
	Yes	6 (4.3)	3 (50.0)		0.72 [0.32–1.61]
Cardiac disorders	None	132 (95.7)	91 (68.9)	NC	Reference
	Yes	6 (4.3)	4 (66.7)		0.97 [0.54–1.72]
Renal impairment	None	136 (98.6)	95 (69.9)	NC	Reference
	Yes	2 (1.4)	0 (0.0)		NC
Concomitant drug					
Glucocorticoids	None	43 (31.2)	32 (74.4)	0.428	Reference
	Yes	95 (68.8)	63 (66.3)		0.89 [0.71–1.12]
Colchicine	None	61 (44.2)	48 (78.7)	0.028	Reference
	Yes	77 (55.8)	47 (61.0)		0.78 [0.62–0.97]
5-aminosalicylic acid	None	60 (43.5)	45 (75.0)	0.197	Reference
	Yes	78 (56.5)	50 (64.1)		0.85 [0.69–1.07]
Metronidazole	None	136 (98.6)	94 (69.1)	NC	Reference
	Yes	2 (1.4)	1 (50.0)		0.72 [0.18–2.91]
Azathioprine or mercaptopurine	None	104 (75.4)	72 (69.2)	1.000	Reference
	Yes	34 (24.6)	23 (67.6)		0.98 [0.75–1.27]
Cyclosporine	None	129 (93.5)	92 (71.3)	NC	Reference
	Yes	9 (6.5)	3 (33.3)		0.47 [0.18–1.19]
Tacrolimus	None	135 (97.8)	94 (69.6)	NC	Reference
	Yes	3 (2.2)	1 (33.3)		0.48 [0.10–2.38]
Methotrexate	None	105 (76.1)	71 (67.6)	0.670	Reference
	Yes	33 (23.9)	24 (72.7)		1.08 [0.84–1.38]
Antimycobacterial drugs	None	127 (92.0)	87 (68.5)	1.000	Reference
	Yes	11 (8.0)	8 (72.7)		1.06 [0.73–1.55]
Other drugs	None	22 (15.9)	14 (63.6)	0.618	Reference
	Yes	116 (84.1)	81 (69.8)		1.10 [0.78–1.54]
Combination therapy					
Surgical treatment	None	124 (89.9)	87 (70.2)	0.366	Reference
	Yes	14 (10.1)	8 (57.1)		0.81 [0.51–1.30]
Total parenteral nutrition	None	126 (91.3)	88 (69.8)	0.515	Reference
	Yes	12 (8.7)	7 (58.3)		0.84 [0.51–1.37]
Enteral nutrition	None	128 (92.8)	87 (68.0)	0.724	Reference
	Yes	10 (7.2)	8 (80.0)		1.18 [0.84–1.64]
Other	None	136 (98.6)	95 (69.9)	NC	Reference
	Yes	2 (1.4)	0 (0.0)		NC

Data are shown as n or n (%).

Factors with a difference in symptom improvement were defined as those with a statistically significant difference ($P < 0.05$) or ratios of < 0.50 or > 2.00 in ≥ 5 patients among the factor categories (excluding unknown or not described).

[a]Including seven patients with both intestinal Behçet's disease and neurological Behçet's disease, and four patients with both intestinal Behçet's disease and vascular Behçet's disease.

[b]*P*-values calculated using Fisher's exact test for categories (for categorical factors with two levels) or a chi-square test (for categorical factors with three or more levels) with ≥ 5 patients per group.

ADR adverse drug reaction, *CI* confidence interval, *NC* not calculated.

Table S9. Effectiveness (global improvement) in patients with vascular Behçet's disease by background factors and concomitant treatment and combination therapy used at least once during the observation period.

		Patients	Patients with no worsening at final evaluation	*P*-value[b]	Ratio [95% CI]
All patients		36[a]	33 (91.7)		
Sex					
Male		24 (66.7)	22 (91.7)	1.000	Reference
Female		12 (33.3)	11 (91.7)		1.00 [0.81–1.23]
Age, years					
< 65		29 (80.6)	26 (89.7)	1.000	Reference
≥ 65		7 (19.4)	7 (100.0)		1.12 [0.99–1.26]
Disease duration, years					
< 3		20 (55.6)	20 (100.0)	NC	Reference
3 to < 5		3 (8.3)	2 (66.7)		0.67 [0.30–1.48]
5 to < 10		3 (8.3)	3 (100.0)		NC
10 to < 15		3 (8.3)	3 (100.0)		NC
≥ 15		4 (11.1)	2 (50.0)		0.50 [0.19–1.33]
Body mass index, kg/m^2					
< 25		26 (72.2)	24 (92.3)	NC	Reference
25 kg/m^2 to < 30		4 (11.1)	4 (100.0)		1.08 [0.97–1.21]
≥ 30		2 (5.6)	2 (100.0)		1.08 [0.97–1.21]
ADR history					
None		31 (86.1)	28 (90.3)	NC	Reference
Yes		4 (11.1)	4 (100.0)		1.11 [0.99–1.24]
Allergy history					
None		32 (88.9)	29 (90.6)	NC	Reference
Yes		3 (8.3)	3 (100.0)		1.10 [0.99–1.23]
Unknown		1 (2.8)	1 (100.0)		NC
Malignancy history					
None		35 (97.2)	32 (91.4)	NC	Reference
Yes		1 (2.8)	1 (100.0)		1.09 [0.99–1.21]
Respiratory disease history					
None		35 (97.2)	32 (91.4)	NC	Reference
Yes		1 (2.8)	1 (100.0)		1.09 [0.99–1.21]
Comorbidities					
None		13 (36.1)	12 (92.3)	1.000	Reference
Yes		23 (63.9)	21 (91.3)		0.99 [0.81–1.21]
Respiratory disease	None	33 (91.7)	30 (90.9)	NC	Reference
	Yes	3 (8.3)	3 (100.0)		1.10 [0.99–1.23]
Cardiac disorders	None	31 (86.1)	28 (90.3)	1.000	Reference
	Yes	5 (13.9)	5 (100.0)		1.11 [0.99–1.24]

Renal impairment	None	35 (97.2)	32 (91.4)	NC	Reference
	Yes	1 (2.8)	1 (100.0)		1.09 [0.99–1.21]
Diabetes mellitus	None	33 (91.7)	30 (90.9)	NC	Reference
	Yes	3 (8.3)	3 (100.0)		1.10 [0.99–1.23]
Concomitant drug					
Glucocorticoids	None	5 (13.9)	5 (100.0)	1.000	Reference
	Yes	31 (86.1)	28 (90.3)		0.90 [0.80–1.01]
Colchicine	None	14 (38.9)	13 (92.9)	1.000	Reference
	Yes	22 (61.1)	20 (90.9)		0.98 [0.80–1.19]
Azathioprine or mercaptopurine	None	32 (88.9)	29 (90.6)	NC	Reference
	Yes	4 (11.1)	4 (100.0)		1.10 [0.99–1.23]
Methotrexate	None	24 (66.7)	22 (91.7)	1.000	Reference
	Yes	12 (33.3)	11 (91.7)		1.00 [0.81–1.23]
Cyclophosphamide	None	35 (97.2)	32 (91.4)	NC	Reference
	Yes	1 (2.8)	1 (100.0)		1.09 [0.99–1.21]
Antiplatelet drugs	None	25 (69.4)	24 (96.0)	0.216	Reference
	Yes	11 (30.6)	9 (81.8)		0.85 [0.64–1.14]
Anticoagulants	None	22 (61.1)	21 (95.5)	0.547	Reference
	Yes	14 (38.9)	12 (85.7)		0.90 [0.71–1.13]
Antimycobacterial drugs	None	31 (86.1)	29 (93.5)	NC	Reference
	Yes	5 (13.9)	4 (80.0)		0.86 [0.55–1.34]
Other drugs	None	3 (8.3)	3 (100.0)	NC	Reference
	Yes	33 (91.7)	30 (90.9)		0.91 [0.82–1.01]
Combination therapy					
Surgical treatment	None	33 (91.7)	31 (93.9)	NC	Reference
	Yes	3 (8.3)	2 (66.7)		0.71 [0.32–1.59]

Data are shown as n or n (%).

Factors with a difference in no worsening were defined as those with a statistically significant difference ($P < 0.05$) or ratios of < 0.50 or > 2.00 in ≥ 5 patients among the factor categories (excluding unknown or not described).

[a]Including four patients with both vascular Behçet's disease and intestinal Behçet's disease, and one patient with both vascular Behçet's disease and neurological Behçet's disease.

[b]*P*-values calculated using Fisher's exact test (for categorical factors with two levels) or a chi-square test (for categorical factors with three or more levels) for categories with ≥ 5 patients per group.

ADR adverse drug reaction, *CI* confidence interval, *NC* not calculated.