ONLINE SUPPLEMENTARY APPENDICES

A. Exploratory and post-hoc endpoints, methods of analyses for these endpoints, and methods of statistical analysis for sensitivity analyses of ASAS response.

B. Efficacy, pharmacodynamic, and safety results by ADA status.

C. Sensitivity analyses: proportion of AS patients with ASAS20 response, ASAS40 response and ASAS partial remission.

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APPENDIX A

Exploratory and post hoc endpoints, and methods of analyses for these endpoints

Exploratory and post hoc endpoints included: Assessment of SpondyloArthritis international Society (ASAS)20 response by anti-drug antibody (ADA) status; level of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) by ADA status; incidence of infusion-related reactions and anaphylaxis by ADA status; and ADA persistency.

For subgroup of analysis of ASAS20 response, CRP and ESR, a visit-based approach was used to count the number of patients with ADAs (i.e. ADA rate at week 54 and week 102). In subgroup analysis of the incidence of infusion-related reactions and anaphylaxis, patients were grouped according to their seroconversion status, which was defined as ADA-positive if the patient had a negative ADA test followed by a positive ADA test at a subsequent visit; all other patients who provided at least one ADA test result were defined as ADA-negative. ADA persistency was defined as transient when a patient tested positive for ADAs at one or more time-point but negative at the last available time-point.[A] The remaining patients with positive ADA results were considered to have shown a sustained ADA response.

Methods of statistical analysis for sensitivity analyses of ASAS response

Sensitivity analyses using a last observation carried forward (LOCF) approach were conducted according to EULAR recommendations and EMA Committee for Proprietary Medicinal Products (CPMP) guidelines, both for the extension study ITT population (i.e. those entering the extension study only) and the main study ITT population (i.e. using the original number of patients entering PLANETAS as the denominator).[B, C] One approach was to compare the full-set analysis (LOCF) with complete-case analysis (MEX) and another was to compare the main study ITT population with the extension study ITT population. A non-responder imputation (NRI) approach was also adopted for the main study ITT population in order to show the results from the most conservative of analyses.

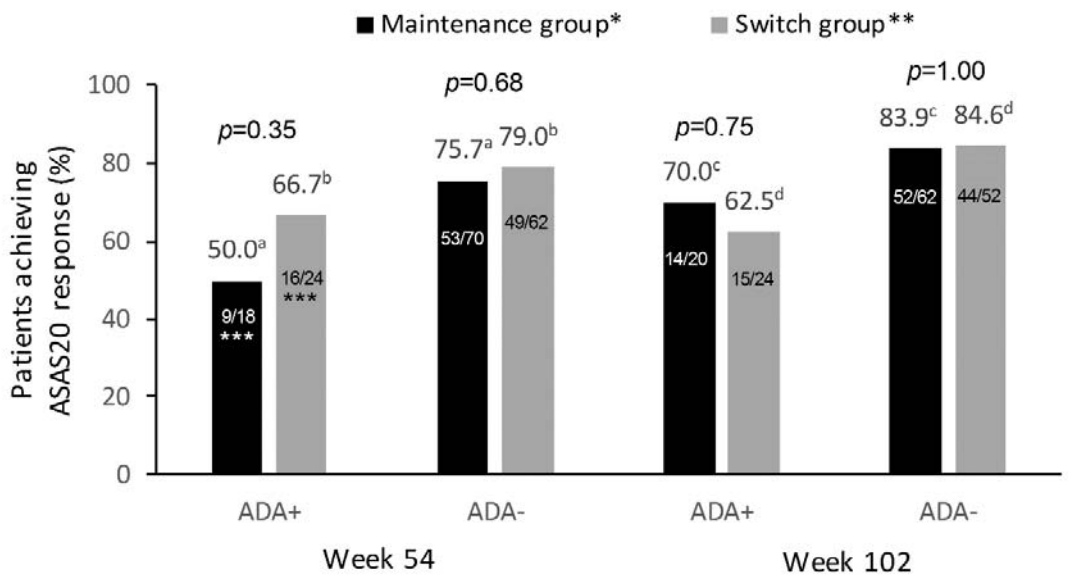
References:

A. Vande Casteele N, Gils A, Singh S, et al. Antibody response to infliximab and its impact on pharmacokinetics can be transient. Am J Gastroenterol 2013;108:962-71.

B. Buch MH, Silva-Fernandez L, Carmona L, et al. Development of EULAR recommendations for the reporting of clinical trial extension studies in rheumatology. Ann Rheum Dis 2015;74:963-9.
C. European Medicines Agency. Committee for Proprietary Medicinal Products (CPMP). Guideline on Missing Data in Confirmatory Clinical Trials(EMA/CPMP/EWP/1776/99 Rev. 1). 2 July 2010. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500096793.pdf (accessed 13 October 2015).

APPENDIX B: Efficacy, pharmacodynamics, and safety results by ADA status

Figure B-1. Summary of the proportion of patients achieving ASAS20 response by visit, according to ADA status (efficacy population).



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ADA results were obtained from samples taken at the same time-points as efficacy assessments (i.e. at week 54 and week 102).

*Patients treated with CT-P13 during the 54 weeks of the main study and the 48-week extension study.

**Patients treated with RP during the 54 weeks of the main study and then switched to CT-P13 during the 48-week extension study.

***Values are n/N where n is the number of patients with ASAS20 response among patients with ADA-positive (or negative) results, and N is the number of patients with ADA-positive (or negative) results, at each time point in each group.

Statistical significance was determined using Fisher's exact test.

Comparisons of ADA subgroups within treatment groups: [a]p=0.04; [b]p=0.27; [c]p=0.20; [d]p=0.04.

ADA, anti-drug antibody; ASAS, Assessment of SpondyloArthritis international Society; RP, reference product.

Table B-1. Descriptive statistics for change from baseline of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) by visit, according to ADA status (safety population).

CRP (mg/dL)

Visit	ADA status[1]	Maintenance group		Switch group		p-value[2]
		n	mean (SD)	n	mean (SD)	
Week 54	ADA-positive	20	0.2 (3.44)	22	-0.5(3.03)	0.46
	ADA-negative	69	-1.3 (3.02)	61	-1.8 (2.14)	0.33
	p-value[2]		0.05		0.04	
Week 102	ADA-positive	21	-0.4 (1.62)	23	-0.6 (3.81)	0.87
	ADA-negative	62	-1.8 (2.80)	51	-1.5 (2.01)	0.46
	p-value[2]		0.03		0.18	

ESR (mm/h)

Visit	ADA status[1]	Maintenance group		Switch group		p-value[2]
		n	mean (SD)	n	mean (SD)	
Week 54	ADA-positive	20	-15.3 (22.53)	19	-15.3 (33.43)	1.00
	ADA-negative	69	-24.1 (22.59)	62	-23.9 (16.01)	0.96
	p-value[2]		0.13		0.13	
Week 102	ADA-positive	21	-12.0 (20.11)	20	-14.4 (33.21)	0.78
	ADA-negative	61	-24.6 (23.01)	52	-21.3 (21.25)	0.42
	p-value[2]		0.03		0.30	

[1]ADA results were obtained from samples taken at the same time-points as efficacy assessments (i.e. at week 54 and week 102).

[2]p-value calculated using T-test.

ADA, anti-drug antibody; RP, reference product; SD, standard deviation.

Table B-2. Infusion-related reactions by ADA status in the extension study (safety population).

	ADA status	Maintenance group (N=90) n/N' (%)	Switch group (N=84) n/N' (%)	p-value[1]
Infusion-related reactions	ADA-positive	4/32 (12.5)	4/28 (14.3)	1.00
	ADA-negative	3/58 (5.2)	2/56 (3.6)	1.00
	p-value[1]	0.24	0.09	

[1]Fisher's exact test p-value.

N'= the number of patients in each ADA subgroup of each treatment.

ADA, anti-drug antibody.

APPENDIX C: Proportion of AS patients with an ASAS20 response, ASAS40 response and ASAS PR* in PLANETAS (the main 54-week parallel-group study and the extension study)

Table C-1. Sensitivity analyses: ASAS20 response, ASAS40 response and ASAS PR (ITT population in PLANETAS extension study with LOCF approach).

Visit	Efficacy parameter	Group	Responder n/N' (%)	Odds ratio[†]	95% CI of odds ratio	p-value[‡]
Week 14	ASAS20	Maintenance**	58/88 (65.9)	1.01	0.54, 1.90	0.971
		Switch***	56/86 (65.1)			
	ASAS40	Maintenance	40/88 (45.5)	0.95	0.52, 1.73	0.838
		Switch	40/86 (46.5)			
	ASAS PR	Maintenance	14/88 (15.9)	1.13	0.48, 2.66	0.593
		Switch	12/86 (14.0)			
Week 30	ASAS20	Maintenance	65/88 (73.9)	0.85	0.43, 1.70	0.359
		Switch	66/86 (76.7)			
	ASAS40	Maintenance	50/88 (56.8)	1.19	0.65, 2.18	0.783
		Switch	45/86 (52.3)			
	ASAS PR	Maintenance	14/88 (15.9)	0.95	0.42, 2.15	0.997
		Switch	14/86 (16.3)			
Week 54	ASAS20	Maintenance	62/88 (70.5)	0.75	0.38, 1.48	0.455
		Switch	65/86 (75.6)			
	ASAS40	Maintenance	51/88 (56.8)	1.20	0.66, 2.18	0.592
		Switch	46/86 (53.5)			
	ASAS PR	Maintenance	15/88 (17.0)	1.00	0.45, 2.20	0.915
		Switch	15/86 (17.4)			
Week 78	ASAS20	Maintenance	62/88 (70.5)	0.74	0.38, 1.46	0.095
		Switch	65/88 (75.6)			
	ASAS40	Maintenance	50/88 (56.8)	1.20	0.66, 2.20	0.095
		Switch	45/86 (52.3)			

	ASAS PR	Maintenance	18/88 (20.5)	1.12	0.53, 2.38	0.222
		Switch	16/86 (18.6)			
Week 102	ASAS20	Maintenance	71/88 (80.7)	1.42	0.69, 2.94	0.499
		Switch	64/88 (74.4)			
	ASAS40	Maintenance	56/88 (63.6)	1.14	0.61, 2.10	0.550
		Switch	52/86 (60.5)			
	ASAS PR	Maintenance	16/88 (18.2)	0.84	0.40, 1.79	0.214
		Switch	18/86 (20.9)			

Table C-2. Sensitivity analyses: ASAS20 response, ASAS40 response and ASAS PR (ITT population in PLANETAS main study with LOCF approach).

Visit	Efficacy parameter	Group	Responder n/N (%)	Odds ratio[†]	95% CI of odds ratio	p-value[‡]
Week 14	ASAS20	CT-P13	72/125 (57.6)	0.79	0.47, 1.31	0.683
		RP	79/125 (63.2)			
	ASAS40	CT-P13	48/125 (38.4)	0.77	0.47, 1.28	0.573
		RP	56/125 (44.8)			
	ASAS PR	CT-P13	19/125 (15.2)	1.22	0.60, 2.51	0.631
		RP	16/125 (12.8)			
Week 30	ASAS20	CT-P13	81/125 (64.8)	0.80	0.47, 1.36	0.148
		RP	87/125 (69.6)			
	ASAS40	CT-P13	60/125 (48.0)	1.13	0.69, 1.87	0.973
		RP	56/125 (44.8)			
	ASAS PR	CT-P13	18/125 (14.4)	1.23	0.59, 2.57	0.976
		RP	15/125 (12.0)			
Week 54	ASAS20	CT-P13	73/125 (58.4)	0.73	0.44, 1.23	0.684
		RP	82/125 (65.6)			
	ASAS40	CT-P13	59/125 (47.2)	1.10	0.67, 1.81	0.763

		RP	56/125 (44.8)			
	ASAS PR	CT-P13	18/125 (14.4)	1.01	0.50, 2.06	0.862
		RP	18/125 (14.4)			
Week 78#	ASAS20	CT-P13	73/125 (58.4)	0.73	0.44, 1.22	0.252
		RP	82/125 (65.6)			
	ASAS40	CT-P13	58/125 (46.4)	1.10	0.67, 1.81	0.257
		RP	55/125 (44.0)			
	ASAS PR	CT-P13	21/125 (16.8)	1.13	0.57, 2.23	0.087
		RP	19/125 (15.2)			
Week 102#	ASAS20	CT-P13	82/125 (65.6)	1.04	0.62, 1.74	0.687
		RP	81/125 (64.8)			
	ASAS40	CT-P13	64/125 (51.2)	1.07	0.65, 1.75	0.536
		RP	62/125 (49.6)			
	ASAS PR	CT-P13	19/125 (15.2)	0.89	0.45, 1.76	0.408
		RP	21/125 (16.8)			

Table C-3. Sensitivity analyses: ASAS20 response, ASAS40 response and ASAS PR (ITT population in PLANETAS main study with NRI approach).

Visit	Efficacy parameter	Group	Responder n/N (%)	Odds ratio†	95% CI of odds ratio	p-value‡
Week 14	ASAS20	CT-P13	72/125 (57.6)	0.79	0.47, 1.31	0.683
		RP	79/125 (63.2)			
	ASAS40	CT-P13	48/125 (38.4)	0.77	0.47, 1.28	0.573
		RP	56/125 (44.8)			
	ASAS PR	CT-P13	19/125 (15.2)	1.22	0.60, 2.51	0.631
		RP	16/125 (12.8)			
Week 30	ASAS20	CT-P13	79/125 (63.2)	0.84	0.50, 1.41	0.178
		RP	84/125 (67.2)			
	ASAS40	CT-P13	58/125 (46.4)	1.10	0.66, 1.81	0.974

		RP	55/125 (44.0)			
	ASAS PR	CT-P13	17/125 (13.6)	1.15	0.55, 2.42	0.994
		RP	15/125 (12.0)			
Week 54	ASAS20	CT-P13	71/125 (56.8)	0.88	0.53, 1.45	0.453
		RP	75/125 (60.0)			
	ASAS40	CT-P13	58/125 (46.4)	1.18	0.71, 1.94	0.438
		RP	53/125 (42.4)			
	ASAS PR	CT-P13	17/125 (13.6)	1.01	0.49, 2.09	0.794
		RP	17/125 (13.6)			
Week 78#	ASAS20	CT-P13	61/125 (48.8)	0.91	0.55, 1.49	0.401
		RP	64/125 (51.2)			
	ASAS40	CT-P13	50/125 (40.0)	1.28	0.76. 2.13	0.076
		RP	43/125 (34.4)			
	ASAS PR	CT-P13	18/125 (14.4)	1.15	0.56, 2.37	0.606
		RP	16/125 (12.8)			
Week 102#	ASAS20	CT-P13	67/125 (53.6)	1.27	0.77, 2.10	0.588
		RP	60/125 (48.0)			
	ASAS40	CT-P13	53/125 (42.4)	1.19	0.71, 1.99	0.731
		RP	48/125 (38.4)			
	ASAS PR	CT-P13	16/125 (12.8)	0.87	0.42, 1.81	0.177
		RP	18/125 (14.4)			

*PR was defined as a value of <20 on a 0–100 scale in each of the following four domains: patient global assessment, pain, function and inflammation.

**Patients treated with CT-P13 during the 54 weeks of the main study and the 48-week extension study.

***Patients treated with RP during the 54 weeks of the main study and then switched to CT-P13 during the 48-week extension study.

Participants in the extension study were treated with CT-P13.

†The odds ratio was estimated using a logistic regression model with treatment as a fixed effect, and region and baseline BASDAI score as covariates. An odds ratio of >1 indicates increased odds in favour of the maintenance group.

‡The p-value was calculated using the Hosmer-Lemeshow test for the goodness-of-fit of the logistic regression model. The test is significant at the 5% level.

ASAS, Assessment of SpondyloArthritis international Society; ASAS20, 20% response according to the ASAS International Working Group criteria for improvement; ASAS40, 40% response according to the ASAS International Working Group criteria for improvement; CI, confidence interval; ITT, intent-to-treat; LOCF, last observation carried forward; n, number of patients with response; NRI, non-responder imputation; N', number of patients with assessment; N, number of patients in group; PR, partial remission; RP, reference product.

APPENDIX D: TEAEs reported during the extension study

Table D-1. TEAEs during the extension study

	Maintenance* group 5 mg/kg (N=90)	Switch** group 5 mg/kg (N=84)	Total (N=174)
Patients with ≥1 TEAE, n (%)	44 (48.9)	60 (71.4)	104 (59.8)
Related	20 (22.2)	33 (39.3)	53 (30.5)
Unrelated	33 (36.7)	44 (52.4)	77 (44.3)
Blood and lymphatic system disorders, n (%)	1 (1.1)	6 (7.1)	7 (4.0)
Related	0	2 (2.4)	2 (1.1)
Unrelated	1 (1.1)	4 (4.8)	5 (2.9)
Anaemia	0	2 (2.4)	2 (1.1)
Unrelated	0	2 (2.4)	2 (1.1)
Eosinophilia	0	2 (2.4)	2 (1.1)
Related	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Lymphocytosis	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Neutropenia	1 (1.1)	2 (2.4)	3 (1.7)
Related	0	1 (1.2)	1 (0.6)
Unrelated	1 (1.1)	1 (1.2)	2 (1.1)
Cardiac disorders, n (%)	2 (2.2)	3 (3.6)	5 (2.9)
Unrelated	2 (2.2)	3 (3.6)	5 (2.9)
Arrythmia	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Atrial fibrillation	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Coronary syndrome	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Tachyarrhythmia	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)

Tachycardia	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Ear and labyrinth disorders, n (%)	0	1 (1.2)	1 (0.6)
Related	0	1 (1.2)	1 (0.6)
Tinnitus	0	1 (1.2)	1 (0.6)
Related	0	1 (1.2)	1 (0.6)
Eye disorders, n (%)	2 (2.2)	2 (2.4)	4 (2.3)
Related	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	2 (2.4)	3 (1.7)
Chalazion	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Conjunctivitis	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Uveitis	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Vision blurred	1 (1.1)	0	1 (0.6)
Related	1 (1.1)	0	1 (0.6)
Gastrointestinal disorders, n (%)	4 (4.4)	12 (14.3)	16 (9.2)
Related	0	4 (4.8)	4 (2.3)
Unrelated	4 (4.4)	9 (10.7)	13 (7.5)
Abdominal pain	0	2 (2.4)	2 (1.1)
Related	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Colitis	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Diarrhoea	0	4 (4.8)	4 (2.3)
Related	0	1 (1.2)	1 (0.6)
Unrelated	0	3 (3.6)	3 (1.7)
Dyspepsia	0	1 (1.2)	1 (0.6)
Related	0	1 (1.2)	1 (0.6)
Enteritis	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Gastritis	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Gastroduodenitis	0	1 (1.2)	1 (0.6)

Unrelated	0	1 (1.2)	1 (0.6)
Gastrooesophageal reflux disease	1 (1.1)	1 (1.2)	2 (1.1)
Unrelated	1 (1.1)	1 (1.2)	2 (1.1)
Inguinal hernia	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Lower gastrointestinal haemorrhage	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Oesophagitis	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Rectal fissure	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Rectal haemorrhage	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Toothache	0	1 (1.2)	1 (0.6)
Related	0	1 (1.2)	1 (0.6)
General disorders and administration site conditions, n (%)	1 (1.1)	1 (1.2)	2 (1.1)
Unrelated	1 (1.1)	1 (1.2)	2 (1.1)
Spinal pain	1 (1.1)	1 (1.2)	2 (1.1)
Unrelated	1 (1.1)	1 (1.2)	2 (1.1)
Hepatobiliary disorders, n (%)	0	3 (3.6)	3 (1.7)
Related	0	1 (1.2)	1 (0.6)
Unrelated	0	2 (2.4)	2 (1.1)
Cholelithiasis	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Hepatic steatosis	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Hepatitis	0	1 (1.2)	1 (0.6)
Related	0	1 (1.2)	1 (0.6)
Infections and infestations, n (%)	24 (26.7)	29 (34.5)	53 (30.5)
Related	9 (10.0)	10 (11.9)	19 (10.9)
Unrelated	16 (17.8)	21 (25.0)	37 (21.3)
Abscess neck	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)

Acute tonsillitis	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Appendicitis	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Gastroenteritis	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Genital infection fungal	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Herpes virus infection	1 (1.1)	2 (2.4)	3 (1.7)
Related	1 (1.1)	0	1 (0.6)
Unrelated	0	2 (2.4)	2 (1.1)
Influenza	1 (1.1)	1 (1.2)	2 (1.1)
Related	1 (1.1)	0	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Latent tuberculosis	5 (5.6)	7 (8.3)	12 (6.9)
Related	2 (2.2)	4 (4.8)	6 (3.4)
Unrelated	3 (3.3)	3 (3.6)	6 (3.4)
Lower respiratory tract infection	4 (4.4)	2 (2.4)	6 (3.4)
Related	2 (2.2)	1 (1.2)	3 (1.7)
Unrelated	2 (2.2)	2 (2.4)	4 (2.3)
Pyelonephritis chronic	0	2 (2.4)	2 (1.1)
Unrelated	0	2 (2.4)	2 (1.1)
Rhinitis	1 (1.1)	1 (1.2)	2 (1.1)
Unrelated	1 (1.1)	1 (1.2)	2 (1.1)
Sinusitis	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Tinea	0	1 (1.2)	1 (0.6)
Related	0	1 (1.2)	1 (0.6)
Tonsillitis	1 (1.1)	0	1 (0.6)
Related	1 (1.1)	0	1 (0.6)
Tuberculosis	1 (1.1)	1 (1.2)	2 (1.1)
Related	1 (1.1)	1 (1.2)	2 (1.1)
Upper respiratory tract infection	10 (11.1)	8 (9.5)	18 (10.3)
Related	3 (3.3)	2 (2.4)	5 (2.9)
Unrelated	7 (7.8)	6 (7.1)	13 (7.5)

Urinary tract infection	4 (4.4)	5 (6.0)	9 (5.2)
Related	0	2 (2.4)	2 (1.1)
Unrelated	4 (4.4)	3 (3.6)	7 (4.0)
Injury, poisoning and procedural complications, n (%)	9 (10.0)	8 (9.5)	17 (9.8)
Related	7 (7.8)	6 (7.1)	13 (7.5)
Unrelated	3 (3.3)	3 (3.6)	6 (3.4)
Arthropod bite	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Burns	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Infusion related reaction	7 (7.8)	6 (7.1)	13 (7.5)
Related	7 (7.8)	6 (7.1)	13 (7.5)
Laceration	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Ligament injury	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Limb injury	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Procedural pain	0	1(1.2)	1 (0.6)
Unrelated	0	1(1.2)	1 (0.6)
Investigations, n (%)	10 (11.1)	16 (19.0)	26 (14.9)
Related	7 (7.8)	9 (10.7)	16 (9.2)
Unrelated	3 (3.3)	8 (9.5)	11 (6.3)
Blood bilirubin increased	0	1 (1.2)	1 (0.6)
Related	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Blood creatine phosphokinase increased	3 (3.3)	4 (4.8)	7 (4.0)
Related	2 (2.2)	1 (1.2)	3 (1.7)
Unrelated	1 (1.1)	3 (3.6)	4 (2.3)
Blood lactate dehydrogenase increased	0	1 (1.2)	1 (0.6)
Related	0	1 (1.2)	1 (0.6)
C-reactive protein increased	0	1 (1.2)	1 (0.6)

Unrelated	0	1 (1.2)	1 (0.6)
Liver function test abnormal	5 (5.6)	9 (10.7)	14 (8.0)
Related	4 (4.4)	4 (4.8)	8 (4.6)
Unrelated	1 (1.1)	5 (6.0)	6 (3.4)
Neutrophil count decreased	0	1 (1.2)	1 (0.6)
Related	0	1 (1.2)	1 (0.6)
Prostatic specific antigen increased	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Red blood cell sedimentation rate increased	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Vitamin D decreased	0	1 (1.2)	1 (0.6)
Related	0	1 (1.2)	1 (0.6)
Weight decreased	1 (1.1)	2 (2.4)	3 (1.7)
Related	1 (1.1)	1 (1.2)	2 (1.1)
Unrelated	0	1 (1.2)	1 (0.6)
Weight increased	1 (1.1)	0	1 (0.6)
Related	1 (1.1)	0	1 (0.6)
Metabolism and nutrition disorders, n (%)	2 (2.2)	3 (3.6)	5 (2.9)
Related	2 (2.2)	1 (1.2)	3 (1.7)
Unrelated	0	2 (2.4)	2 (1.1)
Decreased appetite	1 (1.1)	0	1 (0.6)
Related	1 (1.1)	0	1 (0.6)
Hyperlipidaemia	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Hyponatraemia	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Hypophosphataemia	1 (1.1)	1 (1.2)	2 (1.1)
Related	1 (1.1)	1 (1.2)	2 (1.1)
Musculoskeletal and connective tissue disorders, n (%)	5 (5.6)	11 (13.1)	16 (9.2)
Related	2 (2.2)	3 (3.6)	5 (2.9)
Unrelated	3 (3.3)	8 (9.5)	11 (6.3)

Ankylosing spondylitits	0	3 (3.6)	3 (1.7)
Unrelated	0	3 (3.6)	3 (1.7)
Arthralgia	0	1 (1.2)	1 (0.6)
Related	0	1 (1.2)	1 (0.6)
Back pain	0	5 (6.0)	5 (2.9)
Related	0	3 (3.6)	3 (1.7)
Unrelated	0	2 (2.4)	2 (1.1)
Bursitis	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Fibromyalgia	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Myalgia	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Neck pain	0	1 (1.2)	1 (0.6)
Related	0	1 (1.2)	1 (0.6)
Osteonecrosis	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Plantar fasciitis	1 (1.1)	0	1 (0.6)
Related	1 (1.1)	0	1 (0.6)
Rotator cuff syndrome	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Tendonitis	2 (2.2)	0	2 (1.1)
Related	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps), n (%)	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Prostate cancer	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Nervous system disorders, n (%)	5 (5.6)	4 (4.8)	9 (5.2)
Related	0	1 (1.2)	1 (0.6)
Unrelated	5 (5.6)	3 (3.6)	8 (4.6)
Dizziness	1 (1.1)	1 (1.2)	2 (1.1)
Unrelated	1 (1.1)	1 (1.2)	2 (1.1)

Headache	2 (2.2)	2 (2.4)	4 (2.3)
Related	0	1 (1.2)	1 (0.6)
Unrelated	2 (2.2)	1 (1.2)	3 (1.7)
Intercostal neuralgia	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Post herpetic neuralgia	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Trigeminal neuralgia	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Psychiatric disorder, n (%)	0	5 (6.0)	5 (2.9)
Related	0	1 (1.2)	1 (0.6)
Unrelated	0	4 (4.8)	4 (2.3)
Alcohol abuse	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Alcohol withdrawal syndrome	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Depression	0	2 (2.4)	2 (1.1)
Unrelated	0	2 (2.4)	2 (1.1)
Insomnia	0	2 (2.4)	2 (1.1)
Related	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Stress	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Renal and urinary disorders, n (%)	2 (2.2)	3 (3.6)	5 (2.9)
Related	0	1 (1.2)	1 (0.6)
Unrelated	2 (2.2)	3 (3.6)	5 (2.9)
Calculus urinary	0	2 (2.4)	2 (1.1)
Unrelated	0	2 (2.4)	2 (1.1)
Haematuria	1 (1.1)	2 (2.4)	3 (1.7)
Related	0	1 (1.2)	1 (0.6)
Unrelated	1 (1.1)	1 (1.2)	2 (1.1)
Nocturia	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Pollakiuria	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)

Renal colic	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Renal cyst	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Reproductive system and breast disorders, n (%)	2 (2.2)	3 (3.6)	5 (2.9)
Unrelated	2 (2.2)	3 (3.6)	5 (2.9)
Benign prostatic hyperplasia	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Breast calcifications	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Penis disorder	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Prostatitis	0	2 (2.4)	2 (1.1)
Unrelated	0	2 (2.4)	2 (1.1)
Respiratory, thoracic and mediastinal disorders, n (%)	1 (1.1)	4 (4.8)	5 (2.9)
Related	1 (1.1)	2 (2.4)	3 (1.7)
Unrelated	0	2 (2.4)	2 (1.1)
Bronchospasm	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Cough	1 (1.1)	1 (1.2)	2 (1.1)
Related	1 (1.1)	1 (1.2)	2 (1.1)
Nasal obstruction	1 (1.1)	0	1 (0.6)
Related	1 (1.1)	0	1 (0.6)
Oropharyngeal pain	0	1 (1.2)	1 (0.6)
Unrelated	0	1 (1.2)	1 (0.6)
Rhinorrhoea	0	1 (1.2)	1 (0.6)
Related	0	1 (1.2)	1 (0.6)
Skin and subcutaneous tissue disorders, n (%)	9 (10.0)	0	9 (5.2)
Related	2 (2.2)	0	2 (1.1)
Unrelated	7 (7.8)	0	7 (4.0)
Cold sweat	1 (1.1)	0	1 (0.6)
Related	1 (1.1)	0	1 (0.6)

Dermatitis	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Dermatitis allergic	3 (3.3)	0	3 (1.7)
Unrelated	3 (3.3)	0	3 (1.7)
Intertrigo	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Pruritus	1 (1.1)	0	1 (0.6)
Related	1 (1.1)	0	1 (0.6)
Rash	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Rosacea	1 (1.1)	0	1 (0.6)
Unrelated	1 (1.1)	0	1 (0.6)
Vascular disorders, n (%)	1 (1.1)	1 (1.2)	2 (1.1)
Unrelated	1 (1.1)	1 (1.2)	2 (1.1)
Hypertension	1 (1.1)	1 (1.2)	2 (1.1)
Unrelated	1 (1.1)	1 (1.2)	2 (1.1)

*Patients treated with CT-P13 during the 54 weeks of the main study and the 48-week extension study.

**Patients treated with RP during the 54 weeks of the main study and then switched to CT-P13 during the 48-week extension study.

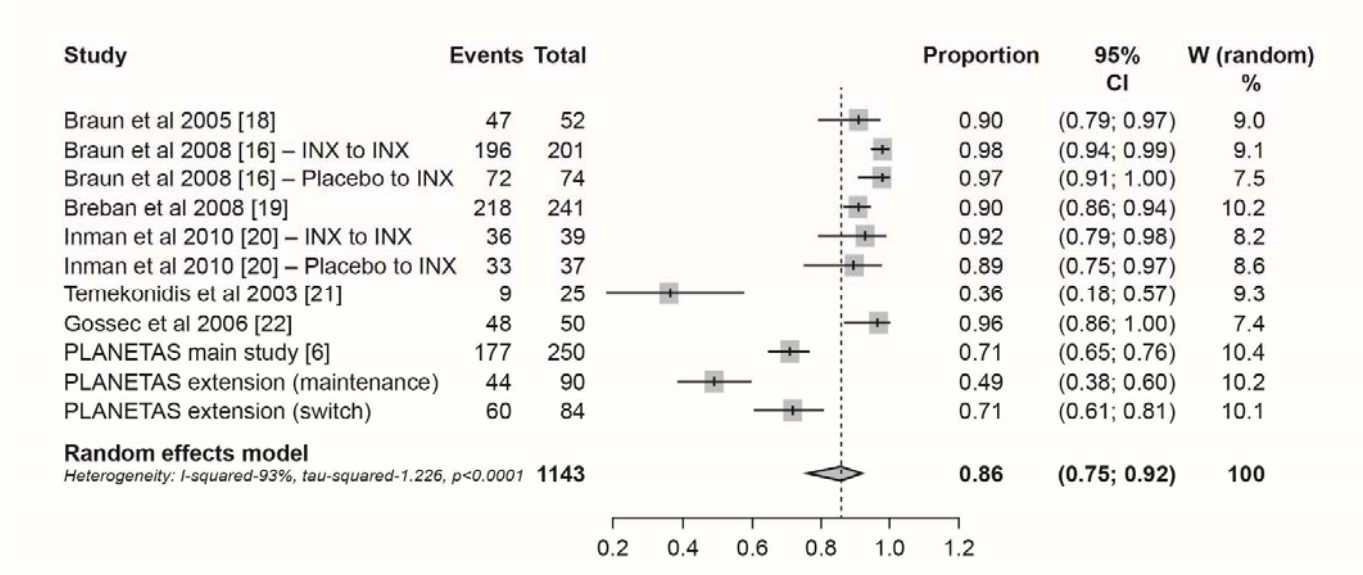
APPENDIX E: Safety meta-analysis: historical incidence of TEAEs with infliximab RP

Methods

A literature search was conducted to identify studies in AS patients focusing on randomised studies or those with an observational design, with a duration of at least 54 weeks and long-term cohorts and observational studies capturing safety reporting up to 2 years. Only studies which reported the methodology of collecting safety data and incidence of adverse events using reliable denominators were included in the meta-analysis.

Results

Figure E-1. Comparison of TEAEs in the PLANETAS main and extension studies and historical AS studies with infliximab RP up to 2 years.



CI, confidence interval; INX, infliximab.

APPENDIX F: Incidence of TEAEs during the extension studies of PLANETAS and PLANETRA

Table F-1. Incidence of TEAEs during the extension studies of PLANETAS and PLANETRA (safety population).

Study	Maintenance group* n/N (%)	Switch group** n/N (%)	Total n/N (%)
PLANETAS	44/90 (48.9)	60/84 (71.4)	104/174 (59.8)
PLANETRA	85/159 (53.5)	77 /143 (53.8)	162/302 (53.6)
Total	129/249 (51.8)	137/227 (60.4)	266/476 (55.9)

*Patients treated with CT-P13 during the 54 weeks of the main study and the 48-week extension study.

**Patients treated with RP during the 54 weeks of the main study and then switched to CT-P13 during the 48-week extension study.

RP, reference product; TEAE, treatment-emergent adverse event.