SUPPLEMENTARY MATERIAL

Patient Preference for Subcutaneous Versus Intravenous Administration With Every 6-Week Natalizumab (Tysabri®) Dosing: NOVA Phase IIIb Extension Study (Part 2)

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Table S1 Listing of Ethics Committees

Site No.	Principal Investigator Name	Name / Address of Ethics Committee
180	Grand'Maison, Francois	WIRB / 1019 39th Avenue SE Suite 120 Puyallup, WA 98374-2115
181	Jacques, Francois	WIRB / 1019 39th Avenue SE Suite 120 Puyallup, WA 98374-2115
183	Vosoughi, Reza	St. Michael's Hospital Research Ethics Board / St. Michael's Hospital 30 Bond St Toronto, Ontario M5B 1W8, Canada
201	Van der Walt, Anneke	The Alfred Hospital Research Governance (RGO) / 55 Commercial Rd, Melbourne VIC 3004
202	Dwyer, Christopher	Melbourne Health Human Research Ethics Committee / St. Vincent's Hospital (Melbourne) Limited, 41 Victoria Parade, Fitzroy, VIC, 3065
203	Buzzard, Katherine	Eastern Health Research and Ethics Committee (RGO) / Eastern Health, Level 4 5 Arnold St, Box Hill Victoria 3128
204	Spies, Judith	University of Sydney (RGO) Michael Spence Building (F23), University of Sydney NSW 2006 Royal Prince Alfred Hospital Research Governance Officer (RGO), RPAH, Missenden Rd, Camperdown NSW 2050
205	Parratt, John	General Enquiries Email: NSLHD-Research@health.nsw.gov.au Phone: +61 2 94 50 7089 Postal Address NSLHD Research Office, Level 13 Kolling Building, Royal North Shore Hospital, Reserve Road, St Leonards, NSW, 2065

300	Van Pesch, Vincent	Comité d'éthique hospitalo-Facultaire Cliniques universitaires Saint Luc / Promenade de l'Alma 51 bte B1.43.03 1200 Bruxelles
302	Gaspard, Nicolas	Comité d'éthique hospitalo-Facultaire Cliniques universitaires Saint Luc / Promenade de l'Alma 51 bte B1.43.03 1200 Bruxelles
303	Quivron, Bénédicte	Comité d'éthique hospitalo-Facultaire Cliniques universitaires Saint Luc / Promenade de l'Alma 51 bte B1.43.03 1200 Bruxelles
401	De Seze, Jerome	Comité de Protection des Personnes Sud-Est V / CHU de Grenoble Comité de Protection des Personnes Sud Est V CS 10217 38043 GRENOBLE Cedex 9
402	Lebrun Frenay, Christine	Comité de Protection des Personnes Sud-Est V / CHU de Grenoble Comité de Protection des Personnes Sud Est V CS 10217 38043 GRENOBLE Cedex 9
404	Ruet, Aurélie	Comité de Protection des Personnes Sud-Est V / CHU de Grenoble Comité de Protection des Personnes Sud Est V CS 10217 38043 GRENOBLE Cedex 9
405	Laplaud, David-Axel	Comité de Protection des Personnes Sud-Est V / CHU de Grenoble Comité de Protection des Personnes Sud Est V CS 10217 38043 GRENOBLE Cedex 9
600	Lus, Giacomo	Comitato Etico Azienda Ospedaliera Universitaria

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601	Centonze, Diego	Comitato Etico dell'I.R.C.C.S. Neuromed-Istituto Neurologico Mediterraneo / Via Atinense, 18, 86077 Pozzilli IS, Italy
602	Patti, Francesco	Comitato Etico Catania 1 / COMITATO ETICO CATANIA 1, VIA S. SOFIA 78, 95123, CATANIA, Sicilia, ITALY
604	Grimaldi, Luigi	Comitato Etico Palermo 1 / A.O.U. Paolo Giaccone Via del Vespro, 129 90127 Palermo
699	Achiron, Anat	Chaim Sheba MC Ethics Committee / Ministry of Health- 39 Yirmiyahu Street POB 1176, Clinical Trials Dept. Jerusalem, 9101002
700	Hupperts, Raymond	Medical research Ethics Committees United / MEC-U Koekoekslaan 1 3435 CM Nieuwegein
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902	Pearson, Owen	NRES Committee - Wales REC 1 / Health and Care Research Wales Castlebridge 4 15-19, Cowbridge Road East Cardiff, CF11 9AB
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Table S2 Part 2 schedule of activities — EID versus IV OLE for participants who transitioned from part 1

Study week	**78**	**84[a]**	**90**	**96**	**102**	**108**	**114**	**120**	**126**	**132**	**138**	**144**	**150**	**156**	**Follow-up EOS visit 168**	**ET visit[b]**	**Unscheduled visit (neurological worsening and relapse assessment)[c]**	**Follow-up safety phone call 180[d]**
Study day	**546** (–2/+5)	**588** (–2/+5)	**630** (–2/+5)	**672** (–2/+5)	**714** (–2/+5)	**756** (–2/+5)	**798** (–2/+5)	**840** (–2/+5)	**882** (–2/+5)	**924** (–2/+5)	**966** (–2/+5)	**1008** (–2/+5)	**1050** (–2/+5)	**1092** (–2/+5)	**1176** (±10)	—	—	**1260** (±10)
Informed consent form for part 2[e]	X																	
Eligibility criteria check for part 2[e]	X																	
Randomization						X												
Vital signs[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical examination[a]		X				X				X				X	X	X	X	
Body weight[a]		X				X				X				X				
C-SSRS[a,g]		X																
EQ-5D-5L						X				X				X				
TSQM						X				X				X				
NeuroQoL Fatigue						X				X				X				
MSIS-29						X				X				X				
EDSS		X				X				X				X		X	X	
Neurological examination (MS signs and symptoms)		X				X				X				X		X	X	
Blood hematology[h]		X				X				X				X	X	X	X	
Blood chemistry[i]		X													X	X	X	
Urine pregnancy test[j]																		

Study week	**78**	**84[a]**	**90**	**96**	**102**	**108**	**114**	**120**	**126**	**132**	**138**	**144**	**150**	**156**	**Follow-up EOS visit 168**	**ET visit[b]**	**Unscheduled visit (neurological worsening and relapse assessment)[c]**	**Follow-up safety phone call 180[d]**
Study day	**546** (–2/ +5)	**588** (–2/ +5)	**630** (–2/ +5)	**672** (–2/ +5)	**714** (–2/ +5)	**756** (–2/ +5)	**798** (–2/ +5)	**840** (–2/ +5)	**882** (–2/ +5)	**924** (–2/ +5)	**966** (–2/ +5)	**1008** (–2/ +5)	**1050** (–2/ +5)	**1092** (–2/ +5)	**1176** (±10)	—	—	**1260** (±10)
PD assessments (whole blood)[h]				X		X	X	X	X	X	X	X	X	X				
PK natalizumab concentration (serum)[h]				X		X	X	X	X	X	X	X	X	X				
Anti-natalizumab antibodies[h]						X		X		X		X		X			X	
Serum biomarkers[h]						X				X				X				
Anti-JCV antibody index[h]				X		X				X				X				
Brain MRI[k]						X				X				X		X		
Natalizumab EID IV infusion	X	X	X	X	X									X				
Natalizumab EID SC-IV crossover[l]						X	X	X	X	X	X	X	X	X[m]				
PPQ[n]											X		X			X		
Safety (AE, SAEs)	Any AE collected between the signing of the part 2 ICF and EOS visit is to be recorded regardless of the severity of the event or its relationship to study treatment; any SAE experienced by the participant between the time of the signing of the ICF and the follow-up safety phone call is to be recorded (more details in Section 15.3 of the protocol)																	
Concomitant therapy and procedures[o]	Record as per Section 11.5 of the protocol																	X
Assessment of new neurological symptoms[p]																		X

AE adverse event, *CRF* case report form, *C-SSRS* Columbia Suicide Severity Rating Scale, *EDSS* Expanded Disability Status Scale, *EID* extended interval dosing, *EOS* end of study, *EQ-5D-5L* EuroQol-5 dimensions 5-level questionnaire, *ET* early termination, *Gd+* gadolinium-enhancing, *ICF* informed consent form, *IV* intravenous, *JCV* John Cunningham virus, *MRI* magnetic resonance imaging, *MSIS-29* Multiple Sclerosis Impact Scale, *NeuroQoL* Neurology Quality of Life questionnaire, *OLE* open-label extension, *PD* pharmacodynamic, *PK* pharmacokinetic, *PPQ* Patient Preference Questionnaire, *SAE* serious adverse event, *SC* subcutaneous, *TSQM* Treatment Satisfaction Questionnaire for Medication

[a]Informed consent can be obtained any time between day –42 and the day of the last pre-study dose of natalizumab. The last pre-study dose of natalizumab must occur between days –33 and –26 from the baseline visit. Some screening assessments must be performed immediately prior to the last pre-study dose of natalizumab (see footnote g). All other screening assessments can occur any time between the day of the last pre-study natalizumab dose and baseline. Randomization to crossover study treatment should be done at the week 108 visit to confirm crossover treatment allocation

[b]The part 1 and part 2 assessments at week 84 are the same and should be performed only once

[c]If a participant chooses to withdraw from the study, an ET visit should occur as soon as possible but no later than 4 weeks after the last dose of study treatment, to be followed by a final EOS visit at 12 weeks (± 10 days) and the follow-up safety phone call at 24 weeks after the last dose of study treatment

[d]Participants who suspect that they are experiencing new or worsening neurological symptoms, including possible relapse, need to phone the Investigator within 72 hours of the onset of the symptoms. The participant is to be evaluated by the neurologist within 5 days of the onset of symptoms. Relapses should be documented in the relapse assessment form. The maximum number of samples eligible for collection and analysis is two (one for each unscheduled visit)

[e]Participants should have a follow-up safety phone call 24 weeks after their last dose of study treatment

[f]The part 2 informed consent and eligibility assessment should be performed during week 72 of part 1 if possible. In the event that this cannot be performed at that time, informed consent and eligibility assessment should be conducted prior to the participant starting part 2 at the week 78 or week 84 visit. Randomization enrollment in part 2 of the study

[g]Vital signs collected at each of the specified timepoints include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate. Vital signs collected as part of the participant's standard of care on the same day as a study visit do not need to be repeated for the study if Biogen has access to the information and data recorded in the participant's CRF. Vital signs on a study treatment day must be performed prior to the administration of study treatment

[h]The part 1 "baseline/screening" C-SSRS must be completed at the part 1 screening visit; at all other visits, the "since last visit" C-SSRS must be used

[i]Sample to be collected prior to dosing

[j]If a participant experiences signs and symptoms suggestive of liver failure (such as jaundice, vomiting, anorexia, nausea, fatigue, and right upper abdominal discomfort), liver function tests (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyl transferase, bilirubin, and albumin) must be performed at the local laboratory on an expedited basis

[k]Follow-up testing for women of childbearing potential throughout the study will be done at the discretion of the Investigator or as required by local law. In each case of delayed menstruation (> 1 month between menstrual periods), a urine pregnancy test should be performed

[l]All post-baseline MRIs are to be completed within a 7-day window of the dosing visit. If a participant's MRI is scheduled to occur < 4 weeks after the last dose of steroid treatment for relapse, the MRI should be rescheduled so it is performed either before the steroid treatment or between 4 and 8 weeks after the last dose of steroid treatment. MRI does not need to be performed at the ET visit if the last MRI was performed within the previous 4 weeks. In the event of an early termination for a pregnancy, a Gd+ MRI should not be conducted

[m]The time required for drug preparation and drug administration should be recorded in detail for each occasion of treatment administration during the crossover period

[n]Participants in part 2 will receive a final dose of natalizumab 300 mg by SC injection or IV infusion at the week 156 visit with the route of administration being the participant's choice

[o]PPQ assessments at week 138 and week 150 must be collected after study treatment administration

[p]Participants should be contacted by phone 24 weeks after the last dose of study treatment to discuss if there has been any new development of neurological symptoms. PML or new neurological symptoms indicative of progressive multifocal leukoencephalopathy (new or sudden change in thinking, vision, balance, or strength persisting over several days) must be immediately reported as a SAE

Table S3 Summary of PPQ by visit (mITT population)[a]

	IV/SC (*N* = 66)	SC/IV (*N* = 65)	Total (*N* = 131)
No. of participants with PPQ data at week 42/150	62	61	123
Main reasons for preference of IV[b], *n* (%)			
Feels less emotionally distressing	2 (3.2)	2 (3.3)	4 (3.3)
Requires less time in the clinic	0	0	0
Lower level of injection site pain	3 (4.8)	2 (3.3)	5 (4.1)
Feels more comfortable during administration	3 (4.8)	2 (3.3)	5 (4.1)
Other	2 (3.2)	2 (3.3)	4 (3.3)
Main reasons for preference of SC[b], *n* (%)			
Feels less emotionally distressing	13 (21)	10 (16.4)	23 (18.7)
Requires less time in the clinic	48 (77.4)	54 (88.5)	102 (82.9)
Lower level of injection site pain	8 (12.9)	6 (9.8)	14 (11.4)
Feels more comfortable during administration	27 (43.5)	26 (42.6)	53 (43.1)
Other	7 (11.3)	14 (23)	21 (17.1)

IV intravenous, *mITT* modified intention-to-treat, *PPQ* Patient Preference Questionnaire, *SC* subcutaneous

mITT: all randomized participants who received at least one dose of SC natalizumab after randomization in part 2 and who completed at least the first question in the PPQ on one occasion

PPQ was collected twice, once after the second dose after switching treatments and again after the fourth (and last) dose after switching treatments (two periods, four doses per period)

[a]Participants with at least one answer to the first question of the PPQ are included in the analysis

[b]Participants were asked to provide two reasons

Table S4 Treatment-emergent AEs with ≥ 5% in either IV or SC route of administration[a,b]

	IV/SC (*N* = 75)	SC/IV (*N* = 66)	IV (*N* = 136)	SC (*N* = 132)	Total (*N* = 141)
No. of participants with any event, *n* (%)	63 (84.0)	49 (74.2)	78 (57.4)	83 (62.9)	112 (79.4)
Infection and infestations	50 (66.7)	37 (56.1)	46 (33.8)	57 (43.2)	87 (61.7)
COVID-19	36 (48.0)	23 (34.8)	28 (20.6)	31 (23.5)	59 (41.8)
Nasopharyngitis	12 (16.0)	4 (6.1)	3 (2.2)	13 (9.8)	16 (11.3)
Urinary tract infection	2 (2.7)	5 (7.6)	7 (5.1)	2 (1.5)	7 (5.0)
Nervous system disorders	16 (21.3)	11 (16.7)	13 (9.6)	15 (11.4)	27 (19.1)
Headache	7 (9.3)	3 (4.5)	7 (5.1)	4 (3.0)	10 (7.1)
Musculoskeletal and connective tissue disorders	13 (17.3)	11 (16.7)	12 (8.8)	12 (9.1)	24 (17.0)
Arthralgia	6 (8.0)	4 (6.1)	2 (1.5)	8 (6.1)	10 (7.1)

AE adverse event, *COVID-19* coronavirus disease 2019, *IV* intravenous, *IV/SC* crossover from IV to SC, *SC* subcutaneous, *SC/IV* crossover from SC to IV

[a]By system organ class and preferred term

[b]Safety population

Table S5 PROs: change from baseline[a] in NeuroQoL Fatigue scale, MSIS-29 Physical and Psychological subscales, and EQ-5D-5L (full analysis set)

	NeuroQoL Fatigue Scale		**MSIS-29 Physical Subscale**		**MSIS-29 Psychological Subscale**		**EQ-5D-5L**	
Dose route	IV (*N* = 136)	SC (*N* = 132)	IV (*N* = 136)	SC (*N* = 132)	IV (*N* = 136)	SC (*N* = 132)	IV (*N* = 136)	SC (*N* = 132)
N[b]	127	127	127	127	127	127	127	127
LS Mean	–0.51	0.01	–0.12	–0.01	–1.50	0.37	0.02	–0.02
SE of LS Mean	0.410	0.415	0.605	0.610	0.793	0.800	0.011	0.011
Difference		0.51		0.11		1.88		–0.05
95% CI		(–0.83, 1.86)		(–1.89, 2.12)		(–0.55, 4.30)		(–0.08, –0.01)
P value		0.450		0.911		0.129		0.004

CI confidence interval, *EID* extended interval dosing, *EQ-5D-5L* EuroQol-5 dimensions 5-level questionnaire, *IV* intravenous, *LS* least squares, *MSIS-29* 29-item Multiple Sclerosis Impact Scale, *NeuroQoL* Quality of Life in Neurological Disorders, *PRO* patient-reported outcome, *SC* subcutaneous, *SE* standard error, *SID* standard interval dosing

[a]Baseline was defined as the last assessment before the first dose administration during that period. Change from baseline was calculated relative to the start of each period. A linear mixed effects model was performed including factors for treatment, period, sequence, crossover baseline body weight (continuous variable), duration of natalizumab exposure at baseline (≤ 3 years vs. > 3 years), stratification factor (SID, EID, new participants), and baseline EQ-5D score. An unstructured variance-covariance matrix structure was used

[b]Participants with baseline data were included in the analysis. Missing post-baseline data were imputed prior to analyzing