

SUPPLEMENTARY MATERIALS

TABLE S1 ALGORITHM FOR MAPPING PRO ASSESSMENTS TO NOMINAL WEEKS

	Nominal week	NTDT-PRO	FACIT-F/SF-36v2®/PGI-C
Baseline	0	Days -7 to -1	Day of dosing of the first dose of study drug (screening if missing)
Weeks 1–12	1	Days 1 to 7	None
	2	Days 8 to 14	None
	3	Days 15 to 21	None
	4	Days 22 to 28	None
	5	Days 29 to 35	None
	6	Days 36 to 42	Days 22 to 63
	7	Days 43 to 49	None
	8	Days 50 to 56	None
	9	Days 57 to 63	None
	10	Days 64 to 70	None
	11	Days 71 to 77	None
	12	Days 78 to 84	Days 64 to 105
Weeks 13–24	13	Days 85 to 91	None
	14	Days 92 to 98	None
	15	Days 99 to 105	None
	16	Days 106 to 112	None
	17	Days 113 to 119	None
	18	Days 120 to 126	Days 106 to 147
	19	Days 127 to 133	None
	20	Days 134 to 140	None
	21	Days 141 to 147	None
	22	Days 148 to 154	None
	23	Days 155 to 161	None
	24	Days 162 to 168	Days 148 to 189

FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; NTDT, non-transfusion-dependent β -thalassaemia; PRO, patient-reported outcomes; SF-36v2®, Short Form Health Survey version 2.

Table S2 Known-groups validity at week 24

	n	NTDT-PRO T/W domain			NTDT-PRO SoB domain		
		LS mean	95% CI	p value ^a	LS mean	95% CI	p value ^a
FACIT-F FS				<0.001			<0.001
Very severe (≤ 37)	62	4.04	3.39, 4.69		3.67	2.99, 4.36	
Severe (>37 to 40)	16	2.63	1.61, 3.65		2.14	1.06, 3.22	
Moderate (>40 to 43)	18	2.52	1.59, 3.45		2.50	1.52, 3.48	
Mild (>43 to 46)	17	2.31	1.40, 3.23		2.01	1.04, 2.98	
Very mild/no symptoms (>46)	31	1.05	0.27, 1.82		0.62	-0.21, 1.44	
FACIT-F item HI12^b				<0.001			<0.001
Very much (0)	3	6.57	4.68, 8.46		4.93	2.79, 7.07	
Quite a bit (1)	10	4.44	3.39, 5.49		3.85	2.67, 5.04	
Somewhat (2)	16	3.29	2.45, 4.12		3.39	2.44, 4.33	
A little bit (3)	40	2.77	2.20, 3.34		2.36	1.72, 3.00	
Not at all (4)	27	1.23	0.55, 1.92		0.93	0.16, 1.71	
FACIT-F item An2^b				<0.001			0.002
Very much (0)	3	6.62	4.57, 8.68		4.92	2.68, 7.17	
Quite a bit (1)	11	4.08	3.01, 5.16		3.41	2.23, 4.58	
Somewhat (2)	15	3.36	2.45, 4.27		3.59	2.59, 4.58	
A little bit (3)	48	2.34	1.76, 2.93		1.96	1.32, 2.60	
Not at all (4)	19	1.78	0.91, 2.65		1.31	0.36, 2.26	
SF-36v2[®] vitality				<0.001			<0.001
Very poor (≤ 36.6)	7	5.37	4.07, 6.67		4.53	3.10, 5.96	
Poor (>36.6 to 43.3)	11	4.45	3.41, 5.49		4.04	2.90, 5.18	
Normal (>43.3 to 56.7)	41	2.98	2.40, 3.56		2.79	2.15, 3.43	
Better (>56.7 to 63.4)	29	1.72	1.05, 2.39		1.25	0.51, 1.98	
Much better (>63.4)	8	1.56	0.31, 2.80		1.48	0.11, 2.84	
SF-36v2[®] item 9e^c				<0.001			0.001
All of the time (1)	3	3.13	1.10, 5.17		1.55	-0.72, 3.82	
Most of the time (2)	40	1.79	1.20, 2.39		1.58	0.92, 2.25	
Some of the time (3)	30	2.99	2.34, 3.64		2.76	2.03, 3.48	
A little of the time (4)	15	4.06	3.12, 5.00		3.51	2.47, 4.56	
None of the time (5)	8	5.13	3.88, 6.39		4.44	3.04, 5.85	
SF-36v2[®] item 9g^c				<0.001			<0.001
All of the time (1)	5	5.67	4.24, 7.09		4.67	3.11, 6.24	
Most of the time (2)	4	5.03	3.35, 6.71		4.58	2.74, 6.43	
Some of the time (3)	18	3.79	3.01, 4.58		3.57	2.71, 4.43	
A little of the time (4)	44	2.62	2.07, 3.16		2.37	1.77, 2.97	
None of the time (5)	25	1.20	0.51, 1.90		0.78	0.02, 1.54	
SF-36v2[®] item 9i^c				<0.001			<0.001
All of the time (1)	3	6.20	4.23, 8.17		6.47	4.30, 8.64	
Most of the time (2)	17	4.36	3.53, 5.19		3.56	2.64, 4.47	
Some of the time (3)	25	2.77	2.03, 3.50		2.53	1.72, 3.34	
A little of the time (4)	44	1.99	1.42, 2.56		1.76	1.14, 2.39	
None of the time (5)	7	1.58	0.25, 2.91		1.49	0.02, 2.96	

	n	NTDT-PRO T/W domain			NTDT-PRO SoB domain		
		LS mean	95% CI	p value ^a	LS mean	95% CI	p value ^a
PGI-S				<0.001			<0.001
0 to 2 (no symptoms)	43	1.13	0.72, 1.54		0.93	0.37, 1.48	
>2 to 4 (mild)	33	3.43	2.97, 3.89		3.32	2.69, 3.94	
>4 to 6 (moderate)	21	4.31	3.70, 4.91		3.63	2.82, 4.44	
>6 to 8 (severe)	11	5.60	4.85, 6.34		4.99	3.99, 6.00	
>8 (very severe)	2	6.81	5.07, 8.55		4.34	1.99, 6.69	

^aF-test comparing T/W and SoB domain scores across subgroups (ANCOVA).

^b“Please select 1 answer [...] to indicate your response as it applies to the past 7 days”: item HI12, “I feel weak all over”; item An2, “I feel tired”.

^c“How much of the time during the past week did you...”: item 9e, “...have a lot of energy?”; item 9g, “...feel worn out?”; item 9i, “...feel tired?”

ANCOVA, analysis of covariance; CI, confidence interval; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; FS, Fatigue Subscale; LS, least squares; PGI-S, Patient Global Impression of Severity; SF-36v2[®], Short Form Health Survey version 2; SoB, Shortness of Breath; T/W, Tiredness/Weakness.

Table S3 Demographics and baseline clinical characteristics

Characteristic	N=145
Age (years)	
Mean (SD)	39.9 (12.8)
Median (range)	40 (18 to 71)
Female, n (%)	82 (56.6)
Race, n (%)	
Asian	44 (30.3)
White	87 (60.0)
Other	14 (9.7)
Ethnicity, n (%)	
Hispanic or Latino	3 (2.1)
Not Hispanic or Latino	142 (97.9)
Body mass index (kg/m ²), n (%)	
<20	53 (36.6)
20 to <25	66 (45.5)
25 to <30	21 (14.5)
≥30	5 (3.5)
Geographic region, n (%)	
North America and Europe	90 (62.1)
Middle East	17 (11.7)
Asia Pacific	38 (26.2)
β-thalassaemia diagnosis, n (%)	
β-thalassaemia	97 (66.9)
Haemoglobin E/β-thalassaemia	39 (26.9)
β-thalassaemia plus α-thalassaemia	9 (6.2)
Baseline haemoglobin level (g/dL)	
Mean (SD)	8.2 (1.2)
Median (range)	8.2 (7.3 to 9.2)
Categories of baseline haemoglobin level, n (%)	
≥8.5 g/dL	60 (41.4)
<8.5 g/dL	85 (58.6)
Baseline transfusion burden (units of red blood cells in the 24 weeks before the first dose of study drug)	
Mean (SD)	0.3 (0.9)
Median (range)	0 (0 to 6)
6-minute walk test, n (%)	
≤450 m	82 (56.6)
>450 m	63 (43.4)
Left ventricular ejection fraction (%)	
Mean (SD)	65.6 (5.5)
Median (range)	65.0 (55.4 to 79.0)
Tricuspid valve regurgitation velocity, n (%)	
≤2.8 m/s (low probability of pulmonary hypertension)	111 (76.6)
>3.4 m/s (high probability of pulmonary hypertension)	1 (0.7)
ECOG performance status, n (%)	
0	100 (69.0)
1	45 (31.0)

ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

Table S4 Completeness of NTDT-PRO item entry at baseline and week 24

Number of days with missing NTDT-PRO data ^a	n (%)	
	Baseline (N=145)	Week 24 (N=128)
0	56 (38.6)	51 (39.8)
1	44 (30.3)	31 (24.2)
2	24 (16.6)	20 (15.6)
3	19 (13.1)	6 (4.7)
4	1 (0.7)	10 (7.8)
5	1 (0.7)	7 (5.5)
6	0	3 (2.3)
7	0	0

^aThere was no item-level missing data (participants either completed all 6 NTDT-PRO items or none of them).

NTDT-PRO, non-transfusion-dependent β -thalassaemia-patient-reported outcomes.

Table S5 Baseline PRO score distributions

	Mean (SD)	Median (Q1, Q3)	Range	Skewness	Kurtosis	Floor effect (%) ^a	Ceiling effect (%) ^b
NTDT-PRO							
Item 1-TiredNA	3.2 (2.2)	3.0 (1.5, 4.8)	0.0 to 9.0	0.2	-0.6	11.7	0.0
Item 2-TiredPA	5.0 (2.5)	5.2 (3.4, 7.0)	0.0 to 10.0	-0.3	-0.7	1.4	2.1
Item 3-WeakNA	3.1 (2.2)	3.0 (1.3, 4.8)	0.0 to 9.3	0.3	-0.5	11.7	0.7
Item 4-WeakPA	4.9 (2.6)	5.0 (3.0, 7.0)	0.0 to 10.0	-0.2	-0.8	2.8	2.1
Item 5-SobNA	2.4 (2.1)	2.2 (0.3, 4.0)	0.0 to 8.9	0.7	-0.2	20.7	0.0
Item 6-SobPA	4.2 (2.7)	4.4 (2.0, 6.4)	0.0 to 10.0	0.1	-1.0	7.6	2.8
T/W domain (items 1 to 4)	4.1 (2.2)	4.3 (2.5, 5.7)	0.0 to 9.5	0.0	-0.6	1.4	1.4
SoB domain (items 5 and 6)	3.3 (2.3)	3.4 (1.2, 5.1)	0.0 to 9.4	0.2	-0.8	7.6	0.7
PGI-S	3.7 (2.4)	3.8 (1.8, 5.4)	0.0 to 9.5	0.1	-0.8		
SF-36v2[®]							
Physical functioning	47.7 (7.7)	48.0 (44.2, 53.7)	23.1 to 57.5	-0.8	0.2	-	-
Role-physical	47.6 (7.8)	48.2 (41.4, 54.9)	25.7 to 57.2	-0.4	-0.7	-	-
Bodily pain	51.5 (9.2)	51.5 (42.6, 62.0)	30.6 to 62.0	-0.3	-1.1	-	-
General health	42.2 (10.2)	41.3 (34.2, 50.8)	19.0 to 66.5	0.1	-0.6	-	-
Vitality	49.2 (10.6)	49.6 (40.7, 58.5)	25.9 to 70.4	-0.3	-0.9	-	-
Social functioning	46.7 (9.3)	47.3 (37.3, 57.3)	22.3 to 57.3	-0.5	-0.8	-	-
Role-emotional	46.6 (8.8)	49.2 (38.8, 52.7)	17.9 to 56.2	-0.7	-0.4	-	-
Mental health	47.2 (9.6)	48.3 (40.4, 56.1)	24.7 to 64.0	-0.5	-0.6	-	-
PCS	48.0 (7.1)	48.8 (43.1, 53.3)	28.4 to 63.6	-0.4	-0.1	-	-
MCS	46.9 (9.2)	47.7 (40.6, 53.9)	23.3 to 63.1	-0.5	-0.4	-	-
FACIT-F							
Physical well-being	22.9 (3.9)	24.0 (20.0, 26.0)	11.0 to 28.0	-0.8	0.0	-	-
Social/family well-being	19.4 (5.3)	20.0 (16.3, 23.0)	4.7 to 28.0	-0.4	-0.5	-	-
Emotional well-being	18.2 (3.5)	19.0 (16.0, 21.0)	8.0 to 24.0	-0.6	-0.4	-	-
Functional well-being	18.0 (5.4)	18.0 (14.0, 22.0)	3.0 to 28.0	0.0	-0.6	-	-
FACT-G total score	78.4 (14.6)	80.0 (67.0, 90.3)	42.0 to 105.8	-0.1	-0.7	-	-
FACIT-F FS	36.4 (9.9)	39.0 (29.0, 44.5)	1.0 to 51.0	-0.7	0.0	-	-
FACIT-F TOI	77.2 (17.2)	81.0 (64.0, 91.0)	29.0 to 105.0	-0.4	-0.7	-	-
FACIT-F total score	114.8 (22.8)	118.5 (100.0, 133.2)	62.0 to 155.8	-0.3	-0.7	-	-

^aScore of 0.

^bScore of >9.

FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-G, Functional Assessment of Cancer Therapy – General; FS, Fatigue Subscale; MCS, Mental Component Summary; PCS, Physical Component Summary; PGI-S, Patient Global Impression of Severity; PRO, patient-reported outcome; Q1, first quartile; Q3, third quartile; SD, standard deviation; SF-36v2[®], Short Form Health Survey version 2; SoB, Shortness of Breath; SobNA, shortness of breath not doing physical activity; SobPA, shortness of breath doing physical activity; TiredNA, tiredness not doing physical activity; TiredPA, tiredness doing physical activity; TOI, trial outcome index; T/W, Tiredness/Weakness; WeakNA, weakness not doing physical activity; WeakPA, weakness doing physical activity.

Table S6 Variability of weekly NTDT-PRO item scores across missing day scenarios

		Number of missing days						
		0	1	2	3	4	5	6
Item 1-TiredNA	Mean	2.36	2.36	2.37	2.39	2.31	2.33	2.30
	SD	1.913	1.913	1.917	1.908	1.930	1.931	1.947
	<i>p</i> value ^a	–	0.971	0.949	0.971	0.962	0.869	0.962
Item 2-TiredPA	Mean	4.44	4.44	4.44	4.42	4.46	4.44	4.45
	SD	2.315	2.319	2.308	2.316	2.328	2.352	2.338
	<i>p</i> value ^a	–	1.000	0.953	0.970	0.978	0.827	0.873
Item 3-WeakNA	Mean	2.60	2.60	2.61	2.61	2.59	2.58	2.60
	SD	1.879	1.872	1.872	1.877	1.895	1.917	1.961
	<i>p</i> value ^a	–	0.941	0.930	0.955	0.888	0.786	0.576
Item 4-WeakPA	Mean	4.42	4.42	4.42	4.40	4.44	4.43	4.44
	SD	2.378	2.381	2.392	2.396	2.365	2.369	2.416
	<i>p</i> value ^a	–	0.997	0.973	0.892	0.871	0.965	0.764
Item 5-SobNA	Mean	2.02	2.02	2.01	2.03	2.01	2.05	2.05
	SD	1.894	1.892	1.884	1.911	1.884	1.939	1.928
	<i>p</i> value ^a	–	0.997	0.940	0.911	0.945	0.772	0.788
Item 6-SobPA	Mean	3.76	3.77	3.75	3.76	3.76	3.79	3.74
	SD	2.547	2.546	2.546	2.555	2.548	2.566	2.596
	<i>p</i> value ^a	–	0.982	0.970	0.958	0.993	0.859	0.849

The mean and SD were calculated by first calculating the average score across all weeks for each participant and then calculating the mean and SD across participants.

^aBrown–Forsythe test comparing SD values for individual missing day scenarios with the SD when 0 days were missing.

NTDT-PRO, non-transfusion-dependent β -thalassaemia-patient-reported outcomes; SD, standard deviation; SobNA, shortness of breath not doing physical activity; SobPA, shortness of breath doing physical activity; TiredNA, tiredness not doing physical activity; TiredPA, tiredness doing physical activity; WeakNA, weakness not doing physical activity; WeakPA, weakness doing physical activity.

Table S7 NTDT-PRO internal consistency reliability

	Domain	Cronbach's alpha	Deleted item ^a	Cronbach's alpha	
Baseline	T/W	0.95			
			Item 1-TiredNA	0.93	
				Item 2-TiredPA	0.94
				Item 3-WeakNA	0.94
				Item 4-WeakPA	0.94
	SoB	0.89			
Week 24	T/W	0.94			
			Item 1-TiredNA	0.92	
				Item 2-TiredPA	0.92
				Item 3-WeakNA	0.92
				Item 4-WeakPA	0.92
	SoB	0.85			
Weeks 13–24	T/W	0.95			
			Item 1-TiredNA	0.93	
				Item 2-TiredPA	0.93
				Item 3-WeakNA	0.93
				Item 4-WeakPA	0.93
	SoB	0.84			

^aThe effect of removing individual items could not be evaluated for the SoB domain, because it consists of only 2 items.

NTDT-PRO, non-transfusion-dependent β -thalassaemia-patient-reported outcomes; SoB, Shortness of Breath; TiredNA, tiredness not doing physical activity; TiredPA, tiredness doing physical activity; WeakNA, weakness not doing physical activity; WeakPA, weakness doing physical activity; T/W, Tiredness/Weakness.

Table S8 Known-groups validity at baseline

	n	NTDT-PRO T/W domain			NTDT-PRO SoB domain		
		LS mean	95% CI	p value ^a	LS mean	95% CI	p value ^a
FACIT-F FS				<0.001			<0.001
Very severe (≤ 37)	62	5.27	4.84, 5.71		4.35	3.79, 4.91	
Severe (>37 to 40)	16	3.06	2.33, 3.80		3.30	2.36, 4.24	
Moderate (>40 to 43)	18	3.16	2.45, 3.86		2.84	1.93, 3.75	
Mild (>43 to 46)	17	2.94	2.21, 3.68		1.74	0.79, 2.68	
Very mild/no symptoms (>46)	31	1.59	1.05, 2.13		1.13	0.44, 1.83	
FACIT-F item HI12^b				<0.001			<0.001
Very much (0)	3	7.11	5.47, 8.75		6.23	4.10, 8.36	
Quite a bit (1)	25	5.76	5.16, 6.35		4.80	4.03, 5.57	
Somewhat (2)	24	4.69	4.04, 5.34		4.06	3.22, 4.90	
A little bit (3)	54	3.58	3.18, 3.99		3.08	2.55, 3.60	
Not at all (4)	38	1.71	1.23, 2.18		1.15	0.54, 1.77	
FACIT-F item An2^b				<0.001			<0.001
Very much (0)	3	7.87	6.21, 9.54		8.02	5.91, 10.13	
Quite a bit (1)	25	5.87	5.26, 6.48		4.89	4.11, 5.66	
Somewhat (2)	37	4.31	3.79, 4.83		3.90	3.24, 4.56	
A little bit (3)	59	3.08	2.68, 3.48		2.31	1.80, 2.82	
Not at all (4)	20	1.43	0.79, 2.08		1.26	0.44, 2.08	
SF-36v2[®] vitality				<0.001			<0.001
Very poor (≤ 36.6)	20	6.14	5.43, 6.84		5.57	4.66, 6.48	
Poor (>36.6 to 43.3)	19	5.42	4.70, 6.15		4.11	3.17, 5.05	
Normal (>43.3 to 56.7)	64	3.73	3.32, 4.13		3.15	2.63, 3.68	
Better (>56.7 to 63.4)	25	2.09	1.48, 2.69		1.73	0.95, 2.51	
Much better (>63.4)	13	1.71	0.90, 2.52		1.12	0.07, 2.17	
SF-36v2[®] item 9e^c				<0.001			<0.001
All of the time (1)	11	2.09	1.14, 3.04		1.17	-0.02, 2.37	
Most of the time (2)	33	2.21	1.64, 2.77		1.95	1.24, 2.65	
Some of the time (3)	46	3.79	3.27, 4.31		3.24	2.59, 3.89	
A little of the time (4)	37	5.12	4.52, 5.73		4.18	3.42, 4.93	
None of the time (5)	14	5.80	4.91, 6.70		5.06	3.94, 6.19	
SF-36v2[®] item 9g^c				<0.001			<0.001
All of the time (1)	1	6.64	3.62, 9.66		5.74	2.00, 9.47	
Most of the time (2)	24	5.67	5.02, 6.32		4.79	3.99, 5.59	
Some of the time (3)	39	4.43	3.92, 4.93		3.97	3.35, 4.60	
A little of the time (4)	41	2.78	2.27, 3.29		2.24	1.60, 2.87	
None of the time (5)	36	2.07	1.54, 2.60		1.40	0.75, 2.06	
SF-36v2[®] item 9i^c				<0.001			<0.001
All of the time (1)	5	8.00	6.69, 9.31		7.70	6.01, 9.38	
Most of the time (2)	36	5.26	4.73, 5.79		4.34	3.66, 5.03	
Some of the time (3)	45	4.14	3.66, 4.61		3.58	2.97, 4.19	
A little of the time (4)	44	2.66	2.21, 3.11		2.08	1.50, 2.66	
None of the time (5)	11	1.21	0.35, 2.08		0.94	-0.18, 2.05	

	NTDT-PRO T/W domain				NTDT-PRO SoB domain		
	n	LS mean	95% CI	p value ^a	LS mean	95% CI	p value ^a
PGI-S				<0.001			<0.001
0 to 2 (no symptoms)	40	1.33	0.95, 1.71		1.06	0.51, 1.60	
>2 to 4 (mild)	37	3.70	3.31, 4.10		2.83	2.27, 3.40	
>4 to 6 (moderate)	44	4.90	4.52, 5.29		4.08	3.53, 4.63	
>6 to 8 (severe)	19	5.75	5.21, 6.30		5.17	4.39, 5.96	
>8 (very severe)	5	7.70	6.67, 8.72		7.43	5.96, 8.91	

^aF-test comparing T/W and SoB domain scores across subgroups (ANCOVA).

^b“Please select 1 answer [...] to indicate your response as it applies to the past 7 days”: item HI12, “I feel weak all over”; item An2, “I feel tired”.

“How much of the time during the past week did you...”: item 9e, “...have a lot of energy?”; item 9g, “...feel worn out?”; item 9i, “...feel tired?”

ANCOVA, analysis of covariance; CI, confidence interval; FACIT-F, Functional Assessment of Chronic Illness Therapy – Fatigue; FS, Fatigue Subscale; LS, least squares; NTDT-PRO, non-transfusion-dependent β -thalassaemia-patient-reported outcomes; PGI-S, Patient Global Impression of Severity; SF-36v2[®], Short Form Health Survey version 2; SoB, Shortness of Breath; T/W, Tiredness/Weakness.

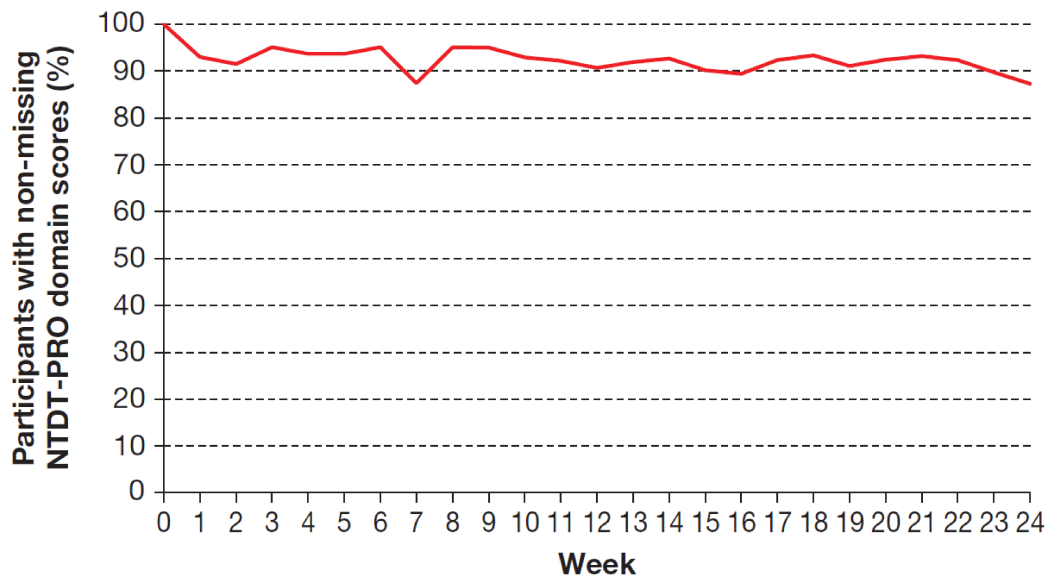


Figure S1 Percentage of participants with non-missing weekly NTDT-PRO domain scores. The percentage for a given week was calculated as the number of participants with non-missing weekly NTDT-PRO domain scores divided by the number of participants who remained on-study. For all weeks, percentages were the same for both the T/W and SoB domains. NTDT-PRO, non-transfusion-dependent β -thalassaemia-patient-reported outcomes; SoB, Shortness of Breath; T/W, Tiredness/Weakness.