Sponsor
Novartis Pharmaceuticals

Generic Drug Name
NA

Trial Indication(s)
Multiple Sclerosis

Protocol Number
COMB157G3001

Protocol Title
Risk perception in multiple sclerosis

Clinical Trial Phase
NA

Phase of Drug Development
NA

Study Start/End Dates
Study start date: 09/09/2021

Study Completion date: 17/09/2021

Reason for Termination

NA

Study Design/Methodology

This study was a retrospective, non-interventional, cross-sectional, multi-cohort study of patients clinically diagnosed with RMS (RRMS and SPMS). Patients were classified according to the immediate previous treatment in two groups, those who were prescribed with high efficacy treatments (HETs) and those who were prescribed with non-high efficacy treatments (non-HETs). HET include alemtuzumab, ofatumumab, ocrelizumab, natalizumab, cladribine, fingolimod and ozanimod; and non-HETs include molecules classified as with moderate or modest efficacy such as: interferons, glatiramer acetate, dimethyl fumarate and teriflunomide.

The study cohort consisted of RMS patients identified in the Adelphi Real World MS DSP, which was current up until the Q2/2021. The study was using waves VI-IX of the Adelphi DSP dataset.

Study period: Q1 2017 – Q1 & Q2 2021 (waves VI-IX of Adelphi DSP dataset).

Identification period: Q1 2017 – Q1 & Q2 2021 (waves VI-IX of Adelphi DSP dataset).

Index date: defined as the dates when the surveys were carried out (Q1 2017 – Q1 & Q2 2021).

Centers

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Objectives:

Primary objective(s)

- To compare the treatment switches based on risk perception between patients treated previously with non-HET versus those treated previously with HET.

Secondary objective(s)

- To explore the top 3 reasons for switching patients treated previously with non-HET versus those treated previously with HET.
- To estimate the number of patients who switched due to lack of efficacy in patients treated previously with non-HET versus those treated previously with HET.

- To assess to which molecule the patient was switched between patients treated previously with non-HET versus those treated previously with HET.
- To assess the differences in clinical/demographics between patients treated previously with non-HET versus those treated previously with HET.

Test Product (s), Dose(s), and Mode(s) of Administration

NA

Statistical Methods

Adelphi Real World performed all analyses. Unless otherwise stated, tables and figures were on all subjects included in the analysis set under consideration.

Summary statistics was provided by groups and overall. Continuous endpoints were summarized using standard summary statistics (n, mean, standard deviation [SD], median, 25th and 75th percentiles, minimum, maximum and IQR) while categorical endpoints were summarized using frequency counts and percentages. A missing category was only presented when any patients reported with missing data. The maximum number of decimal places to be displayed was limited to three unless more than three were necessary (such as 0.0001 rather than 0.000 to show a small but non-zero SD).

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- Patients included in the database with a diagnosis of RRMS and SPMS.
- Patients with current treatment at the index date.
- Patients with previous treatment at the index date.
- Patients to whom the physician decided to switch the treatment from the previous treatment to current treatment at the index date.
- Patients (males & females) with 18 years or older at index date.

Exclusion criteria

- Patients included in the database with the diagnosis of primary progressive MS (PPMS).
- Patients with other major neurological or psychiatric condition, which could potentially hinder the analysis.

Participant Flow

The table below shows the attrition of RMS cohort currently treated with injectable DMTs for each selection criterion. A total of 4361 patients were analyzed for the secondary endpoint 3 and 4, and a total of 4129 patients whom the reason for switch from previous DMT provided by physician were included for the analysis of primary and secondary endpoint 1 and 2.

Eligibility criteria	Patients remaining N (%)	Patients excluded N (%)
Adelphi MS DSP Waves V-IX	17307 (100%)	0
With a diagnosis of relapsing remitting (RRMS) or secondary progressive MS	16031 (92.6%)	1276 (7.4%)
Patients with current DMT	13285 (76.8%)	2746 (15.9%)
Patients with previous DMT	6144 (35.5%)	7141 (41.3%)
18 years or older	6144 (35.5%)	0
Patients with no other major neurological or psychiatric conditions	4482 (25.9%)	1662 (9.6%)
Single current named DMT	4415 (25.5%)	63 (0.4%)
Single previous named DMT	4361 (25.2%)	37 (0.2%)
Reason for switch from previous DMT provided by physician	4129 (23.9%)	232 (1.3%)

Baseline Characteristics

Variable	Overall	Previous Non-HET	Previous HET
Age			
n	4361	3768	593
mean	42.1	42	42.5
SD	11	11.1	10.4
med	41	41	42
IQR	34.0 , 50.0	34.0 , 50.0	35.0 , 50.0
min, max	18.0 , 90.0	18.0 , 90.0	20.0 , 76.0
Sex, n (%)			
n	4361	3768	593
Male	1505 (34.5)	1326 (35.2)	179 (30.2)
Female	2856 (65.5)	2442 (64.8)	414 (69.8)
Status, n (%)			
n	4361	3768	593
Outpatient	4249 (97.4)	3679 (97.6)	570 (96.1)
Inpatient	112 (2.6)	89 (2.4)	23 (3.9)
Status (Female only), n (%)			
n	2762	2372	390
Not Pregnant	2746 (99.4)	2362 (99.6)	384 (98.5)
Pregnant	16 (0.6)	10 (0.4)	6 (1.5)
Plans (Female only), n (%)			
n	2487	2131	356
No Plans to get pregnant	2428 (97.6)	2083 (97.7)	345 (96.9)
Plans to get pregnant	59 (2.4)	48 (2.3)	11 (3.1)
Smoking Status, n (%)			
n	3996	3452	544
Current smoker	527 (13.2)	460 (13.3)	67 (12.3)
Ex-smoker	959 (24.0)	812 (23.5)	147 (27.0)
Never smoked	2510 (62.8)	2180 (63.2)	330 (60.7)
Patient employment status, n (%)			
n	4304	3718	586
Working full time	2052 (47.7)	1821 (49.0)	231 (39.4)
Working part time	667 (15.5)	572 (15.4)	95 (16.2)
On long term sick leave	124 (2.9)	97 (2.6)	27 (4.6)
Homemaker	517 (12.0)	443 (11.9)	74 (12.6)
Student	171 (4.0)	158 (4.2)	13 (2.2)
Retired	414 (9.6)	332 (8.9)	82 (14.0)
Unemployed	359 (8.3)	295 (7.9)	64 (10.9)
Patient home circumstances, n (%)			
n	4361	3768	593
Lives alone	634 (14.5)	553 (14.7)	81 (13.7)
Lives with partner/spouse	3207 (73.5)	2769 (73.5)	438 (73.9)
Lives with other family/friends	498 (11.4)	429 (11.4)	69 (11.6)
Nursing home	12 (0.3)	9 (0.2)	3 (0.5)
Sheltered housing	7 (0.2)	5 (0.1)	2 (0.3)
Day care/respite care	2 (0.0)	2 (0.1)	0 (0.0)
Homeless	1 (0.0)	1 (0.0)	0 (0.0)
Patient relationship status, n (%)			
n	4319	3734	585
Married	2794 (64.7)	2423 (64.9)	371 (63.4)
Divorced/Separated	305 (7.1)	251 (6.7)	54 (9.2)
In long term relationship	518 (12.0)	440 (11.8)	78 (13.3)
Single	689 (16.0)	609 (16.3)	80 (13.7)

Variable	Overall	Previous Non-HET	Previous HET
Widowed	13 (0.3)	11 (0.3)	2 (0.3)
Whether anyone responsible for patient's daily needs, n (%)			
n	4276	3700	576
No Caregiver	3358 (78.5)	2939 (79.4)	419 (72.7)
Caregiver	918 (21.5)	761 (20.6)	157 (27.3)
Time since initial MS symptoms (years)			
n	2642	2302	340
mean	7.6	7.4	8.6
SD	5.7	5.7	5.7
med	6.1	6	7.6
IQR	3.5, 10.1	3.4 , 9.8	4.6, 11.1
min, max	0.1, 82.0	0.1, 82.0	0.4, 34.6
Time since initial MS diagnosis (years)			
n	3640	3144	496
mean	8.1	7.9	9.5
SD	6.1	6	6.4
med	6.6	6.2	8.1
IQR	3.6, 10.9	3.4, 10.7	4.8, 12.2
min, max	0.1, 43.9	0.1, 43.9	0.2, 34.1
Initial MS diagnosis, n (%)			
n	4357	3764	593
RRMS	3683 (84.5)	3179 (84.5)	504 (85.0)
SPMS	139 (3.2)	113 (3.0)	26 (4.4)
PPMS	11 (0.3)	9 (0.2)	2 (0.3)
Clinically isolated syndrome (CIS)	524 (12.0)	463 (12.3)	61 (10.3)
Current MS diagnosis, n (%)			
n	4361	3768	593
RRMS	3672 (84.2)	3245 (86.1)	427 (72.0)
SPMS	689 (15.8)	523 (13.9)	166 (28.0)
Patient progression profile, n (%)			
n	4360	3767	593
Improving	299 (6.9)	269 (7.1)	30 (5.1)
Stable	2908 (66.7)	2549 (67.7)	359 (60.5)
Deteriorating slowly	1073 (24.6)	892 (23.7)	181 (30.5)
Deteriorating rapidly	80 (1.8)	57 (1.5)	23 (3.9)
EDSS: Current			
n	3907	3366	541
mean	2.8	2.7	3.5
SD	1.8	1.7	1.9
med	2.5	2.5	3
IQR	1.5 , 4.0	1.5, 3.5	2.0 , 4.5

Variable	Overall	Previous Non-HET	Previous HET
min, max	0, 9.0	0, 9.0	0, 8.5
Previous Disease Modifying treatment, n (%)			
n	4361	3768	593
Avonex (IFN beta-1a) (Non-HET)	906 (20.8)	906 (24.0)	0
Betaseron (IFN beta-1b) (Non-HET)	425 (9.7)	425 (11.3)	0
Extavia (IFN beta-1b) (Non-HET)	110 (2.5)	110 (2.9)	0
Rebif (IFN beta 1a) (Non-HET)	662 (15.2)	662 (17.6)	0
Copaxone 20mg (Glatiramer acetate) (Non-HET)	685 (15.7)	685 (18.2)	0
Copaxone 40mg (Glatiramer acetate) (Non-HET)	337 (7.7)	337 (8.9)	0
Glatopa/Brabio (Glatiramer acetate) (Non-HET)	6 (0.1)	6 (0.2)	0
Plegridy (PegIFN-beta-1a) (Non-HET)	60 (1.4)	60 (1.6)	0
Aubagio (teriflunomide) (Non-HET)	168 (3.9)	168 (4.5)	0
Tecfidera/Vumerity (dimethyl fumarate and diroximel fumarate) (Non-HET)	409 (9.4)	409 (10.9)	0
Mavenclad (Cladribine) (HET)	5 (0.1)	0	5 (0.8)
Gilenya (fingolimod) (HET)	285 (6.5)	0	285 (48.1)
Ocrevus (ocrelizumab) (HET)	7 (0.2)	0	7 (1.2)
Tysabri (natalizumab) (HET)	259 (5.9)	0	259 (43.7)
Lemtrada (alemtuzumab) (HET)	9 (0.2)	0	9 (1.5)
Rituxan (Rituximab) (HET)	8 (0.2)	0	8 (1.3)
MabThera (Rituximab) (HET)	1 (0.0)	0	1 (0.2)
Novantrone (Mitoxantrone) (HET)	14 (0.3)	0	14 (2.4)
Mayzent (Siponimod) (HET)	1 (0.0)	0	1 (0.2)
Zeposia (ozanimod) (HET)	4 (0.1)	0	4 (0.7)
Previous Disease Modifying treatment - HET, n (%)			
n	4361	3768	593
Previous Non-HET	3768 (86.4)	3768 (100.0)	0
Previous HET	593 (13.6)	0	593 (100.0)
Duration of previous treatment (years)			
n	3232	2753	479
mean	3.3	3.3	3
SD	3.2	3.3	2.4
med	2.2	2.2	2.2
IQR	1.1, 4.5	1.1, 4.5	1.2, 4.2
min, max	0, 20.5	0, 20.5	0, 17.2
Whether currently on a patient support programme, n (%)			
n	1391	1161	230

Variable	Overall	Previous Non-HET	Previous HET
Not on a patient support programme	1139 (81.9)	954 (82.2)	185 (80.4)
On a patient support programme	252 (18.1)	207 (17.8)	45 (19.6)
Whether patient prescribed treatment for MS symptoms, n (%)			
n	4361	3768	593
Not Symptomatic treatment	2348 (53.8)	2102 (55.8)	246 (41.5)
Symptomatic treatment	2013 (46.2)	1666 (44.2)	347 (58.5)
Whether hospitalised in the last 12 months related to MS, n (%)			
n	3632	3147	485
No hospitalisations	3333 (91.8)	2921 (92.8)	412 (84.9)
Hospitalisations	299 (8.2)	226 (7.2)	73 (15.1)
Hospitalisations (no. of admissions) in the last 12 months related to MS			
n	3632	3147	485
mean	0.2	0.1	0.2
SD	0.8	0.8	0.9
med	0	0	0
IQR	0.0 , 0.0	0.0 , 0.0	0.0 , 0.0
min, max	0.0 , 16.0	0.0 , 12.0	0.0 , 16.0

Primary Outcome Result(s)

The primary endpoint was the proportion of patients who were switched based on risk perception (infections, malignancies, others) between groups at the country and regional level.

Physicians' risk perception of malignancies and infections as a reason for switching therapies stratified between previous non-HET and previous HET patients (global analysis)

	Overall N=4129		Previous non-HET N=3538		Previous HET N=591		p-value
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	
Reason for switch from previous regimen - Risk of malignancies							p<0.0001
No switch due to risk of malignancies	4115 (99.7)	99.43, 99.81	3533 (99.9)	99.67, 99.95	582 (98.5)	97.13, 99.30	
Switch due to risk of malignancies	14 (0.3)	0.19, 0.57	5 (0.1)	0.05, 0.33	9 (1.5)	0.70, 2.87	
Reason for switch from previous regimen - Risk of infection							p=0.0851
No switch due to risk of infection	4103 (99.4)	99.08, 99.59	3519 (99.5)	99.16, 99.68	584 (98.8)	97.57, 99.52	
Switch due to risk of infection	26 (0.6)	0.41, 0.92	19 (0.5)	0.32, 0.84	7 (1.2)	0.48, 2.43	
Reason for switch from previous regimen - Risk of infection/malignancies							p=0.0002
No switch due to risk of infection/malignancies	4093 (99.1)	98.79, 99.39	3516 (99.4)	99.06, 99.61	577 (97.6)	96.06, 98.70	
Switch due to risk of infection/malignancies	36 (0.9)	0.61, 1.21	22 (0.6)	0.39, 0.94	14 (2.4)	1.30, 3.94	

Secondary Outcome Result(s)

The secondary endpoint 1 was the ranking of the frequency of switches due to risk perception in both groups of patients.

Physicians' reasons for switching from previous treatment stratified between non-HET and HET groups (global analysis)

	Overall N=4129	Previous Non-HET N=3538	Previous HET N=591
Lack of efficacy	2099 (50.8)	1887 (53.3)	212 (35.9)
MRI has shown either new T2 or Gadolinium enhancing lesion	446 (10.8)	340 (9.6)	106 (17.9)
Progression in EDSS	341 (8.3)	252 (7.1)	89 (15.1)
Increased number of lesions	790 (19.1)	717 (20.3)	73 (12.4)
Enlargement of existing lesions	335 (8.1)	309 (8.7)	26 (4.4)
Relapse severity	745 (18.0)	658 (18.6)	87 (14.7)
Relapse frequency	1038 (25.1)	948 (26.8)	90 (15.2)
Treatment holiday	35 (0.8)	26 (0.7)	9 (1.5)
Patient request	784 (19.0)	728 (20.6)	56 (9.5)
Patient compliance issues	444 (10.8)	429 (12.1)	15 (2.5)
Lymphocytopenia	94 (2.3)	56 (1.6)	38 (6.4)
Thrombocytopenia	20 (0.5)	14 (0.4)	6 (1.0)
Risk of PML	159 (3.9)	18 (0.5)	141 (23.9)
Risk of malignancies	14 (0.3)	5 (0.1)	9 (1.5)
Risk of infection	26 (0.6)	19 (0.5)	7 (1.2)
Cardiac events	16 (0.4)	11 (0.3)	5 (0.8)
Macular oedema	20 (0.5)	6 (0.2)	14 (2.4)
Headache	182 (4.4)	170 (4.8)	12 (2.0)
Rash	110 (2.7)	102 (2.9)	8 (1.4)
Urticaria	34 (0.8)	32 (0.9)	2 (0.3)
Fever	150 (3.6)	145 (4.1)	5 (0.8)
Nausea	148 (3.6)	135 (3.8)	13 (2.2)
Sleep deprivation	37 (0.9)	35 (1.0)	2 (0.3)
Fatigue	262 (6.3)	245 (6.9)	17 (2.9)
Mental fatigue	14 (0.3)	10 (0.3)	4 (0.7)
Physical fatigue	24 (0.6)	17 (0.5)	7 (1.2)
Injection site reaction	574 (13.9)	572 (16.2)	2 (0.3)
Urinary tract infections	26 (0.6)	18 (0.5)	8 (1.4)
Flu-like symptoms	467 (11.3)	457 (12.9)	10 (1.7)
Slow/irregular heart beat	15 (0.4)	6 (0.2)	9 (1.5)
GI Risk	88 (2.1)	84 (2.4)	4 (0.7)
COVID-19	2 (0.0)	0 (0.0)	2 (0.3)
Pregnancy	29 (0.7)	20 (0.6)	9 (1.5)
Cardiac risk/need for cardiac monitoring	13 (0.3)	6 (0.2)	7 (1.2)
Abnormal LFT results	56 (1.4)	45 (1.3)	11 (1.9)
JCV status - increased risk	37 (0.9)	4 (0.1)	33 (5.6)
JCV status - increased risk due to length of time on therapy	30 (0.7)	5 (0.1)	25 (4.2)
JCV status - increased risk of seroconversion	16 (0.4)	0 (0.0)	16 (2.7)
Insurance coverage	51 (1.2)	38 (1.1)	13 (2.2)
Treatment cost	35 (0.8)	24 (0.7)	11 (1.9)
Formulary changes	47 (1.1)	44 (1.2)	3 (0.5)
Formulary restrictions	22 (0.5)	16 (0.5)	6 (1.0)
Other	224 (5.4)	181 (5.1)	43 (7.3)

Secondary endpoint 2 was the proportion of patients who switched due to lack of efficacy due to new or enlarging lesions on MRI, increase in the frequency and/or severity of the relapses, progression in physical disability measured by EDSS or patient compliance issues between groups.

Lack of efficacy between previous non-HET and previous HET groups (global analysis)

	Overall N=4129		Previous Non-HET N=3538		Previous HET N=591		p-value, 95% CI
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	
Reasons for switching from previous treatment: Lack of efficacy							p<0.0001
Switch without lack of efficacy	2030 (49.2)	47.63, 50.70	1651 (46.7)	45.01, 48.32	379 (64.1)	60.11, 68.00	
Switch due to lack of efficacy	2099 (50.8)	49.30, 52.37	1887 (53.3)	51.68, 54.99	212 (35.9)	32.00, 39.89	

Secondary endpoint 3 was the proportion of patients who changed treatment group versus patients who continued in the same treatment group.

Molecule switched to stratified by previous non-HET and previous HET groups (global analysis)

Variable	Overall N=4361	Previous Non-HET N=3768	Previous HET N=593
Current Disease Modifying treatment, n (%)			
Avonex (IFN beta-1a) (Non-HET)	173 (4.0)	158 (4.2)	15 (2.5)
Betaseron (IFN beta-1b) (Non-HET)	73 (1.7)	64 (1.7)	9 (1.5)
Extavia (IFN beta-1b) (Non-HET)	47 (1.1)	45 (1.2)	2 (0.3)
Rebif (IFN beta 1a) (Non-HET)	122 (2.8)	114 (3.0)	8 (1.3)
Copaxone 20mg (Glatiramer acetate) (Non-HET)	109 (2.5)	100 (2.7)	9 (1.5)
Copaxone 40mg (Glatiramer acetate) (Non-HET)	318 (7.3)	295 (7.8)	23 (3.9)

Variable	Overall N=4361	Previous Non-HET N=3768	Previous HET N=593
Glatopa/Brabio (Glatiramer acetate) (Non-HET)	20 (0.5)	19 (0.5)	1 (0.2)
Plegridy (PegIFN-beta-1a) (Non-HET)	92 (2.1)	89 (2.4)	3 (0.5)
Aubagio (teriflunomide) (Non-HET)	457 (10.5)	434 (11.5)	23 (3.9)
Tecfidera/Vumerity (dimethyl fumarate and diroximel fumarate) (Non-HET)	816 (18.7)	739 (19.6)	77 (13)
Mavenclad (Cladribine) (HET)	60 (1.4)	40 (1.1)	20 (3.4)
Gilenya (fingolimod) (HET)	803 (18.4)	720 (19.1)	83 (14.0)
Ocrevus (ocrelizumab) (HET)	367 (8.4)	244 (6.5)	123 (20.7)
Kesimpta (Ofatumumab) (HET)	3 (0.1)	2 (0.1)	1 (0.2)
Tysabri (natalizumab) (HET)	607 (13.9)	539 (14.3)	68 (11.5)
Lemtrada (alemtuzumab) (HET)	150 (3.4)	74 (2.0)	76 (12.8)
Rituxan (Rituximab) (HET)	29 (0.7)	15 (0.4)	14 (2.4)
MabThera (Rituximab) (HET)	2 (0.0)	1 (0.0)	1 (0.2)
Novantrone (Mitoxantrone) (HET)	50 (1.1)	41 (1.1)	9 (1.5)
Mayzent (Siponimod) (HET)	53 (1.2)	25 (0.7)	28 (4.7)
Zeposia (ozanimod) (HET)	10 (0.2)	10 (0.3)	0 (0.0)
Current Disease Modifying treatment - HET, n (%)			
Current Non-HET	2227 (51.1)	2057 (54.6)	170 (28.7)
Current HET	2134 (48.9)	1711 (45.4)	423 (71.3)
Duration of current treatment (years)			
n	3976	3425	551
mean	2.1	2.2	1.7
SD	3	3.1	2.3
med	1.3	1.4	1.1
IQR	0.6, 2.8	0.7, 2.9	0.5, 2.1
min, max	0.0 , 117.2	0.0 , 117.2	0.0, 21.9

The secondary endpoint 4 was to describe the variables such as number of relapses, EDSS, age, gender, employment status, diagnosis, disease, treatment history and country. (**Refer to demographics section for the results)**

Safety Results

Not applicable.

Other Relevant Findings

Not applicable.

Conclusion

The use of non - High Efficacy Therapy (HET) treatment in MS (escalation approach) continues being dominant notwithstanding the erratic and frequently progressive and devastating course of the disease. MS initially affects young adults in the prime of life with well-known consequences (high score in Expanded Disability Status Scale (EDSS), less people working full time, frequent hospitalizations, need of nurses or caregivers, etc.). New, high active Disease Modifying Therapies (DMTs) are perceived to come with a high cost of frequent adverse events and safety concerns. The study showed that this risk perception is not the main driver for switching, the most frequent cause being the lack of efficacy. The high turnover between molecules due to lack of efficacy exposes the patient to wash-out periods and potential additive effects on the immune system through different mechanisms of actions, in addition of missing the opportunity to treat the patient with potent anti-inflammatory molecules in the precise moment when the inflammation drives the physiopathology of the disease.

The study found a profound mismatch between the high number of patients switching from non-HET treatment due to lack of efficacy and the low level of risk perception due to safety concerns. HET could be used early on in the MS treatment paradigm, thereby ensuring patients' control of their disease combined with a proper monitoring process.

Date of Clinical Study Report

28 January, 2022