Sponsor
Novartis Pharmaceuticals

Generic Drug Name
Fingolimod

Trial Indication(s)
Multiple Sclerosis

Protocol Number
CFTY720DUS45

Protocol Title
Impact of fingolimod adherence on outcomes

Clinical Trial Phase
NA

Phase of Drug Development
NA

Study Start/End Dates
Study start date: 18 May 2020

Study Completion date: 20 November 2020

Reason for Termination

NA

Study Design/Methodology

The study sample comprised commercial and MAPD enrollees who initiated fingolimod treatment during the identification period of 01 January 2012 through 10 May 2018. The date of the first fingolimod pharmacy claim during the identification period was the index date.

All patients were continuously enrolled in the health plan for 24 months. The 6-month pre-index period, ending the day before the index date, was used to assess patients' clinical characteristics (e.g., comorbid conditions and MS symptoms). The 18-month post-index period started on the index date. The first 6 months of the post-index period (initiation period) were used to assess MS symptoms and adherence. Months 7 – 18 of the post-index period (post-initiation period) were used to measure adherence and outcomes. The 24-month observation period for each patient comprised the 6-month pre-index and 18-month post-index periods.

Centers

Novartis Investigative Site

Objectives:

Primary objective(s)

The primary objective was to estimate the effect of fingolimod adherence on the odds of MS relapse in a 12-month period.

Secondary objective(s)

The secondary objectives described in the protocol were to estimate the effect of fingolimod adherence on the number MS-related inpatient admissions, ER visits, and costs during a 12-month period for DMT treatment-naïve adult MS patients in the commercial and MAPD populations.

The endpoints for those admissions were modified and expanded to the following:

- Occurrence of any MS-related inpatient admission
- Number of MS-related ER visits
- Occurrence of any MS-related ER visit
- All-cause total (medical plus pharmacy) health care costs
- All-cause medical health care costs
- All-cause total (medical plus pharmacy) health care costs excluding fingolimod

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

NA

Statistical Methods

All pre-index, initiation, and post-initiation variables were analyzed descriptively. Post-index variables were analyzed for the initiation period and each quarter of the post-initiation period. Counts, percentages, and 95% confidence intervals (CIs) were reported for binary and categorical variables. Means, standard deviations, medians, interquartile ranges, and 95% CIs were reported for continuous variables.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

- ≥18 years old during year of index date with valid gender and geographic information
- Continuous enrollment (CE) in the health plan with medical and pharmacy benefits for ≥6 months (180ii days) before the index date (*pre-index period*)
- CE with medical and pharmacy benefits for ≥18 months (540ii days) beginning on the index date (*post-index period*)
  - All patients had uniform 6-month pre-index and 18-month post-index periods
- ≥1 medical claim with an MS diagnosis codeiii in any position during the pre-or post-index periods
- ≥1 claim for fingolimod after the index date (i.e., from index date +1 to 539 days post-index)

– By requiring ≥1 medical claim with an MS diagnosis code and ≥2 claims with an NDC for fingolimod, the inclusion criteria essentially incorporated the preferred/overall best performing MS case-finding definition validated by Culpepper et al. The criteria for that definition required at least 3 separate encounters from any of the following: MS-related ambulatory visits, MS-related inpatient stays, and DMT claims during a 12-month period. Slightly higher accuracy was found when a 24-month period was used.

Exclusion criteria

- ≥1 pharmacy or medical claim for any MS DMT during the pre-index period

Participant Flow

The analytic sample of adult MS patients initiating fingolimod included 694 patients

Patient Identification and Attrition

Criteria	Subjects Remaining		Subjects Excluded	
	N	%	N	%
≥ 1 claim for fingolimod on pharmacy claims only during the identification period 01 January 2012 through 10 May 2018 (index date)	5.413			
≥ 18 years old during year of index date and valid gender and geographic information	5.394	99,65%	19	0,35%
Continuous enrollment (CE) in the health plan with medical and pharmacy benefits for ≥ 6 months (180 days) before the index date (pre-index period)	2.850	52,84%	2.544	47,16%
CE with medical and pharmacy benefits for ≥ 18 months (540 days) beginning on the index date (post-index period)	1.884	66,11%	966	33,89%
≥ 1 medical claim with an MS diagnosis code* in any position during the pre-or post-index periods	1.876	99,58%	8	0,42%
No medical claims with an NDC code for fingolimod during the post-index period	1.867	99,52%	9	0,48%
≥ 1 pharmacy claim for fingolimod after the index date (i.e., from index date +1 to 539 days post-index)	1.784	95,55%	83	4,45%
No pharmacy or medical claims for any MS DMT during the pre-index period	694	38,90%	1.090	61,10%
All patients have uniform 6-month and 18-month post-index periods * MS diagnosis: ICD-9-CM 340.xx, ICD-10-CM G35.xxx				

Baseline Characteristics

Patient Demographics

Demographics		Total (N=694)
Age (continuous)	mean	44,30
	SD	10,85
	median	44,00
Age group		
18-24	n	21
	%	3,03
25-34	n	113
	%	16,28
35-44	n	221
	%	31,84
45-54	n	203
	%	29,25
55-64	n	123
	%	17,72
≥ 65	n	13
	%	1,87
Gender		
Female	n	527
	%	75,94
Male	n	167
	%	24,06

Region		
Northeast	n	78
	%	11,24
Midwest	n	215
	%	30,98
South	n	291
	%	41,93
West	n	110
	%	15,85
Other	n	0
	%	0,00
Insurance type		
Commercial	n	562
	%	80,98
Medicare	n	132
	%	19,02

Index Year		
2012	n	149
	%	21,47
2013	n	114
	%	16,43
2014	n	94
	%	13,54
2015	n	109
	%	15,71
2016	n	80
	%	11,53
2017	n	113
	%	16,28
2018	n	35
	%	5,04

SD: Standard Deviation

Primary Outcome Result(s)

Post-initiation Quarterly Mean Relapse Counts by Prior Adherence (PDC ≥ 0.8)

Prior PDC	Post-initiation Quarterly Relapse Mean Counts																			
	Q3 (N=694)					Q4 (N=694)					Q5 (N=694)					Q6 (N=694)				
	valid N	mean	SD	lower 95% CI	upper 95% CI	valid N	mean	SD	lower 95% CI	upper 95% CI	valid N	mean	SD	lower 95% CI	upper 95% CI	valid N	mean	SD	lower 95% CI	upper 95% CI
Previous time period[1]																				
≥ 0.8	552	0,09	0,31	0,06	0,11	492	0,06	0,25	0,04	0,09	443	0,06	0,24	0,04	0,08	405	0,07	0,25	0,04	0,09
< 0.8	142	0,06	0,23	0,02	0,09	202	0,08	0,30	0,04	0,13	251	0,10	0,33	0,05	0,14	289	0,11	0,36	0,07	0,15

[1]Previous time period is the previous quarter except for Q3 where the previous time period is the initiation period (Q1 and Q2)
SD: Standard Deviation; CI: Confidence Interval
Each relapse is counted only in the time period in which it started
Wald 95% confidence limits were used for means of continuous measures

Secondary Outcome Result(s)

Post-initiation Quarterly Mean MS-related Inpatient Admission Counts by Prior Adherence (PDC ≥ 0.8)

	Post-initiation Quarterly Mean Inpatient Admission Counts																			
	Q3 (N=694)					Q4 (N=694)					Q5 (N=694)					Q6 (N=694)				
Prior PDC	valid N	mean	SD	lower 95% CI	upper 95% CI	valid N	mean	SD	lower 95% CI	upper 95% CI	valid N	mean	SD	lower 95% CI	upper 95% CI	valid N	mean	SD	lower 95% CI	upper 95% CI
Previous time period[1]																				
≥ 0.8	552	0,03	0,22	0,01	0,04	492	0,04	0,23	0,02	0,06	443	0,02	0,14	0,01	0,03	405	0,02	0,17	0,01	0,04
< 0.8	142	0,05	0,22	0,01	0,09	202	0,03	0,17	0,01	0,05	251	0,02	0,15	0,00	0,04	289	0,03	0,16	0,01	0,05

[1]Previous time period is the previous quarter except for Q3 where the previous time period is the initiation period (Q1 and Q2)
SD: Standard Deviation; CI: Confidence Interval
Each hospitalization is counted only in the time period in which it started
Wald 95% confidence limits were used for means of continuous measures

Post-initiation Quarterly Mean MS-related ER Visit Counts by Prior Adherence (PDC ≥ 0.8)

	Post-initiation Quarterly Mean ER Visit Counts																			
	Q3 (N=694)					Q4 (N=694)					Q5 (N=694)					Q6 (N=694)				
Prior PDC	valid N	mean	SD	lower 95% CI	upper 95% CI	valid N	mean	SD	lower 95% CI	upper 95% CI	valid N	mean	SD	lower 95% CI	upper 95% CI	valid N	mean	SD	lower 95% CI	upper 95% CI
Previous time period[1]																				
≥ 0.8	552	0,07	0,36	0,04	0,10	492	0,09	0,49	0,05	0,14	443	0,09	0,42	0,05	0,13	405	0,10	0,48	0,05	0,15
< 0.8	142	0,12	0,40	0,05	0,19	202	0,10	0,56	0,03	0,18	251	0,05	0,28	0,01	0,08	289	0,08	0,33	0,04	0,12

[1]Previous time period is the previous quarter except for Q3 where the previous time period is the initiation period (Q1 and Q2)
ER: Emergency Room, SD: Standard Deviation; CI: Confidence Interval
Wald 95% confidence limits were used for means of continuous measures

Post-initiation Quarterly Mean All-cause Health Care Costs by Prior Adherence (PDC ≥ 0.8)

	Post-initiation Quarterly All-cause Health Care Costs																			
	Q3 (N=694)					Q4 (N=694)					Q5 (N=694)					Q6 (N=694)				
Prior PDC	valid N	mean	SD	lower 95% CI	upper 95% CI	valid N	mean	SD	lower 95% CI	upper 95% CI	valid N	mean	SD	lower 95% CI	upper 95% CI	valid N	mean	SD	lower 95% CI	upper 95% CI
Previous time period[1]																				
≥ 0.8	552	21.810,98	11.524,18	20.847,49	22.774,46	492	22.585,08	25.563,70	20.320,63	24.849,52	443	22.390,88	12.412,55	21.231,84	23.549,91	405	23.462,21	14.313,69	22.063,99	24.860,43
< 0.8	142	12.599,24	12.972,88	10.447,03	14.751,45	202	12.691,88	10.975,36	11.169,18	14.214,58	251	12.546,25	12.373,42	11.008,07	14.084,44	289	13.824,22	15.830,39	11.991,40	15.657,04

[1]Previous time period is the previous quarter except for Q3 where the previous time period is the initiation period (Q1 and Q2)
SD: Standard Deviation; CI: Confidence Interval
All hospitalization costs are included in the time period associated with the admission date
Wald 95% confidence limits were used for means of continuous measures

. Post-initiation Quarterly Mean All-cause Health Care Costs, Excluding Fingolimod, by Prior Adherence (PDC ≥ 0.8)

	Post-initiation Quarterly All-cause Health Care Costs, Excluding Fingolimod																			
	Q3 (N=694)					Q4 (N=694)					Q5 (N=694)					Q6 (N=694)				
Prior PDC	valid N	mean	SD	lower 95% CI	upper 95% CI	valid N	mean	SD	lower 95% CI	upper 95% CI	valid N	mean	SD	lower 95% CI	upper 95% CI	valid N	mean	SD	lower 95% CI	upper 95% CI
Previous time period[1]																				
≥ 0.8	552	3.911,97	9.967,26	3.078,66	4.745,29	492	5.204,74	25.369,67	2.957,49	7.452,00	443	4.006,78	11.467,03	2.936,03	5.077,53	405	4.382,19	14.049,42	3.009,79	5.754,60
< 0.8	142	5.675,04	11.316,28	3.797,66	7.552,42	202	5.881,13	9.218,75	4.602,14	7.160,12	251	6.366,97	11.491,35	4.938,44	7.795,50	289	8.001,92	15.251,42	6.236,13	9.767,70

[1]Previous time period is the previous quarter except for Q3 where the previous time period is the initiation period (Q1 and Q2)
SD: Standard Deviation; CI: Confidence Interval
All hospitalization costs are included in the time period associated with the admission date
Wald 95% confidence limits were used for means of continuous measures

All-cause Health Care Costs (Plan and Patient Paid Amounts): Initiation Period and Post-initiation Quarters

All-Cause Health Care Costs ($)		Initiation Period (Q1 and Q2) (N=694)	Q3 (N=694)	Q4 (N=694)	Q5 (N=694)	Q6 (N=694)
Total (medical + pharmacy) costs	mean	45.323,19	19.926,15	19.705,50	18.830,36	19.448,70
	SD	18.184,79	12.396,20	22.763,55	13.262,96	15.690,54
	median	43.176,97	19.426,78	18.829,54	19.036,58	18.534,95
	IQR	15.628,25	9.225,05	10.568,40	12.411,92	12.803,28
	lower 95% CI	43.967,89	19.002,27	18.008,95	17.841,88	18.279,29
	upper 95% CI	46.678,49	20.850,03	21.402,05	19.818,84	20.618,10
Medical costs	mean	4.561,37	2.792,33	3.639,61	3.089,94	3.921,12
	SD	9.474,32	8.954,38	20.959,78	10.391,68	13.358,90
	median	1.799,28	647,85	735,72	577,39	663,33
	IQR	3.716,81	1.878,94	2.274,72	2.006,59	2.361,00
	lower 95% CI	3.855,26	2.124,96	2.077,49	2.315,46	2.925,49
	upper 95% CI	5.267,49	3.459,69	5.201,73	3.864,43	4.916,75
Ambulatory	mean	2.943,15	1.691,32	2.598,67	2.353,04	3.149,73
	SD	5.317,49	5.225,70	20.303,39	9.068,20	12.429,13
	median	1.384,09	458,64	501,21	464,93	488,52
	IQR	2.890,58	1.326,67	1.663,80	1.522,21	1.503,14
	lower 95% CI	2.546,85	1.301,85	1.085,47	1.677,19	2.223,39
	upper 95% CI	3.339,46	2.080,79	4.111,87	3.028,88	4.076,06
Office visits	mean	1.429,45	848,28	753,64	976,22	1.438,64
	SD	3.381,22	2.940,13	1.851,94	3.201,65	7.704,27
	median	707,38	291,44	316,83	301,24	284,44
	IQR	1.228,49	580,37	578,17	597,26	587,80
	lower 95% CI	1.177,45	629,15	615,62	737,60	864,44
	upper 95% CI	1.681,45	1.067,41	891,66	1.214,83	2.012,83
Outpatient visits	mean	1.513,70	843,04	1.845,03	1.376,82	1.711,09
	SD	3.882,38	4.006,34	20.077,59	8.317,09	8.547,42
	median	139,28	0,00	0,00	0,00	0,00
	IQR	1.522,04	241,85	509,18	348,19	484,60

	lower 95% CI	1.224,35	544,45	348,66	756,95	1.074,06
	upper 95% CI	1.803,05	1.141,63	3.341,40	1.996,69	2.348,13
Emergency room visits	mean	138,46	83,74	93,45	79,57	88,60
	SD	526,89	396,98	437,53	440,22	400,00
	median	0,00	0,00	0,00	0,00	0,00
	IQR	0,00	0,00	0,00	0,00	0,00
	lower 95% CI	99,19	54,15	60,84	46,76	58,79
	upper 95% CI	177,73	113,33	126,06	112,38	118,42
Inpatient stays	mean	890,09	537,11	627,04	312,38	365,67
	SD	5.811,39	5.586,64	4.633,49	2.585,24	3.653,44
	median	0,00	0,00	0,00	0,00	0,00
	IQR	0,00	0,00	0,00	0,00	0,00
	lower 95% CI	456,97	120,75	281,71	119,70	93,38
	upper 95% CI	1.323,21	953,48	972,37	505,05	637,96
Other medical costs	mean	589,67	480,15	320,45	344,96	317,12
	SD	2.242,60	3.424,57	1.324,82	1.542,05	1.462,60
	median	38,95	0,00	5,47	0,00	0,00
	IQR	237,41	91,74	104,71	105,88	87,23
	lower 95% CI	422,53	224,92	221,71	230,03	208,11
	upper 95% CI	756,81	735,38	419,18	459,88	426,12
Pharmacy costs	mean	40.761,82	17.133,83	16.065,89	15.740,42	15.527,57
	SD	14.811,75	8.737,86	9.596,51	9.701,92	10.646,26
	median	40.304,97	17.466,14	16.869,09	17.152,41	17.061,03
	IQR	14.250,59	8.785,71	10.692,76	14.697,07	15.550,82
	lower 95% CI	39.657,91	16.482,60	15.350,67	15.017,34	14.734,11
	upper 95% CI	41.865,73	17.785,06	16.781,11	16.463,49	16.321,03
Pharmacy costs, excluding fingolimod	mean	2.594,29	1.480,39	1.762,01	1.770,45	1.968,42
	SD	9.247,54	4.566,45	5.792,65	4.594,42	5.736,60
	median	381,78	171,45	169,76	189,25	199,80
	IQR	1.540,75	784,75	862,00	955,06	1.033,72

	lower 95% CI		1.905,08	1.140,05	1.330,29	1.428,03	1.540,87
	upper 95% CI		3.283,51	1.820,72	2.193,73	2.112,87	2.395,96

SD: Standard Deviation; IQR: Interquartile Range; CI: Confidence Interval
Costs are adjusted using the annual medical care component of the Consumer Price Index (CPI) to reflect inflation to year 2019.
US Department of Labor, Bureau of Labor Statistics. Consumer Price Index. Medical Care. Series ID: CUUR0000SAM. Washington, DC: U.S. Dept. of Labor, Bureau of Labor Statistics. http://data.bls.gov/cgi-bin/surveymost?cu
Initiation (6-month) and post-initiation quarters are not directly comparable due to different period lengths
Wald 95% confidence limits were used for means of continuous measures

Safety Results
This study utilized de-identified secondary administrative claims data. Adverse events/adverse reactions were not captured.

Other Relevant Findings
None

Conclusion
After adjusting for time-dependent and independent confounders, adherence was a statistically significant predictor of a lower odds of relapse (OR 0.526, P=0.009), lower all-cause medical costs (CR 0.612, P<0.001), and lower all-cause total costs excluding fingolimod (CR 0.543, P<0.001). Due the high cost of fingolimod, adherence was associated with higher total (medical plus pharmacy) costs (CR 1.647, P<0.001).

Date of Clinical Study Report
26 February 2021