NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis

Generic Drug Name

Ofatumumab

Trial Indication(s)

Relapsing multiple sclerosis

Protocol Number

COMB157G2102

Protocol Title

A 12 week randomized open label parallel group multicenter study to evaluate bioequivalence of 20 mg subcutaneous ofatumumab injected by pre-filled syringe or
autoinjector in adult RMS patients

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: September 2018 (Actual)
Primary Completion Date: August 2019 (Actual)
Study Completion Date: May 2020 (Actual)

Reason for Termination (If applicable)

Study Design/Methodology

This was a randomized, open-label, multi-center, parallel group, 12-week study to evaluate the PK bioequivalence of ofatumumab injected by PFS or autoinjector devices

The study had three parts: screening (Part 1), treatment (Part 2), and safety follow-up (Part 3). In order for patients to increase the potential benefit from participation in the study, continued treatment with ofatumumab was offered to the eligible patients through enrollment into the umbrella open-label Phase III extension study (COMB157G2399).

Part 1 – Screening: Lasted up to 30 days and consisted of Screening and Baseline assessments.

Part 2 – Treatment: Treatment period consisted of an open-label administration of ofatumumab 20 mg s.c. as loading dose regimen (three weekly doses on Day 1, Day 7 and Day 14), followed by a maintenance dose regimen of 20 mg every 4 weeks starting at Week 4. Evaluation of primary endpoint, bioequivalence, was performed between the AI-abdomen and the PFS-abdomen groups.

Part 3 – Safety follow-up: The Safety follow-up period was applicable for the patients who either completed the Treatment period (i.e. Week 12) on study drug and did not enter the planned extension study or prematurely discontinued the study treatment.

All Safety follow-up visits were scheduled relative to the end of study visit. All patients were followed for up to 9 months or until the B-cells' repletion back to baseline value or to lower limit of normal (LLN), whichever came first after study drug discontinuation.

Centers

41 centers in 9 countries: United States(13), Austria(2), Czech Republic(5), Estonia(2), Latvia(3), Russia(6), Lithuania(2), Spain(4), Bulgaria(4)

Objectives:

The primary objective was to demonstrate bioequivalence of 20 mg ofatumumab injected s.c. by the pre-filled syringe assembled in a needle safety device (referred hereafter as PFS) versus the pre-filled syringe assembled in an autoinjector device (referred hereafter as autoinjector, or AI while referring to treatment groups).

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

Ofatumumab 20mg (50 mg/mL, 0.4 mL content) for subcutaneous injection by pre-filled syringe (PFS) or autoinjector (AI)

Statistical Methods

Unless otherwise stated, summary tables/figures/listings were derived based on data from all patients in the respective analysis sets.

The analysis sets used in the study were: bioequivalence (BE) analysis set, pharmacokinetics (PK) analysis set, and Safety set.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
• Diagnosis of multiple sclerosis (MS)
• Relapsing MS: relapsing-remitting course (RRMS), or Secondary progressive (SPMS) course
• EDSS score of 0 to 5.5
• Documentation of at least: 1 relapse during the previous year OR 2 relapses during the previous 2 years prior to Screening OR a positive Gd-enhancing MRI scan during the year prior to randomization.
• Neurologically stable within 1 month prior to randomization

Exclusion Criteria:
• Patients with primary progressive MS or SPMS without disease activity
• Disease duration of more than 10 years in patients with EDSS score of 2 or less
• Patients with an active chronic disease of the immune system other than MS
• Patients with active systemic bacterial, viral or fungal infections, or known to have AIDS or to test positive for HIV antibody at

Screening
• Patients with neurological findings consistent with Progressive Multifocal Leukoencephalopathy (PML), or confirmed PML

Participant Flow Table

Overall Study

	OMB 20mg AI abdomen	OMB 20mg PFS abdomen	OMB 20mg AI thigh	OMB 20mg PFS thigh	Total
Arm/Group Description	Ofatumumab 20 mg subcutaneous (s.c.) injection with autoinjector (AI) administrated on abdomen	Ofatumumab 20 mg subcutaneous (s.c.) injection with pre-filled syringes (PFS) administrated on abdomen	Ofatumumab 20 mg subcutaneous (s.c.) injection with autoinjector (AI) administrated on thigh	Ofatumumab 20 mg subcutaneous (s.c.) injection with pre-filled syringes (PFS) administrated on thigh	
Started	128	130	13	13	284
Completed	128	129	13	13	283
Not Completed	0	1	0	0	1
Adverse Event	0	1	0	0	1

Baseline Characteristics

	OMB 20mg AI abdomen	OMB 20mg PFS abdomen	OMB 20mg AI thigh	OMB 20mg PFS thigh	Total
Arm/Group Description	Ofatumumab 20 mg	Ofatumumab 20 mg	Ofatumumab 20 mg	Ofatumumab 20 mg	

	subcutaneous (s.c.) injection with autoinjector (AI) administrated on abdomen	subcutaneous (s.c.) injection with pre-filled syringes (PFS) administrated on abdomen	subcutaneous (s.c.) injection with autoinjector (AI) administrated on thigh	subcutaneous (s.c.) injection with pre-filled syringes (PFS) administrated on thigh	
Number of Participants [units: participants]	128	130	13	13	284
Age, Customized (units: participants)					
18 to 30 years	32	29	5	2	68
31 to 40 years	42	53	3	10	108
41 to 55 years	54	48	5	1	108
Sex: Female, Male (units: participants) Count of Participants (Not Applicable)					
Female	92	90	9	8	199
Male	36	40	4	5	85
Race/Ethnicity, Customized (units: participants)					
American Indian or Alaska Native	1	0	0	0	1
Black or African American	2	4	0	0	6
White	125	125	13	12	275
Mixed	0	1	0	1	2

Primary Outcome Result(s)

Bioequivalence of 20 mg ofatumumab injected by pre-filled syringe (PFS) vs autoinjector (AI) to abdomen as measured by AUCtau

(Time Frame: Week 8 to Week 12 dosing interval)

	OMB 20mg AI abdomen	OMB 20mg PFS abdomen
Arm/Group Description	Ofatumumab 20 mg subcutaneous (s.c.) injection with autoinjector (AI) administrated on abdomen	Ofatumumab 20 mg subcutaneous (s.c.) injection with pre-filled syringes (PFS) administrated on abdomen
Number of Participants Analyzed [units: participants]	128	128
Bioequivalence of 20 mg ofatumumab injected by pre-filled syringe (PFS) vs autoinjector (AI) to abdomen as measured by AUCtau (units: h×µg/mL) Geometric Mean (Geometric Coefficient of Variation)		
n=128,128	487.7 (103.5%)	474.1 (79.7%)

Statistical Analysis

Groups	OMB 20mg AI abdomen, OMB 20mg PFS abdomen	AUCtau
Non-Inferiority/Equivalence Test	Equivalence	Both criteria had to be met: 1) geo-mean ratio needs to fall in [0.8, 1.25]; 2) 95% upper bound of the linearized criterion needs to be <= 0
Other Geo-mean ratio	1.03	
95 % Confidence Interval 2-Sided	.8 to 1.25	

Statistical Analysis

Groups	OMB 20mg AI abdomen, OMB 20mg PFS abdomen	AUCtau
Non-Inferiority/Equivalence Test	Equivalence	Both criteria had to be met: 1) geo-mean ratio needs to fall in [0.8, 1.25]; 2) 95% upper bound of the linearized criterion needs to be <= 0
Other 95% upper bound of the linearized criter	-.3131	
95 % Confidence Interval 1-Sided	to 0	

Bioequivalence of 20 mg ofatumumab injected by pre-filled syringe (PFS) vs autoinjector (AI) to abdomen as measured by Cmax

(Time Frame: Week 8 to Week 12 dosing interval)

	OMB 20mg AI abdomen	OMB 20mg PFS abdomen
Arm/Group Description	Ofatumumab 20 mg subcutaneous (s.c.) injection with autoinjector (AI) administrated on abdomen	Ofatumumab 20 mg subcutaneous (s.c.) injection with pre-filled syringes (PFS) administrated on abdomen
Number of Participants Analyzed [units: participants]	128	128
Bioequivalence of 20 mg ofatumumab injected by pre-filled syringe (PFS) vs autoinjector (AI) to abdomen as measured by Cmax (units: µg/mL) Geometric Mean (Geometric Coefficient of Variation)		
n=128,128	1.409 (89.2%)	1.409 (67.9%)

Statistical Analysis

Groups	OMB 20mg AI abdomen, OMB 20mg PFS abdomen	Cmax
Non-Inferiority/Equivalence Test	Equivalence	Both criteria had to be met: 1) geo-mean ratio needs to fall in [0.8, 1.25]; 2) 95% upper bound of the linearized criterion needs to be <= 0

Other geo-mean ratio	1.00
95 % Confidence Interval 2-Sided	.8 to 1.25

Statistical Analysis

Groups	OMB 20mg AI abdomen, OMB 20mg PFS abdomen	Cmax
Non-Inferiority/Equivalence Test	Equivalence	Both criteria had to be met: 1) geo-mean ratio needs to fall in [0.8, 1.25]; 2) 95% upper bound of the linearized criterion needs to be <= 0
Other 95% upper bound of the linearized criter	-0.2446	
95 % Confidence Interval 1-Sided	to 0	

Secondary Outcome Result(s)

Pharmacokinetics of the study drug as measured by AUCtau for PFS and AI devices when administered to abdomen or thigh

(Time Frame: Week 8 to Week 12 dosing interval)

	OMB 20mg AI abdomen	**OMB 20mg PFS abdomen**	**OMB 20mg AI thigh**	**OMB 20mg PFS thigh**
Arm/Group Description	Ofatumumab 20 mg subcutaneous (s.c.) injection with	Ofatumumab 20 mg subcutaneous (s.c.) injection with pre-filled	Ofatumumab 20 mg subcutaneous (s.c.) injection with	Ofatumumab 20 mg subcutaneous (s.c.) injection with pre-filled

	autoinjector (AI) administrated on abdomen	syringes (PFS) administrated on abdomen	autoinjector (AI) administrated on thigh	syringes (PFS) administrated on thigh
Number of Participants Analyzed [units: participants]	128	128	13	13
Pharmacokinetics of the study drug as measured by AUCtau for PFS and AI devices when administered to abdomen or thigh (units: h×µg/mL) Geometric Mean (Geometric Coefficient of Variation)				
	487.7 (103.5%)	474.1 (79.7%)	476.0 (73.1%)	544.1 (93.8%)

Pharmacokinetics of the study drug as measured by Cmax for PFS and AI devices when administered to abdomen or thigh

(Time Frame: Week 8 to Week 12 dosing interval)

	OMB 20mg AI abdomen	**OMB 20mg PFS abdomen**	**OMB 20mg AI thigh**	**OMB 20mg PFS thigh**
Arm/Group Description	Ofatumumab 20 mg subcutaneous (s.c.) injection with autoinjector (AI) administrated on abdomen	Ofatumumab 20 mg subcutaneous (s.c.) injection with pre-filled syringes (PFS) administrated on abdomen	Ofatumumab 20 mg subcutaneous (s.c.) injection with autoinjector (AI) administrated on thigh	Ofatumumab 20 mg subcutaneous (s.c.) injection with pre-filled syringes (PFS) administrated on thigh
Number of Participants Analyzed [units: participants]	128	128	13	13

Pharmacokinetics of the study drug as measured by Cmax for PFS and AI devices when administered to abdomen or thigh (units: µg/mL) Geometric Mean (Geometric Coefficient of Variation)				
	1.409 (89.2%)	1.409 (67.9%)	1.563 (71.3%)	1.635 (50.7%)

Plasma concentrations of the study drug for PFS and AI devices when administered to abdomen or thigh

(Time Frame: Days 4, 7, 14, 28, 42, 56, 57, 59, 63, 70, 77, 84)

	OMB 20mg AI abdomen	OMB 20mg PFS abdomen	OMB 20mg AI thigh	OMB 20mg PFS thigh
Arm/Group Description	Ofatumumab 20 mg subcutaneous (s.c.) injection with autoinjector (AI) administrated on abdomen	Ofatumumab 20 mg subcutaneous (s.c.) injection with pre-filled syringes (PFS) administrated on abdomen	Ofatumumab 20 mg subcutaneous (s.c.) injection with autoinjector (AI) administrated on thigh	Ofatumumab 20 mg subcutaneous (s.c.) injection with pre-filled syringes (PFS) administrated on thigh
Number of Participants Analyzed [units: participants]	128	130	13	13
Plasma concentrations of the study drug for PFS and AI devices when administered to abdomen or thigh (units: µg/mL) Geometric Mean (Geometric Coefficient of Variation)				
Day 4 n=128,127,13,13	0.43076 (147.591319%)	0.40075 (119.330376%)	0.86747 (24.481350%)	0.55704 (105.432315%)
Day 7 n=128, 130,13,13	0.33544 (133.205087%)	0.30511 (119.511321%)	0.36750 (94.007762%)	0.29662 (119.353006%)
Day 14 n=128, 130,12,11	1.07408 (105.566707%)	0.96359 (105.735963%)	0.89788 (125.726458%)	1.30586 (83.153962%)
Day 28 Week 4 n=127, 130,13,13	0.95571 (113.510035%)	0.95774 (117.852822%)	1.11008 (66.780045%)	1.41434 (117.959678%)

Day 42 Week 6 n=128, 130,13,13	0.97327 (125.421064%)	1.12006 (113.137164%)	1.12006 (86.390639%)	1.18239 (133.082660%)
Day 56 Week 8 n=128, 130,13,13	0.28358 (142.760137%)	0.24644 (133.056913%)	0.23874 (98.041287%)	0.45529 (143.614763%)
Day 57 Week 8 n=127, 127,12,13	0.89424 (121.357310%)	0.80986 (107.929658%)	0.96356 (122.222991%)	1.04905 (54.771002%)
Day 59 Week 8 n=127, 127,13,13	1.24143 (103.274314%)	1.23458 (81.737063%)	1.34837 (82.596695%)	1.52705 (52.253239%)
Day 63 Week 9 n=126, 128,13,13	1.27031 (84.610014%)	1.23163 (77.294222%)	1.28263 (67.076249%)	1.43075 (66.345270%)
Day 70 Week 10 n=128, 127,13,13	0.78732 (97.440131%)	0.74111 (82.870974%)	0.67151 (82.769087%)	0.95821 (83.645358%)
Day 77 Week 11 n=127, 127,13,13	0.40249 (109.581877%)	0.33720 (114.373887%)	0.40173 (52.479338%)	0.54085 (97.862609%)
Early Exit n=0,1,0,0		0.1870		
EOS Week 12 n=126, 118,12,13	0.20290 (113.812416%)	0.17862 (102.507484%)	0.17361 (63.899086%)	0.27276 (98.256573%)

Percentage of patients with anti-ofatumumab antibodies

(Time Frame: Baseline, Week 4, 8, 12 and Overall)

	OMB 20mg AI abdomen	OMB 20mg PFS abdomen	OMB 20mg AI thigh	OMB 20mg PFS thigh
Arm/Group Description	Ofatumumab 20 mg subcutaneous (s.c.) injection with autoinjector (AI) administrated on abdomen	Ofatumumab 20 mg subcutaneous (s.c.) injection with pre-filled syringes (PFS) administrated on abdomen	Ofatumumab 20 mg subcutaneous (s.c.) injection with autoinjector (AI) administrated on thigh	Ofatumumab 20 mg subcutaneous (s.c.) injection with pre-filled syringes (PFS) administrated on thigh

Number of Participants Analyzed [units: participants]	128	130	13	13
Percentage of patients with anti-ofatumumab antibodies (units: percentage of participants)				
Baseline n= 128,130,13,13	0.8	3.1	0.0	7.7
Week 4 n= 128,130,13,13	0.8	0.0	0.0	0.0
Week 8 n= 124,126,13,13	0.0	0.8	0.0	0.0
Week 12 n= 125,121, 12,13	0.8	0.0	0.0	0.0
Overall n= 128,130,13,13	0.8	3.8	0.0	7.7

Safety Results

All-Cause Mortality

	OMB 20mg AI (ABD) N = 128	**OMB 20mg PFS abdomen N = 130**	**OMB 20mg AI (THI) N = 13**	**OMB 20mg PFS (THI) N = 13**
Arm/Group Description	Ofatumumab 20 mg subcutaneous (sc.) injection with autoinjector (AI)	Ofatumumab 20 mg subcutaneous (s.c.) injection with pre-filled syringes (PFS)	Ofatumumab 20 mg subcutaneous (sc.) injection with autoinjector (AI)	Ofatumumab 20 mg subcutaneous (sc.) injection with pre-filled syringes (PFS)

	administrated on abdomen	administrated on abdomen	administrated on thigh	administrated on thigh
Total participants affected	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse events were reported from first dose of study treatment until last administration of study treatment plus 100 days post treatment, up to maximum duration of 226 days
Source Vocabulary for Table Default	MedDRA (23.0)
Assessment Type for Table Default	Systematic Assessment

	OMB 20mg AI (ABD) N = 128	**OMB 20mg PFS abdomen N = 130**	**OMB 20mg AI (THI) N = 13**	**OMB 20mg PFS (THI) N = 13**
Arm/Group Description	Ofatumumab 20 mg subcutaneous (sc.) injection with autoinjector (AI) administrated on abdomen	Ofatumumab 20 mg subcutaneous (s.c.) injection with pre-filled syringes (PFS) administrated on abdomen	Ofatumumab 20 mg subcutaneous (sc.) injection with autoinjector (AI) administrated on thigh	Ofatumumab 20 mg subcutaneous (sc.) injection with pre-filled syringes (PFS) administrated on thigh
Total participants affected	2 (1.56%)	4 (3.08%)	0 (0.00%)	0 (0.00%)
Ear and labyrinth disorders				
Vertigo	0 (0.00%)	1 (0.77%)	0 (0.00%)	0 (0.00%)

Gastrointestinal disorders				
Gastrointestinal motility disorder	1 (0.78%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations				
Appendicitis	0 (0.00%)	1 (0.77%)	0 (0.00%)	0 (0.00%)
Pneumonia	0 (0.00%)	1 (0.77%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications				
Burns second degree	1 (0.78%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Reproductive system and breast disorders				
Menometrorrhagia	0 (0.00%)	1 (0.77%)	0 (0.00%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	Adverse events were reported from first dose of study treatment until last administration of study treatment plus 100 days post treatment, up to maximum duration of 226 days
Source Vocabulary for Table Default	MedDRA (23.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	OMB 20mg AI (ABD) N = 128	**OMB 20mg PFS abdomen N = 130**	**OMB 20mg AI (THI) N = 13**	**OMB 20mg PFS (THI) N = 13**

Arm/Group Description	Ofatumumab 20 mg subcutaneous (sc.) injection with autoinjector (AI) administrated on abdomen	Ofatumumab 20 mg subcutaneous (s.c.) injection with pre-filled syringes (PFS) administrated on abdomen	Ofatumumab 20 mg subcutaneous (sc.) injection with autoinjector (AI) administrated on thigh	Ofatumumab 20 mg subcutaneous (sc.) injection with pre-filled syringes (PFS) administrated on thigh
Total participants affected	61 (47.66%)	53 (40.77%)	7 (53.85%)	7 (53.85%)
Blood and lymphatic system disorders				
Leukopenia	3 (2.34%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Lymphopenia	1 (0.78%)	2 (1.54%)	0 (0.00%)	1 (7.69%)
Gastrointestinal disorders				
Diarrhoea	6 (4.69%)	4 (3.08%)	1 (7.69%)	0 (0.00%)
Nausea	1 (0.78%)	0 (0.00%)	0 (0.00%)	1 (7.69%)
General disorders and administration site conditions				
Asthenia	2 (1.56%)	1 (0.77%)	0 (0.00%)	1 (7.69%)
Fatigue	3 (2.34%)	5 (3.85%)	1 (7.69%)	0 (0.00%)
Injection site pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)
Injection site reaction	11 (8.59%)	17 (13.08%)	0 (0.00%)	1 (7.69%)
Pain	1 (0.78%)	1 (0.77%)	0 (0.00%)	1 (7.69%)
Infections and infestations				
Herpes zoster	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Influenza	1 (0.78%)	1 (0.77%)	0 (0.00%)	1 (7.69%)

Nasopharyngitis	2 (1.56%)	5 (3.85%)	0 (0.00%)	1 (7.69%)
Oral herpes	2 (1.56%)	1 (0.77%)	1 (7.69%)	0 (0.00%)
Rhinitis	3 (2.34%)	3 (2.31%)	0 (0.00%)	1 (7.69%)
Sinusitis	0 (0.00%)	1 (0.77%)	0 (0.00%)	1 (7.69%)
Upper respiratory tract infection	1 (0.78%)	2 (1.54%)	0 (0.00%)	1 (7.69%)
Injury, poisoning and procedural complications				
Injection related reaction	41 (32.03%)	29 (22.31%)	5 (38.46%)	6 (46.15%)
Ligament sprain	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Musculoskeletal and connective tissue disorders				
Muscle contracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (7.69%)
Spinal pain	0 (0.00%)	1 (0.77%)	1 (7.69%)	0 (0.00%)
Tendonitis	2 (1.56%)	0 (0.00%)	0 (0.00%)	1 (7.69%)
Nervous system disorders				
Head discomfort	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Headache	13 (10.16%)	7 (5.38%)	0 (0.00%)	1 (7.69%)
Neuralgia	1 (0.78%)	0 (0.00%)	0 (0.00%)	1 (7.69%)
Post herpetic neuralgia	0 (0.00%)	0 (0.00%)	1 (7.69%)	0 (0.00%)
Psychiatric disorders				
Sleep disorder	2 (1.56%)	1 (0.77%)	1 (7.69%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders				

Cough	1 (0.78%)	2 (1.54%)	0 (0.00%)	1 (7.69%)
Oropharyngeal pain	2 (1.56%)	1 (0.77%)	0 (0.00%)	1 (7.69%)
Rhinitis allergic	1 (0.78%)	0 (0.00%)	0 (0.00%)	1 (7.69%)
Skin and subcutaneous tissue disorders				
Pruritus	0 (0.00%)	3 (2.31%)	1 (7.69%)	0 (0.00%)

Other Relevant Findings

Conclusion:

- Bioequivalence was demonstrated between the pre-filled syringe assembled in an autoinjector device and the pre-filled syringe assembled in a needle safety device, and the systemic exposure to ofatumumab was similar across the tested injection sites (abdomen or thigh).
- Ofatumumab 20 mg administered subcutaneously, either by pre-filled syringe in needle safety device or by pre-filled syringe in autoinjector, successfully led to a rapid depletion (< 10 cells/µL) of B-cell during the loading phase that was sustained through the maintenance phase.
- Ofatumumab administered over 12 weeks was well tolerated and the safety profile of autoinjector and pre-filled syringe in needle safety device administration was similar and consistent with the expected risks associated with anti-CD20 antibody therapy. Most frequent adverse events were mild to moderate injection-related reactions, which occurred primarily at the first injection.
- The safety profile reported in the Safety FU period remained consistent with that reported in the first 12 weeks of the study.

Date of Clinical Trial Report

September 14, 2020