Clinical trial results:
A Multicenter, Single-Arm, Open-Label, Study to Evaluate the Immunogenicity and Pharmacokinetics of BIIB019, Daclizumab High Yield Process (DAC HYP), Prefilled Syringe Administered by Subcutaneous Injection in Subjects With Relapsing-Remitting Multiple Sclerosis

Summary

EudraCT number	2010-023856-97
Trial protocol	HU CZ PL
Global end of trial date	26 January 2016

Results information

Result version number	v1 (current)
This version publication date	08 February 2017
First version publication date	08 February 2017

Trial information

Trial identification

Sponsor protocol code	205MS302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01462318
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen
Sponsor organisation address	225 Binney Street, Cambridge, Massachusetts, United States, 02142
Public contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com
Scientific contact	Biogen Study Medical Director, Biogen, clinicaltrials@biogen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 January 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to assess the immunogenicity of Daclizumab High Yield Process (DAC HYP) 150 mg administered every 4 weeks by subcutaneous (SC) injection using the pre-filled syringe (PFS) in subjects with relapsing-remitting multiple sclerosis (RRMS). The secondary objectives of this study are to characterize the pharmacokinetics (PK) of DAC HYP following single and multiple doses of DAC HYP administered by the PFS in a subset of participants with RRMS and to evaluate the effect of DAC HYP on the PK of probe drugs for cytochrome P450 (CYP) isoenzymes (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A).

Protection of trial subjects:

Written informed consent was obtained from each subject prior to evaluations being performed for eligibility. Subjects were given adequate time to review the information in the informed consent and were allowed to ask, and have answered, questions concerning all portions of the conduct of the study. Through the informed consent process each subject was made aware of the purpose of the study, the procedures, the benefits and risks of the study, the discomforts and the precautions taken. Any side effects or other health issues occurring during the study were followed up by the study doctor. Subjects were able to stop taking part in the study at any time without giving any reason.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 November 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czech Republic: 42
Country: Number of subjects enrolled	Poland: 40
Country: Number of subjects enrolled	United States: 27
Country: Number of subjects enrolled	Hungary: 24
Worldwide total number of subjects	133
EEA total number of subjects	106

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	133
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subject eligibility for the study was determined within 28 days prior to study entry.

Period 1

Period 1 title	Main Study or TP-DI Study
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Main Study

Arm description:

All subjects received DAC HYP 150 mg SC injections every 4 weeks over an initial 24-week treatment period (for a total of 6 injections), followed by a 20-week washout period.

Those subjects from the Main Study who enrolled in the Intensive PK sub-study underwent serial DAC HYP PK sampling over the first and the last dosing intervals (on Day 1 [Week 0] and again on Day 141 [Week 20], the last dosing visit).

Arm type	Experimental
Investigational medicinal product name	Daclizumab HYP
Investigational medicinal product code	BIIB019
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

DAC HYP was administered using a 1 mL pre-filled syringe

Investigational medicinal product name	Omeprazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Oral omeprazole 40 mg (capsule). Part of the probe drug cocktail combination of drugs that was completely administered within 5 minutes. Subjects remained under fasting conditions for another 2 hours after receiving the oral drug combination.

Investigational medicinal product name	Vitamin K
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral vitamin K 10 mg (tablet). Part of the probe drug cocktail combination of drugs that was completely administered within 5 minutes. Subjects remained under fasting conditions for another 2 hours after receiving the oral drug combination. Vitamin K was used to counteract warfarin’s anticoagulant effect prophylactically. If vitamin K tablets were not commercially available, alternate formulations such as SC or IV were used.

Investigational medicinal product name	Dextromethorphan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Syrup
Routes of administration	Oral use

Dosage and administration details:

Oral dextromethorphan 30 mg (syrup). Part of the probe drug cocktail combination of drugs that was completely administered within 5 minutes. Subjects remained under fasting conditions for another 2 hours after receiving the oral drug combination.

Arm title	Therapeutic Protein-Drug Interaction (TP-DI) Sub-study

Arm description:

In Period 1 (Week -1), the probe-drug cocktail (consisting of oral midazolam 5 mg, caffeine 200 mg, S-warfarin 10 mg, vitamin K 10 mg, omeprazole 40 mg, and dextromethorphan 30 mg, where the oral vitamin K was used prophylactically to counteract warfarin's anticoagulant effect) was administered 7 days before the first dose of DAC HYP 150 mg in the 3-year extension phase.

In Period 2, pretreatment with DAC HYP 150 mg was administered at Weeks 0, 4, and 8. The probe-drug cocktail was administered 7 days after the third dose of DAC HYP.

Arm type	Experimental
Investigational medicinal product name	Daclizumab HYP
Investigational medicinal product code	BIIB019
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

DAC HYP was administered using a 1 mL pre-filled syringe

Investigational medicinal product name	Midazolam
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Syrup
Routes of administration	Oral use

Dosage and administration details:

Oral midazolam 5 mg. The preferred formulation was midazolam syrup formulation containing midazolam hydrochloride equivalent to 2 mg of midazolam/mL. Part of the probe drug cocktail combination of drugs that was completely administered within 5 minutes. Subjects remained under fasting conditions for another 2 hours after receiving the oral drug combination.

Investigational medicinal product name	Caffeine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral caffeine 200 mg (tablet or caplet). Part of the probe drug cocktail combination of drugs that was completely administered within 5 minutes. Subjects remained under fasting conditions for another 2 hours after receiving the oral drug combination.

Investigational medicinal product name	warfarin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Oral warfarin 10 mg (tablet). Part of the probe drug cocktail combination of drugs that was completely administered within 5 minutes. Subjects remained under fasting conditions for another 2 hours after receiving the oral drug combination.

Number of subjects in period 1	Main Study	Therapeutic Protein-Drug Interaction (TP-DI) Sub-study
Started	113	20
Enrolled in Intensive PK Substudy	26 [1]	0 [2]
Completed	105	20
Not completed	8	0
Consent withdrawn by subject	2	-
Adverse event, non-fatal	4	-
NotSpecified	2	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Twenty-six subjects from this arm were enrolled in the intensive PK stubstudy.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: No subjects from this arm were enrolled in the intensive PK stubstudy.

Period 2

Period 2 title	Extension Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Extension Phase

Arm description:

After completion of the washout period from the Main Study or the TP-DI sub-study, eligible subjects had the option to resume monthly open-label treatment with DAC HYP 150 mg in the extension phase of the study for up to 3 additional years.

Arm type	Experimental
Investigational medicinal product name	Daclizumab HYP
Investigational medicinal product code	BIIB019
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

DAC HYP was administered using a 1 mL pre-filled syringe

Number of subjects in period 2[3]	Extension Phase
Started	115
Completed	70
Not completed	45
Consent withdrawn by subject	15
Adverse event, non-fatal	22
NotSpecified	1
Investigator Decision	5
Lost to follow-up	1
Disease Progression	1

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: Subjects who resumed monthly open-label treatment with DAC HYP 150 mg in the extension phase of the study.

Baseline characteristics

Reporting groups	
Reporting group title	Main Study

Reporting group description:

All subjects received DAC HYP 150 mg SC injections every 4 weeks over an initial 24-week treatment period (for a total of 6 injections), followed by a 20-week washout period.

Those subjects from the Main Study who enrolled in the Intensive PK sub-study underwent serial DAC HYP PK sampling over the first and the last dosing intervals (on Day 1 [Week 0] and again on Day 141 [Week 20], the last dosing visit).

Reporting group title	Therapeutic Protein-Drug Interaction (TP-DI) Sub-study

Reporting group description:

In Period 1 (Week -1), the probe-drug cocktail (consisting of oral midazolam 5 mg, caffeine 200 mg, S-warfarin 10 mg, vitamin K 10 mg, omeprazole 40 mg, and dextromethorphan 30 mg, where the oral vitamin K was used prophylactically to counteract warfarin's anticoagulant effect) was administered 7 days before the first dose of DAC HYP 150 mg in the 3-year extension phase.

In Period 2, pretreatment with DAC HYP 150 mg was administered at Weeks 0, 4, and 8. The probe-drug cocktail was administered 7 days after the third dose of DAC HYP.

Reporting group values	Main Study	Therapeutic Protein-Drug Interaction (TP-DI) Sub-study	Total
Number of subjects	113	20	133
Age Categorical Units: Subjects			
< 18 years	0	0	0
18 - 19 years	0	1	1
20 - 29 years	28	4	32
30 - 39 years	40	7	47
40 - 49 years	31	5	36
50 - 55 years	14	3	17
> 55 years	0	0	0
Gender, Male/Female Units: Subjects			
Female	72	13	85
Male	41	7	48

End points

End points reporting groups

Reporting group title	Main Study

Reporting group description:

All subjects received DAC HYP 150 mg SC injections every 4 weeks over an initial 24-week treatment period (for a total of 6 injections), followed by a 20-week washout period.

Those subjects from the Main Study who enrolled in the Intensive PK sub-study underwent serial DAC HYP PK sampling over the first and the last dosing intervals (on Day 1 [Week 0] and again on Day 141 [Week 20], the last dosing visit).

Reporting group title	Therapeutic Protein-Drug Interaction (TP-DI) Sub-study

Reporting group description:

In Period 1 (Week -1), the probe-drug cocktail (consisting of oral midazolam 5 mg, caffeine 200 mg, S-warfarin 10 mg, vitamin K 10 mg, omeprazole 40 mg, and dextromethorphan 30 mg, where the oral vitamin K was used prophylactically to counteract warfarin's anticoagulant effect) was administered 7 days before the first dose of DAC HYP 150 mg in the 3-year extension phase.

In Period 2, pretreatment with DAC HYP 150 mg was administered at Weeks 0, 4, and 8. The probe-drug cocktail was administered 7 days after the third dose of DAC HYP.

Reporting group title	Extension Phase

Reporting group description:

After completion of the washout period from the Main Study or the TP-DI sub-study, eligible subjects had the option to resume monthly open-label treatment with DAC HYP 150 mg in the extension phase of the study for up to 3 additional years.

Subject analysis set title	TP-DI Sub-study
Subject analysis set type	Full analysis

Subject analysis set description:

In Period 1 (Week -1), the probe-drug cocktail (consisting of oral midazolam 5 mg, caffeine 200 mg, S-warfarin 10 mg, vitamin K 10 mg, omeprazole 40 mg, and dextromethorphan 30 mg, and oral vitamin K 10 mg used prophylactically to counteract warfarin's anticoagulant effect) was administered 7 days before the first dose of DAC HYP 150 mg in the 3-year extension phase. In Period 2 (Weeks 0, 4, 8, and 9), pretreatment with DAC HYP 150 mg was administered at Weeks 0, 4, and 8. The probe-drug cocktail was administered 7 days after the third dose of DAC HYP 150 mg.

Subject analysis set title	TP-DI Substudy
Subject analysis set type	Full analysis

Subject analysis set description:

In Period 1 (Week -1), the probe-drug cocktail (consisting of oral midazolam 5 mg, caffeine 200 mg, S-warfarin 10 mg, vitamin K 10 mg, omeprazole 40 mg, and dextromethorphan 30 mg, and oral vitamin K 10 mg used prophylactically to counteract warfarin's anticoagulant effect) was administered 7 days before the first dose of DAC HYP 150 mg in the 3-year extension phase. In Period 2 (Weeks 0, 4, 8, and 9), pretreatment with DAC HYP 150 mg was administered at Weeks 0, 4, and 8. The probe-drug cocktail was administered 7 days after the third dose of DAC HYP 150 mg.

Subject analysis set title	TP-DI Substudy
Subject analysis set type	Full analysis

Subject analysis set description:

In Period 1 (Week -1), the probe-drug cocktail (consisting of oral midazolam 5 mg, caffeine 200 mg, S-warfarin 10 mg, vitamin K 10 mg, omeprazole 40 mg, and dextromethorphan 30 mg, and oral vitamin K 10 mg used prophylactically to counteract warfarin's anticoagulant effect) was administered 7 days before the first dose of DAC HYP 150 mg in the 3-year extension phase. In Period 2 (Weeks 0, 4, 8, and 9), pretreatment with DAC HYP 150 mg was administered at Weeks 0, 4, and 8. The probe-drug cocktail was administered 7 days after the third dose of DAC HYP 150 mg.

Primary: Number of Participants With Anti-DAC HYP Binding Antibodies (ADAbs): Electrochemiluminescent (ECL) Anti-Drug Antibody (ADA) Assay

End point title	Number of Participants With Anti-DAC HYP Binding Antibodies (ADAbs): Electrochemiluminescent (ECL) Anti-Drug Antibody (ADA) Assay[1][2]

End point description:

Participants with post-baseline (PB) ADAbs through Week 44, in the treatment period (extends up to 42 days after the last dose during the main study), and in the post-treatment period (43 days after the last dose until the end of the post-treatment period dose).

End point type	Primary

End point timeframe:

Up to 44 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented, per protocol.

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was collected for the Main Study only, per protocol.

End point values	Main Study			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: participants				
PB ADAbs through Week 44=negative; n=113	78			
PB ADAbs through Week 44=positive; n=113	35			
PB ADAbs in treatment period=negative; n=113	92			
PB ADAbs in treatment period=positive; n=113	21			
PB ADAbs in post-treatment period=negative; n=110	89			
PB ADAbs in post-treatment period=positive; n=110	21			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Anti-DAC HYP Neutralizing Antibodies (NAbs): ECL ADA Assay

End point title	Number of Participants With Anti-DAC HYP Neutralizing Antibodies (NAbs): ECL ADA Assay[3][4]

End point description:

Participants with PB NAbs through Week 44, in the treatment period (extends up to 42 days after the last dose during the main study), and in the post-treatment period (43 days after the last dose until the end of the post-treatment period dose).

End point type	Primary

End point timeframe:

Up to 44 weeks

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics are presented, per protocol.

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was collected for the Main Study only, per protocol.

End point values	Main Study			
Subject group type	Reporting group			
Number of subjects analysed	113			
Units: participants				
PB NAbs through Week 44=negative; n=113	105			
PB NAbs through Week 44=positive; n=113	8			
PB NAbs in treatment period=negative; n=113	109			
PB NAbs in treatment period=positive; n=113	4			
PB NAbs in post-treatment period=negative; n=110	104			
PB NAbs in post-treatment period=positive; n=110	6			

Statistical analyses

No statistical analyses for this end point

Primary: TP-DI Sub-study: Area-Under-the-Curve From Zero to Infinity (AUCinf) of Each Probe Drug

End point title	TP-DI Sub-study: Area-Under-the-Curve From Zero to Infinity (AUCinf) of Each Probe Drug[5]

End point description:

AUCinf of each of the following cytochrome P450 (CYP) isoenzyme substrates: midazolam (CYP3A), S-warfarin + vitamin K (CYP2C9), and omeprazole (CYP2C19). The AUC from zero to 12 hours (AUC0-12) was calculated for caffeine (CYP1A2).

End point type	Primary

End point timeframe:

Week 43 (7 days prior to DAC HYP administration) and Week 53 (7 days after DAC HYP administration), pre-cocktail dose and at 0.5 and 1, 2, 3, 4, 6, 8, 10 , 24, 48, 72 and 96 hours post-probe drug cocktail administration

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses are attached as pdfs.

End point values	TP-DI Sub-study			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
Midazolam (Period 1) AUCinf; n=20	786.75 (± 328.794)			
Midazolam+DAC HYP (Period 2) AUCinf; n=19	816.87 (± 403.958)			
S-warfarin (Period 1) AUCinf; n=17	19292.9 (± 5524.6)			
S-warfarin+DAC HYP (Period 2) AUCinf; n=18	19609.3 (± 4620.64)			
Omeprazole (Period 1) AUCinf; n=18	2214.5 (± 2622.15)			

Omeprazole+DAC HYP (Period 2) AUCinf; n=19	1770 (± 1673.8)			
Caffeine (Period 1) AUC0-12; n=20	35742.4 (± 13942.71)			
Caffeine+DAC HYP (Period 2) AUC0-12; n=20	37449.2 (± 14367.04)			

Attachments (see zip file)	Stat Analysis OM3 p2.pdf Stat Analysis OM3 p1.pdf

Statistical analyses

No statistical analyses for this end point

Primary: TP-DI Sub-study: Dextromethorphan to Dextrorphan Urine Concentration Ratio

End point title	TP-DI Sub-study: Dextromethorphan to Dextrorphan Urine Concentration Ratio[6]

End point description:

End point type	Primary

End point timeframe:

Week 43 (7 days prior to DAC HYP administration) and Week 53 (7 days after DAC HYP administration), pre-cocktail dose and for 12 hours after probe-drug cocktail administration

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Statistical analyses are attached as pdfs.

End point values	TP-DI Sub-study			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: ratio				
arithmetic mean (standard deviation)				
Dextromethorphan (Period 1)	0.42468 (± 1.258565)			
Dextromethorphan+DAC HYP (Period 2)	0.48939 (± 1.813077)			

Attachments (see zip file)	Stat Analysis OM4.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Intensive PK sub-study: Maximum Observed Concentration (Cmax) of DAC HYP

End point title	Intensive PK sub-study: Maximum Observed Concentration

	(Cmax) of DAC HYP[7]

End point description:

End point type	Secondary

End point timeframe:

Day 1 and Day 141 (Week 20) at pre-dose and 8, 24, 72 and 120 hours post-dose and 7, 10, 14 and 21 days post-dose

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was collected for the Intensive PK sub-study only, per protocol.

End point values	Main Study			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: mcg/mL				
arithmetic mean (standard deviation)				
Day 1 (Week 0); n=25	12.63 (± 4.639)			
Day 141 (Week 20); n=24	29.07 (± 10.812)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intensive PK sub-study: Time to Reach Maximum Concentration (Tmax) of DAC HYP

End point title	Intensive PK sub-study: Time to Reach Maximum Concentration (Tmax) of DAC HYP[8]

End point description:

End point type	Secondary

End point timeframe:

Day 1 and Day 141 (Week 20) at pre-dose and 8, 24, 72 and 120 hours post-dose and 7, 10, 14 and 21 days post-dose

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was collected for the Intensive PK sub-study only, per protocol.

End point values	Main Study			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: day				
arithmetic mean (standard deviation)				
Day 1 (Week 0); n=25	9.31 (± 6.368)			
Day 141 (Week 20); n=24	6.41 (± 3.273)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intensive PK sub-study: Area-Under-the-Curve From Start to End of the Dosing Interval (AUCtau) of DAC HYP

End point title	Intensive PK sub-study: Area-Under-the-Curve From Start to End of the Dosing Interval (AUCtau) of DAC HYP[9]

End point description:

End point type	Secondary

End point timeframe:

Day 1 and Day 141 (Week 20) at pre-dose and 8, 24, 72 and 120 hours post-dose and 7, 10, 14 and 21 days post-dose

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was collected for the Intensive PK sub-study only, per protocol.

End point values	Main Study			
Subject group type	Reporting group			
Number of subjects analysed	25			
Units: day*mcg/mL				
arithmetic mean (standard deviation)				
Week 0 (Day 1); n=25	255.25 (± 88.569)			
Week 20; n=24	638.1 (± 256.076)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intensive PK sub-study: Minimum Concentrations (Cmin) of DAC HYP

End point title	Intensive PK sub-study: Minimum Concentrations (Cmin) of DAC HYP[10]

End point description:

End point type	Secondary

End point timeframe:

Day 141 (Week 20) at pre-dose and 8, 24, 72 and 120 hours post-dose and 7, 10, 14 and 21 days post-dose

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data was collected for the Intensive PK sub-study only, per protocol.

End point values	Main Study			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: mcg/mL				
arithmetic mean (standard deviation)	14.93 (± 6.327)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intensive PK sub-study: Apparent Volume of Distribution (V/F) of DAC HYP

End point title	Intensive PK sub-study: Apparent Volume of Distribution (V/F) of DAC HYP[11]

End point description:

End point type	Secondary

End point timeframe:

Day 141 (Week 20) at pre-dose and 8, 24, 72 and 120 hours post-dose and 7, 10, 14 and 21 days post-dose

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data was collected for the Intensive PK sub-study only, per protocol.

End point values	Main Study			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: Liters				
arithmetic mean (standard deviation)	8.21 (± 2.81)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intensive PK sub-study: Elimination Half-Life (t½) of DAC HYP

End point title	Intensive PK sub-study: Elimination Half-Life (t½) of DAC

End point description:

End point type	Secondary

End point timeframe:

Day 141 (Week 20) at pre-dose and 8, 24, 72 and 120 hours post-dose and 7, 10, 14 and 21 days post-dose

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was collected for the Intensive PK sub-study only, per protocol.

End point values	Main Study			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: day				
arithmetic mean (standard deviation)	21.92 (± 5.473)			

Statistical analyses

No statistical analyses for this end point

Secondary: Intensive PK sub-study: Apparent Clearance (CL/F) of DAC HYP

End point title	Intensive PK sub-study: Apparent Clearance (CL/F) of DAC

End point description:

End point type	Secondary

End point timeframe:

Day 141 (Week 20) at pre-dose and 8, 24, 72 and 120 hours post-dose and 7, 10, 14 and 21 days post-dose

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Data was collected for the Intensive PK sub-study only, per protocol.

End point values	Main Study			
Subject group type	Reporting group			
Number of subjects analysed	24			
Units: L/day				
arithmetic mean (standard deviation)	0.27 (± 0.108)			

Statistical analyses

No statistical analyses for this end point

Secondary: TP-DI sub-study: Cmax of Each Probe Drug

End point title	TP-DI sub-study: Cmax of Each Probe Drug

End point description:

Cmax of each of the following cytochrome P450 (CYP) isoenzyme substrates: midazolam (CYP3A),

caffeine (CYP1A2), warfarin + vitamin K (CYP2C9), omeprazole (CYP2C19), and dextromethorphan (CYP2D6)

End point type	Secondary

End point timeframe:

Week 43 (7 days prior to DAC HYP administration) and Week 53 (7 days after DAC HYP administration), pre-cocktail dose and at 0.5 and 1, 2, 3, 4, 6, 8, 10 , 24, 48, 72 and 96 hours post-probe drug cocktail administration

End point values	TP-DI Substudy			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: ng/mL				
arithmetic mean (standard deviation)				
Midazolam (Period 1); n=20	271.05 (± 106.925)			
MIdazolam+DACHYP (Period 2); n=19	311.21 (± 147.912)			
Caffeine (Period 1); n=20	4965 (± 1312.69)			
Caffeine+DAC HYP (Period 2); n=19	5399.5 (± 1364.05)			
S-Warfarin (Period 1); n=20	635.65 (± 140.291)			
S-Warfarin+DAC HYP (Period 2); n=19	649.74 (± 155.977)			
Omeprazole (Period 1); n=19	776.95 (± 513.344)			
Omeprazole+DAC HYP (Period 2); n=19	771.16 (± 540.331)			

Attachments (see zip file)	Stat Analysis OM12 p1.pdf Stat Analysis OM12 p2.pdf Stat Analysis OM12 p3.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: TP-DI Sub-study: CL/F of Each Probe Drug

End point title	TP-DI Sub-study: CL/F of Each Probe Drug

End point description:

CL/F of each of the following cytochrome P450 (CYP) isoenzyme substrates: midazolam (CYP3A), caffeine (CYP1A2), warfarin + vitamin K (CYP2C9), omeprazole (CYP2C19), and dextromethorphan (CYP2D6)

End point type	Secondary

End point timeframe:

Week 43 (7 days prior to DAC HYP administration) and Week 53 (7 days after DAC HYP administration), pre-cocktail dose and at 0.5 and 1, 2, 3, 4, 6, 8, 10 , 24, 48, 72 and 96 hours post-probe drug cocktail administration

End point values	TP-DI Substudy			
Subject group type	Subject analysis set			
Number of subjects analysed	20			
Units: mL/hr				
arithmetic mean (standard deviation)				
Midazolam (Period 1); n=20	7625.7 (± 3849.92)			
Midazolam+DAC HYP (Period 2); n=19	7298.6 (± 2844.22)			
S-Warfarin (Period 1); n=17	565.86 (± 184.129)			
S-Warfarin+DAC HYP (Period 2); n=18	541.46 (± 150.298)			
Omeprazole (Period 1); n=18	41612.4 (± 30003.48)			
Omeprazole+DAC HYP (Period 2); n=19	41772.4 (± 29810.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: TP-DI Sub-study: Omeprazole/Hydroxyomeprazole Concentration Ratio at 2 hours Post-Omeprazole Dosing

End point title	TP-DI Sub-study: Omeprazole/Hydroxyomeprazole Concentration Ratio at 2 hours Post-Omeprazole Dosing

End point description:

End point type	Secondary

End point timeframe:

Week 43 (7 days prior to DAC HYP administration) and Week 53 (7 days after DAC HYP administration) at 2 hours after probe drug cocktail administration

End point values	TP-DI Substudy			
Subject group type	Subject analysis set			
Number of subjects analysed	17			
Units: ratio				
arithmetic mean (standard deviation)				
Omeprazole (Period 1)	2.673 (± 4.7878)			
Omeprazole+ DAC HYP (Period 2)	1.028 (± 0.9297)			

Attachments (see zip file)	Stat Analysis OM14.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Screening (for serious adverse events) or first dose of study treatment on Day 1 (for adverse events) through the end of treatment (Week 188 +/- 4 days) plus 24 weeks +/- 10 days after last dose.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	DAC HYP 150 mg

Reporting group description:

DAC HYP 150 mg by SC injection using the PFS every 4 weeks for24 weeks followed by a 20-week washout period. After completion of the washout period, participants could resume monthly DAC HYP 150 mg using the PFS for up to 3 additional years. Participants in the TP-DI sub-study received s probe-drug cocktail administration at Weeks 43 and 53. The probe-drug cocktail consisted of midazolam 5 mg, caffeine 200 mg, S-warfarin 10 mg, vitamin K 10 mg, omeprazole 40 mg, and dextromethorphan 30 mg. The oral vitamin K was used to counteract warfarin's anticoagulant effect prophylactically.

Serious adverse events	DAC HYP 150 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	33 / 133 (24.81%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Pregnancy, puerperium and perinatal conditions			
Abortion missed			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Endometrial hypertrophy			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Endometriosis				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ovarian cyst				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Postmenopausal haemorrhage				
subjects affected / exposed	2 / 133 (1.50%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Depression				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Hepatic enzyme increased				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Toxicity to various agents				
subjects affected / exposed	1 / 133 (0.75%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Multiple sclerosis relapse				

subjects affected / exposed	10 / 133 (7.52%)		
occurrences causally related to treatment / all	0 / 15		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Haemolytic anaemia			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Lymphadenopathy			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Cutaneous sarcoidosis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Erythema nodosum			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lumbar spinal stenosis			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Muscular weakness			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Furuncle			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatitis e			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngitis			

subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 133 (1.50%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Streptococcal urinary tract infection			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Obesity			
subjects affected / exposed	1 / 133 (0.75%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	DAC HYP 150 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	106 / 133 (79.70%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	9 / 133 (6.77%)		
occurrences (all)	13		
Nervous system disorders			
Headache			
subjects affected / exposed	21 / 133 (15.79%)		
occurrences (all)	35		
Hypoaesthesia			
subjects affected / exposed	9 / 133 (6.77%)		
occurrences (all)	11		
Migraine			

subjects affected / exposed	7 / 133 (5.26%)		
occurrences (all)	10		
Multiple sclerosis relapse			
subjects affected / exposed	58 / 133 (43.61%)		
occurrences (all)	147		
Muscle spasticity			
subjects affected / exposed	7 / 133 (5.26%)		
occurrences (all)	9		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	8 / 133 (6.02%)		
occurrences (all)	10		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	12 / 133 (9.02%)		
occurrences (all)	21		
Influenza like illness			
subjects affected / exposed	13 / 133 (9.77%)		
occurrences (all)	90		
Pyrexia			
subjects affected / exposed	12 / 133 (9.02%)		
occurrences (all)	13		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 133 (6.77%)		
occurrences (all)	11		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	11 / 133 (8.27%)		
occurrences (all)	13		
Depression			
subjects affected / exposed	9 / 133 (6.77%)		
occurrences (all)	10		
Insomnia			
subjects affected / exposed	9 / 133 (6.77%)		
occurrences (all)	9		

Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	7 / 133 (5.26%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	10 / 133 (7.52%)		
occurrences (all)	10		
Back pain			
subjects affected / exposed	14 / 133 (10.53%)		
occurrences (all)	16		
Muscle spasms			
subjects affected / exposed	7 / 133 (5.26%)		
occurrences (all)	8		
Muscular weakness			
subjects affected / exposed	10 / 133 (7.52%)		
occurrences (all)	12		
Pain in extremity			
subjects affected / exposed	9 / 133 (6.77%)		
occurrences (all)	13		
Spinal pain			
subjects affected / exposed	7 / 133 (5.26%)		
occurrences (all)	8		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	19 / 133 (14.29%)		
occurrences (all)	30		
Influenza			
subjects affected / exposed	8 / 133 (6.02%)		
occurrences (all)	10		
Oral herpes			
subjects affected / exposed	7 / 133 (5.26%)		
occurrences (all)	16		
Pharyngitis			
subjects affected / exposed	15 / 133 (11.28%)		
occurrences (all)	23		

Sinusitis			
subjects affected / exposed	11 / 133 (8.27%)		
occurrences (all)	24		
Upper respiratory tract infection			
subjects affected / exposed	33 / 133 (24.81%)		
occurrences (all)	63		
Urinary tract infection			
subjects affected / exposed	30 / 133 (22.56%)		
occurrences (all)	56		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 June 2011	- The primary reason for this amendment was to increase subject monitoring for laboratory signals related to hepatic function (LFTs to be assessed monthly throughout the treatment period), and to update criteria for temporary suspension and discontinuation of study treatment for subjects who develop elevations in ALT, AST, or total bilirubin. Subjects who permanently discontinued study treatment due to elevated LFTs were to be evaluated for possible toxicological, infectious, immunological, and metabolic causes of liver injury. - Audit C Questionnaire was added to Medical History at Screening Visit. - Wording of "Interim analyses" section was revised to clarify that ongoing data review/analyses of both the main study data and Intensive PK substudy data may be performed.
16 April 2012	- Changes were made to prohibit concomitant treatment with medications that have an established association with hepatotoxicity or cutaneous hypersensitivity reactions. - Changes were made to provide monthly LFT results to the Neurologist prior to administration of study treatment. - Changes were made to provide subjects with the option of an additional 3 years of open-label treatment with DAC HYP. - The sample size was reduced from 150 to 100 subjects. - The upper limit for the age of eligibility was increased from 55 years to 65 years. - The parameters for concomitant IFN-β treatment were revised. - The criteria for subject withdrawal from the study were revised to include subjects who developed a chronic viral infection.
28 September 2012	- A TP-DI substudy as added as part of the 3-year treatment extension. - PD testing was removed at timepoints that were no longer considered informative for characterizing response to DAC HYP. - The timepoints for the tests and assessments listed in Table 1 were revised. In addition, hematology and blood chemistry testing were removed from the Unscheduled Relapse Assessment. These changes were made to minimize subject burden in the study. - The timing for the confirmatory hematology tests for discontinuation of DAC HYP was revised.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported