EU Clinical Trials Register

Clinical trial results:
A Phase 1, Multicenter, Open-Label, Single-Arm, Multiple Dose Study to Evaluate the Pharmacokinetics and Pharmacodynamics of Natalizumab in Pediatric Subjects with Relapsing Remitting Multiple Sclerosis

Summary

EudraCT number	2012-005082-13
Trial protocol	IT
Global end of trial date	24 September 2014

Results information

Result version number	v1 (current)
This version publication date	04 February 2016
First version publication date	04 April 2015

Trial information

Trial identification

Sponsor protocol code	101MS328

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01884935
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Biogen Idec
Sponsor organisation address	225 Binney Street , Cambridge, United States, 02142
Public contact	Biogen Idec Study Medical Director, Biogen Idec, Clinicaltrials@biogenidec.com
Scientific contact	Biogen Idec Study Medical Director, Biogen Idec, Clinicaltrials@biogenidec.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001095-PIP02-12
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	24 September 2014
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 September 2014
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 determine the pharmacokinetic (PK) profile of multiple doses of natalizumab in pediatric subjects with relapsing remitting multiple sclerosis (RRMS).

Protection of trial subjects:

Parents or legal guardians must provide written, informed consent, and subjects may provide written assent (if appropriate), before any screening tests or assessments are performed. Subjects must remain in the clinic for 1 hour after the infusion of study treatment is complete for observation and for collection of samples for PK and pharmacodynamic (PD) analyses (if applicable). Epinephrine for subcutaneous injection, diphenhydramine for intravenous (IV) injection, and any other medications and resuscitation equipment for the emergency management of anaphylactic reactions must be available in the room where the infusions are being performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 July 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 13
Worldwide total number of subjects	13
EEA total number of subjects	13

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)	1
Adolescents (12-17 years)	12
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Subjects were screened for a maximum of 4 weeks prior to first study infusion.

Period 1

Period 1 title	Natalizumab (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Natalizumab

Arm description:

300 mg IV natalizumab every 4 weeks for 16 weeks (a total of 5 doses)

Arm type	Experimental
Investigational medicinal product name	natalizumab
Investigational medicinal product code	BG00002
Other name	Tysabri
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Natalizumab is supplied as a sterile liquid in vials containing 300 mg natalizumab per vial (15 mL of a 20 mg/mL solution). One vial of natalizumab contains a sufficient volume for a single IV infusion following dilution in 100 mL 0.9% sodium chloride for injection.

Number of subjects in period 1	Natalizumab
Started	13
Completed	13

Baseline characteristics

Reporting groups

Reporting group title	Natalizumab

Reporting group description:

300 mg intravenous (IV) natalizumab every 4 weeks for 16 weeks (a total of 5 doses)

Reporting group values	Natalizumab	Total	
Number of subjects	13	13	
Age categorical			
Units: Subjects			
10 to 11 Years	1	1	
12 to 13 Years	1	1	
14 to 15 Years	4	4	
16 Years	5	5	
17 Years	2	2	
Age continuous			
Units: years			
arithmetic mean	15.2		
standard deviation	± 1.77	-	
Gender categorical			
Units: Subjects			
Female	10	10	
Male	3	3	

End points

End points reporting groups

Reporting group title	Natalizumab
Reporting group description:	
300 mg IV natalizumab every 4 weeks for 16 weeks (a total of 5 doses)	
Subject analysis set title	PK Population
Subject analysis set type	Full analysis
Subject analysis set description:	
The PK population is defined as all subjects who received at least 1 dose of natalizumab and have at least 1 post-baseline measurement of natalizumab concentration.	
Subject analysis set title	PD Population
Subject analysis set type	Full analysis
Subject analysis set description:	
The PD population is defined as all subjects who received at least 1 dose of natalizumab and have at least 1 post-baseline measurement of the PD parameter being assessed.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
The Safety population was defined as all subjects who received at least 1 dose of natalizumab and had at least 1 post-baseline assessment of the safety parameter being analyzed.	

Primary: Maximum Plasma Concentration (Cmax)

End point title	Maximum Plasma Concentration (Cmax)[1]
End point description:	
End point type	Primary
End point timeframe:	
Day 1: within 4 hours prior to start of infusion, within 15 minutes after end of infusion; Day 2: 24 hours (±4 hours) after end of infusion; Day 8; Day 15 (±2 days); Day 22 (±2 days); Weeks 4, 8, 12, and 16: within 4 hours prior to start of infusion	

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: Summary statistics for each PK parameter are presented in the data table.

End point values	PK Population			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: µg/mL				
geometric mean (confidence interval 95%)	142.9 (127.9 to 159.6)			

Statistical analyses

No statistical analyses for this end point

Primary: Predose (Trough) Concentrations (Cpredose) From Multiple Dosing

End point title	Predose (Trough) Concentrations (Cpredose) From Multiple Dosing[2]

End point description:

End point type	Primary

End point timeframe:

Day 1: within 4 hours prior to start of infusion, within 15 minutes after end of infusion; Day 2: 24 hours (±4 hours) after end of infusion; Day 8; Day 15 (±2 days); Day 22 (±2 days); Weeks 4, 8, 12, and 16: within 4 hours prior to start of infusion

Notes:

[2] - 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: Summary statistics for each PK parameter are presented in the data table.

End point values	PK Population			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: µg/mL				
geometric mean (confidence interval 95%)				
Week 4	24.8 (16.79 to 36.62)			
Week 8	22.53 (10.34 to 49.12)			
Week 12	26.59 (12.25 to 57.73)			
Week 16	34.04 (20.51 to 56.5)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration Curve From Time of First to Last Dose (AUClast)

End point title	Area Under the Plasma Concentration Curve From Time of First to Last Dose (AUClast)[3]

End point description:

End point type	Primary

End point timeframe:

Day 1: within 4 hours prior to start of infusion, within 15 minutes after end of infusion; Day 2: 24 hours (±4 hours) after end of infusion; Day 8; Day 15 (±2 days); Day 22 (±2 days); Weeks 4, 8, 12, and 16: within 4 hours prior to start of infusion

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: Summary statistics for each PK parameter are presented in the data table.

End point values	PK Population			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: hr*µg/mL				
geometric mean (confidence interval 95%)	47389.4 (40399 to 55589.4)			

Statistical analyses

No statistical analyses for this end point

Primary: Area Under the Plasma Concentration Curve From Time of First Dose to Infinity (AUC0-inf)

End point title	Area Under the Plasma Concentration Curve From Time of First Dose to Infinity (AUC0-inf)[4]
End point description:	

End point type	Primary
End point timeframe:	

Day 1: within 4 hours prior to start of infusion, within 15 minutes after end of infusion; Day 2: 24 hours (±4 hours) after end of infusion; Day 8; Day 15 (±2 days); Day 22 (±2 days); Weeks 4, 8, 12, and 16: within 4 hours prior to start of infusion

Notes:

[4] - 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: Summary statistics for each PK parameter are presented in the data table.

End point values	PK Population			
Subject group type	Subject analysis set			
Number of subjects analysed	9[5]			
Units: hr*µg/mL				
geometric mean (confidence interval 95%)	48970.4 (39912.5 to 60083.8)			

Notes:

[5] - 4 subjects were excluded as their terminal phase could not be adequately characterized.

Statistical analyses

No statistical analyses for this end point

Primary: Time to Maximum Plasma Concentration (Tmax)

End point title	Time to Maximum Plasma Concentration (Tmax)[6]
End point description:	

End point type	Primary
End point timeframe:	

Day 1: within 4 hours prior to start of infusion, within 15 minutes after end of infusion; Day 2: 24 hours (±4 hours) after end of infusion; Day 8; Day 15 (±2 days); Day 22 (±2 days); Weeks 4, 8, 12, and 16: within 4 hours prior to start of infusion

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: Summary statistics for each PK parameter are presented in the data table.

End point values	PK Population			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: hours				
geometric mean (confidence interval 95%)	7.874 (2.996 to 20.692)			

Statistical analyses

No statistical analyses for this end point

Primary: Clearance (Cl)

End point title	Clearance (Cl)[7]

End point description:

End point type	Primary

End point timeframe:

Day 1: within 4 hours prior to start of infusion, within 15 minutes after end of infusion; Day 2: 24 hours (±4 hours) after end of infusion; Day 8; Day 15 (±2 days); Day 22 (±2 days); Weeks 4, 8, 12, and 16: within 4 hours prior to start of infusion

Notes:

[7] - 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: Summary statistics for each PK parameter are presented in the data table.

End point values	PK Population			
Subject group type	Subject analysis set			
Number of subjects analysed	9[8]			
Units: L/week				
geometric mean (confidence interval 95%)	1.029 (0.839 to 1.263)			

Notes:

[8] - 4 subjects were excluded as their terminal phase could not be adequately characterized.

Statistical analyses

No statistical analyses for this end point

Primary: Volume of Distribution

End point title	Volume of Distribution[9]

End point description:

End point type	Primary

End point timeframe:

Day 1: within 4 hours prior to start of infusion, within 15 minutes after end of infusion; Day 2: 24 hours

(±4 hours) after end of infusion; Day 8; Day 15 (±2 days); Day 22 (±2 days); Weeks 4, 8, 12, and 16: within 4 hours prior to start of infusion

Notes:

[9] - 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: Summary statistics for each PK parameter are presented in the data table.

End point values	PK Population			
Subject group type	Subject analysis set			
Number of subjects analysed	9[10]			
Units: Liters				
geometric mean (confidence interval 95%)	1.902 (1.427 to 2.536)			

Notes:

[10] - 4 subjects were excluded as their terminal phase could not be adequately characterized.

Statistical analyses

No statistical analyses for this end point

Primary: Elimination Half-life (t1/2)

End point title	Elimination Half-life (t1/2)[11]

End point description:

End point type	Primary

End point timeframe:

Day 1: within 4 hours prior to start of infusion, within 15 minutes after end of infusion; Day 2: 24 hours (±4 hours) after end of infusion; Day 8; Day 15 (±2 days); Day 22 (±2 days); Weeks 4, 8, 12, and 16: within 4 hours prior to start of infusion

Notes:

[11] - 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: Summary statistics for each PK parameter are presented in the data table.

End point values	PK Population			
Subject group type	Subject analysis set			
Number of subjects analysed	9[12]			
Units: hours				
geometric mean (confidence interval 95%)	215.1 (159.7 to 289.7)			

Notes:

[12] - 4 subjects were excluded as their terminal phase could not be adequately characterized.

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Alpha4 Integrin Saturation Values

End point title	Summary of Alpha4 Integrin Saturation Values

End point description:

End point type	Secondary

End point values	PD Population			
Subject group type	Subject analysis set			
Number of subjects analysed	13[13]			
Units: percent				
geometric mean (confidence interval 95%)				
Baseline; n=13	3.4 (2.6 to 4.4)			
15 Minutes Post-dose; n=12	96 (89.9 to 102.6)			
Day 2; n=13	94.6 (91.5 to 97.7)			
Day 8; n=13	92.7 (91 to 94.4)			
Day 15; n=13	84 (78.8 to 89.5)			
Day 22; n=13	82.6 (76.9 to 88.6)			
Week 4; n=12	77.2 (67.4 to 88.5)			
Week 8; n=12	56.3 (29.9 to 106.1)			
Week 12; n=12	64.8 (38.6 to 108.9)			
Week 16; n=12	79.5 (71.2 to 88.7)			

Notes:

[13] - n=subjects with an assessment at given time point.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Summary of Adverse Events (AEs)

End point title	Overall Summary of Adverse Events (AEs)

End point description:

An AE is any untoward medical occurrence in a subject administered study drug and that does not necessarily have a causal relationship with this treatment. A serious AE is any untoward medical occurrence that at any dose: results in death; in the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability or incapacity; results in a congenital anomaly or birth defect; any other medically important event that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. AEs were categorized as related or not related to study drug; severity was categorized as mild, moderate, or severe.

End point type	Secondary

End point timeframe:

From first infusion of study treatment through Week 16 (or 12 [±2] weeks after the last infusion)

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: subjects				
Any AE	10			
Moderate or Severe AE	2			
Severe AE	0			
Related AE	3			
Serious AE	1			
Related Serious AE	0			
Discontinuations Due to an AE	0			
Withdrawals From Study Due to an AE	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Infusion Reactions and Acute Infusion-related Hypersensitivity Reactions

End point title	Number of Infusion Reactions and Acute Infusion-related Hypersensitivity Reactions

End point description:

Infusion reactions were defined as those AEs occurring within 2 hours after the start of natalizumab infusion. If the start time of an AE or infusion was missing, but the AE occurred on the same day as the infusion, it was to be assumed to be an infusion reaction.
Acute infusion-related hypersensitivity reactions were defined as hypersensitivity reactions that occurred within 2 hours after the start of natalizumab infusion with preferred terms of: hypersensitivity not otherwise specified (NOS), anaphylactic reaction, anaphylactoid reaction, dermatitis allergic, drug hypersensitivity, urticaria NOS, vasoconstriction, urticaria generalized, and erythema multiforme.

End point type	Secondary

End point timeframe:

From first infusion of study treatment through Week 16 (or 12 [±2] weeks after the last infusion)

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	13[14]			
Units: reactions				
Infusion Reactions	2			
Acute Infusion-related Hypersensitivity Reactions	0			

Notes:

[14] - number of subjects with a reaction=1

Statistical analyses

No statistical analyses for this end point

Secondary: Anti-natalizumab Antibody Summary

End point title	Anti-natalizumab Antibody Summary

End point description:

Number of subjects with positive and negative anti-natalizumab antibody tests at Day 1 and Week 16.

End point type	Secondary

End point timeframe:

Day 1 through Week 16

End point values	Safety Population			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: subjects				
Day 1: Positive	0			
Day 1: Negative	13			
Week 16: Positive	0			
Week 16: Negative	13			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first infusion of study treatment through Week 16 (or 12 [±2] weeks after the last infusion)

Adverse event reporting additional description:

Overall summary for treatment-emergent adverse events (TEAEs) is presented. A TEAE was defined as any AE that had onset on or after the first infusion of study treatment, or any pre-existing condition that had worsened after the first infusion of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Natalizumab

Reporting group description:

300 mg IV natalizumab every 4 weeks for 16 weeks (a total of 5 doses)

Serious adverse events	Natalizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 13 (7.69%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 13 (7.69%)		
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	Natalizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 13 (76.92%)		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Cardiac disorders			

Extrasystoles			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 13 (23.08%)		
occurrences (all)	3		
Dizziness			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Psychomotor hyperactivity			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Tension			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Infections and infestations			
Influenza			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Bronchitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 March 2013	• Included a more restrictive criterion regarding eligibility for treatment with natalizumab in accordance with the clinical requirements, as outlined in the Italian Tysabri Registry. • Clarified that all blood samples and magnetic resonance imaging scans collected from the subjects are to be stored for 15 years and destroyed thereafter. • Clarified that, although the 24-hour sampling period was expected to provide the Cmax and Tmax data for most if not all of the study subjects, the assessments of Cmax and Tmax included samples from the entire sampling schedule as specified in the Schedule of Events. The Cmax and Tmax values presented are representative of the entire sampling schedule and not just of the 24 hour sampling period. • Removed the measurement of serum concentration of soluble vascular adhesion molecule 1 (sVCAM-1). Soluble VCAM-1 was found to be suppressed after administration of natalizumab and was thought to provide an alternative measurement to α4 integrin saturation. However, a consistent relationship between sVCAM-1 serum concentration and α4 integrin saturation could not be established. Therefore, PD assessments in this study were limited to well understood markers of natalizumab therapy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported