Clinical trial results:
A phase II, randomized, open-label, multi-centre study of weekly APG101 + reirradiation versus reirradiation in the treatment of patients with first or second progression of glioblastoma

Summary

EudraCT number	2009-013421-42
Trial protocol	DE AT
Global end of trial date	09 October 2014

Results information

Result version number	v1 (current)
This version publication date	13 August 2016
First version publication date	13 August 2016
Summary attachment (see zip file)	Synopse CSR APG101_CD_002 (Synopse CSR Final.pdf)

Trial information

Trial identification

Sponsor protocol code	APG101_CD_002

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01071837
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Apogenix AG
Sponsor organisation address	Im Neuenheimer Feld 584, Heidelberg, Germany,
Public contact	Dr. Claudia Kunz, Apogenix AG, +49 62215860824, claudia.kunz@apogenix.com
Scientific contact	Dr. Claudia Kunz, Apogenix AG, +49 62215860824, claudia.kunz@apogenix.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	30 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 October 2014
Global end of trial reached?	Yes
Global end of trial date	09 October 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

6 months rate of progression free survival (PFS6)

Protection of trial subjects:

Medication that is considered necessary for the patients' safety and well-being may be given at the discretion of the Investigator(s).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 December 2009
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	Austria: 15
Country: Number of subjects enrolled	Germany: 58
Country: Number of subjects enrolled	Russian Federation: 18
Worldwide total number of subjects	91
EEA total number of subjects	73

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)	69
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Overall, 91 patients were allocated randomly to one of the two treatment groups (APG101 + RT or RT alone) in 26 active trial centres in three countries. Recruitment period: December 2009 to September 2011

Pre-assignment

Screening details:

Patients with a recurrence/progression of glioblastoma (first or second progression) either not being eligible for tumour resection or having macroscopic residual tumour after resection of the recurrence can be included (tumor size must 1-4 cm in T1-weighted MRI). They will be randomized to RT or RT + APG101.

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Re-Irradiation

Arm description:

33% of the patients will be randomized to reirradiation (RT) alone. They will receive 36 Gy (2 Gy per fraction)

Arm type	Re-Irradiation

No investigational medicinal product assigned in this arm

Arm title	Re-Irradiation + APG101

Arm description:

66% of the patients will be randomized to reirradiation (RT) + 400 mg APG101 weekly. They will receive 36 Gy (2 Gy per fraction) and 400 mg APG101 weekly as an intravenous infusion

Arm type	Experimental
Investigational medicinal product name	APG101
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

APG101 was administered as a 30-minute i.v. infusion in a volume of 200 to 290 ml (depending on the size/volume of the NaCl infusion bag to which the total amount of 400 mg APG101 was added). It was administered to the patient before RT.

Number of subjects in period 1	Re-Irradiation	Re-Irradiation + APG101
Started	30	61
Completed	26	58
Not completed	4	3
Consent withdrawn by subject	4	2
Physician decision	-	1

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	91	91	
Age categorical Units: Subjects			
In utero		0	
Preterm newborn infants (gestational age < 37 wks)		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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	57		
full range (min-max)	20 to 79	-	
Gender categorical Units: Subjects			
Female	36	36	
Male	55	55	

End points

End points reporting groups

Reporting group title	Re-Irradiation
Reporting group description:	
33% of the patients will be randomized to reirradiation (RT) alone. They will receive 36 Gy (2 Gy per fraction)	
Reporting group title	Re-Irradiation + APG101
Reporting group description:	
66% of the patients will be randomized to reirradiation (RT) + 400 mg APG101 weekly. They will receive 36 Gy (2 Gy per fraction) and 400 mg APG101 weekly as an intravenous infusion	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
From a total of 91 patients, seven patients (7.7%) received no study treatment because of withdrawal of consent, ineligibility and sponsor decision. Thus, the safety set and the FAS consisted of 84 patients.	

Primary: Efficacy Endpoint (PFS6)

End point title	Efficacy Endpoint (PFS6)
End point description:	
End point type	Primary
End point timeframe:	
Progression-free survival was defined from the day of randomisation to the day of local tumour progression or recurrence, based on the central assessment of MRI or the day of death from any cause.	

End point values	Re-Irradiation	Re-Irradiation + APG101		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	58		
Units: Percent	4	21		

Statistical analyses

Statistical analysis title	Two Stage Simon Design
Comparison groups	Re-Irradiation + APG101 v Re-Irradiation
Number of subjects included in analysis	84
Analysis specification	Pre-specified
Analysis type	other
P-value	≤ 15
Method	Two Stage Simon Design

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Assessed throughout the study	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	12

Reporting groups	
Reporting group title	Re-Irradiation + APG101
Reporting group description: -	
Reporting group title	Re-Irradiation
Reporting group description: -	

Serious adverse events	Re-Irradiation + APG101	Re-Irradiation	
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 58 (24.14%)	8 / 26 (30.77%)	
number of deaths (all causes)	53	25	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 58 (1.72%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	1 / 58 (1.72%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			
subjects affected / exposed	1 / 58 (1.72%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 58 (1.72%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			
subjects affected / exposed	1 / 58 (1.72%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Impaired healing			
subjects affected / exposed	1 / 58 (1.72%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	1 / 58 (1.72%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	1 / 58 (1.72%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 58 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 58 (1.72%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Troponin increased			

subjects affected / exposed	1 / 58 (1.72%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 58 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	0 / 58 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 58 (1.72%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Grand mal convulsion			
subjects affected / exposed	1 / 58 (1.72%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 58 (0.00%)	2 / 26 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsions local			
subjects affected / exposed	0 / 58 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	1 / 58 (1.72%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Dizziness			
subjects affected / exposed	1 / 58 (1.72%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	2 / 58 (3.45%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 58 (1.72%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 58 (1.72%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial seizures			
subjects affected / exposed	1 / 58 (1.72%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Anorectal varices haemorrhage			
subjects affected / exposed	0 / 58 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 58 (1.72%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	1 / 58 (1.72%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	0 / 58 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Calculus urinary			
subjects affected / exposed	1 / 58 (1.72%)	0 / 26 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 58 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 58 (0.00%)	1 / 26 (3.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Re-Irradiation + APG101	Re-Irradiation	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	58 / 58 (100.00%)	25 / 26 (96.15%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 58 (6.90%)	2 / 26 (7.69%)	
occurrences (all)	6	2	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 58 (5.17%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Disease progression			

subjects affected / exposed	6 / 58 (10.34%)	5 / 26 (19.23%)	
occurrences (all)	6	5	
Fatigue			
subjects affected / exposed	15 / 58 (25.86%)	6 / 26 (23.08%)	
occurrences (all)	20	6	
General physical health deterioration			
subjects affected / exposed	6 / 58 (10.34%)	4 / 26 (15.38%)	
occurrences (all)	8	7	
Oedema			
subjects affected / exposed	0 / 58 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	3	
Oedema peripheral			
subjects affected / exposed	6 / 58 (10.34%)	0 / 26 (0.00%)	
occurrences (all)	6	0	
Pyrexia			
subjects affected / exposed	3 / 58 (5.17%)	0 / 26 (0.00%)	
occurrences (all)	6	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 58 (5.17%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Dysphonia			
subjects affected / exposed	3 / 58 (5.17%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 58 (5.17%)	2 / 26 (7.69%)	
occurrences (all)	3	3	
Depression			
subjects affected / exposed	6 / 58 (10.34%)	3 / 26 (11.54%)	
occurrences (all)	6	3	
Sleep disorder			
subjects affected / exposed	5 / 58 (8.62%)	2 / 26 (7.69%)	
occurrences (all)	8	2	
Investigations			

Blood creatine phosphokinase increased			
subjects affected / exposed	3 / 58 (5.17%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
C-reactive protein increased			
subjects affected / exposed	4 / 58 (6.90%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Karnofsky scale worsened			
subjects affected / exposed	7 / 58 (12.07%)	3 / 26 (11.54%)	
occurrences (all)	13	4	
Nervous system disorders			
Epilepsy			
subjects affected / exposed	4 / 58 (6.90%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Apraxia			
subjects affected / exposed	0 / 58 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	3	
Brain oedema			
subjects affected / exposed	9 / 58 (15.52%)	7 / 26 (26.92%)	
occurrences (all)	10	11	
Cognitive disorder			
subjects affected / exposed	9 / 58 (15.52%)	3 / 26 (11.54%)	
occurrences (all)	13	4	
Convulsions local			
subjects affected / exposed	10 / 58 (17.24%)	5 / 26 (19.23%)	
occurrences (all)	25	6	
Coordination abnormal			
subjects affected / exposed	11 / 58 (18.97%)	3 / 26 (11.54%)	
occurrences (all)	15	5	
Depressed level of consciousness			
subjects affected / exposed	3 / 58 (5.17%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Disturbance in attention			
subjects affected / exposed	4 / 58 (6.90%)	0 / 26 (0.00%)	
occurrences (all)	5	0	
Dizziness			

subjects affected / exposed	7 / 58 (12.07%)	2 / 26 (7.69%)	
occurrences (all)	7	2	
Facial paresis			
subjects affected / exposed	4 / 58 (6.90%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Headache			
subjects affected / exposed	27 / 58 (46.55%)	8 / 26 (30.77%)	
occurrences (all)	70	12	
Hemiparesis			
subjects affected / exposed	10 / 58 (17.24%)	6 / 26 (23.08%)	
occurrences (all)	17	6	
Hypoaesthesia			
subjects affected / exposed	8 / 58 (13.79%)	4 / 26 (15.38%)	
occurrences (all)	15	4	
Motor dysfunction			
subjects affected / exposed	7 / 58 (12.07%)	2 / 26 (7.69%)	
occurrences (all)	7	2	
Neurological decompensation			
subjects affected / exposed	6 / 58 (10.34%)	7 / 26 (26.92%)	
occurrences (all)	6	9	
Partial seizures			
subjects affected / exposed	11 / 58 (18.97%)	2 / 26 (7.69%)	
occurrences (all)	25	6	
Sensory disturbance			
subjects affected / exposed	0 / 58 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Syncope			
subjects affected / exposed	3 / 58 (5.17%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Dysphasia			
subjects affected / exposed	4 / 58 (6.90%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	6 / 58 (10.34%)	0 / 26 (0.00%)	
occurrences (all)	6	0	

Lymphopenia			
subjects affected / exposed	3 / 58 (5.17%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Neutropenia			
subjects affected / exposed	3 / 58 (5.17%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Thrombocytopenia			
subjects affected / exposed	6 / 58 (10.34%)	0 / 26 (0.00%)	
occurrences (all)	7	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	5 / 58 (8.62%)	0 / 26 (0.00%)	
occurrences (all)	5	0	
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	0 / 58 (0.00%)	3 / 26 (11.54%)	
occurrences (all)	0	3	
Visual impairment			
subjects affected / exposed	5 / 58 (8.62%)	0 / 26 (0.00%)	
occurrences (all)	9	0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 58 (6.90%)	2 / 26 (7.69%)	
occurrences (all)	5	3	
Diarrhoea			
subjects affected / exposed	4 / 58 (6.90%)	2 / 26 (7.69%)	
occurrences (all)	6	3	
Nausea			
subjects affected / exposed	11 / 58 (18.97%)	3 / 26 (11.54%)	
occurrences (all)	16	3	
Vomiting			
subjects affected / exposed	9 / 58 (15.52%)	1 / 26 (3.85%)	
occurrences (all)	9	1	
Abdominal pain upper			
subjects affected / exposed	4 / 58 (6.90%)	0 / 26 (0.00%)	
occurrences (all)	10	0	
Skin and subcutaneous tissue disorders			

Alopecia			
subjects affected / exposed	4 / 58 (6.90%)	2 / 26 (7.69%)	
occurrences (all)	4	2	
Rash			
subjects affected / exposed	4 / 58 (6.90%)	0 / 26 (0.00%)	
occurrences (all)	6	0	
Renal and urinary disorders			
Incontinence			
subjects affected / exposed	3 / 58 (5.17%)	0 / 26 (0.00%)	
occurrences (all)	4	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 58 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	3	
Muscle spasms			
subjects affected / exposed	6 / 58 (10.34%)	0 / 26 (0.00%)	
occurrences (all)	7	0	
Muscular weakness			
subjects affected / exposed	7 / 58 (12.07%)	0 / 26 (0.00%)	
occurrences (all)	10	0	
Pain in extremity			
subjects affected / exposed	8 / 58 (13.79%)	0 / 26 (0.00%)	
occurrences (all)	12	0	
Infections and infestations			
Herpes zoster			
subjects affected / exposed	0 / 58 (0.00%)	2 / 26 (7.69%)	
occurrences (all)	0	2	
Influenza			
subjects affected / exposed	3 / 58 (5.17%)	0 / 26 (0.00%)	
occurrences (all)	3	0	
Nasopharyngitis			
subjects affected / exposed	6 / 58 (10.34%)	0 / 26 (0.00%)	
occurrences (all)	9	0	
Oral candidiasis			
subjects affected / exposed	3 / 58 (5.17%)	0 / 26 (0.00%)	
occurrences (all)	3	0	

Pneumonia subjects affected / exposed occurrences (all)	0 / 58 (0.00%) 0	2 / 26 (7.69%) 2	
Urinary tract infection subjects affected / exposed occurrences (all)	6 / 58 (10.34%) 6	2 / 26 (7.69%) 2	
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	3 / 58 (5.17%) 3	0 / 26 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported