Apogenix GmbH

ADDENDUM TO INTEGRATED CLINICAL AND STATISTICAL REPORT

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

PRODUCT NAME/NUMBER: APG101

INDICATION: Glioblastoma at first or second progression

STUDY PROTOCOL NUMBER: APG101_CD_002

ADDENDUM REPORT NUMBER: Final Version 1.0

PHASE: Phase II

Date first patient entered:	07 December 2009
Last patient completed:	05 September 2014
Coordinating Investigator:	Prof. Dr. med. Wolfgang Wick Department of Neurooncology, University Clinic Heidelberg Im Neuenheimer Feld 400 69120 Heidelberg, Germany
Name of Sponsor signatory:	PD Dr. med. Harald Fricke Chief Operating Officer/Chief Medical Officer Apogenix GmbH Im Neuenheimer Feld 584 69120 Heidelberg, Germany
Date of this addendum report:	30 July 2015 (Final Version 1.0)
Date of any previous reports:	11 July 2014

This study was performed in compliance with Good Clinical Practices (GCP) and applicable regulatory requirements, including the archiving of essential documents.

2. SYNOPSIS

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Title of study:	A phase II, randomised, open-label, multi-centre study of weekly APG101 + reirradiation versus reirradiation in the treatment of patients with first or second progression of glioblastoma
Investigators:	Prof. Dr. Wolfgang Wick, Heidelberg (Coordinating Investigator) Germany: Prof. Dr. Kirsten Schmieder, (left on 01 September 2012), Successor: Stefanie Brehmer, Mannheim; Dr. Reinhard Wurm, Frankfurt/Oder; Dr. Christian Weiß, Frankfurt/Main; PD Dr. Oliver Heese (left on 01 June 2011), Successor: Dr. Tobias Martens, Hamburg; Prof. Dr. Thomas Wiegel, Ulm; Prof. Dr. Uwe Schlegel, Bochum; Prof. Dr. Rolf Dieter Kortmann, Leipzig; Prof. Dr. Ulrich Herrlinger, Bonn; Prof. Dr. Claus Belka, München; Dr. Minou Nadji-Ohl, Stuttgart; Dr. Sven Klimpe (left on 31 December 2010), Successor: Dr. Bao Khang Nguyen Huu (left on 01.04.2011), Successor: Dr. Thomas Vogt, Mainz; PD Dr. Peter Hau, Regensburg; Prof. Dr. Christianto Lumenta, München; Dr. Christoph Beier, Aachen; Dr. Sabrina Astner, München; Austria: Prof. Dr. Christine Marosi, Wien; Dr. Stefan Oberndorfer (left on 30 September 2011), Successor: Prof. Dr. Wolfgang Grisold, Wien; Prof. Dr. Franz Payer, Graz; Dr. Josef Pichler, Linz; Prof. Dr. Günther Stockhammer, Innsbruck; Russia: Dr. Grigoriy Kobyakov, Moscow; Prof. Sergey Tkachev, Moscow; Prof. Michail Kopp, Samara; Prof. Viktor Kosenok, Omsk; Prof. Svistov, St. Petersburg;
Study centre(s):	The study was conducted in 26 active centres in Germany (16 centres), Austria (five centres) and Russia (five centres).
Publication (reference):	Wick W, Fricke H, Junge K, Kobyakov G, Martens T, Heese O, Wiestler B, Schliesser MG, von Deimling A, Pichler J, Vetlova E, Harting I, Debus J, Hartmann C, Kunz C, Platten M, Bendszus M, Combs SE. A Phase II, Randomized, Study of Weekly APG101+Reirradiation versus Reirradiation in Progressive Glioblastoma. Clin Cancer Res 2014 20:24: 6304-6313.[1].
Studied period (years):	Date of first enrolment: 07 December 2009 Date of last Follow Up: 05 September 2014 Date of database closure: 19 May 2015
Phase of development:	Phase II
Objectives:	
Primary:	The primary objective of the study was the determination of the number of patients with progression-free survival after six months (PFS6).
Secondary:	The secondary objectives of the study were the determination of - Safety and tolerability of APG101 - Progression-free survival - Objective response rates - Duration of response in responders - Overall survival - Quality of life as determined by EORTC QLQ-C15 PAL and the EORTC brain module QLQ-BN20. - Cognitive function determined by Mini Mental State Examination
Methodology:	This study was a phase II, randomised, open-label, multi-centre study of reirradiation with or without APG101 in patients with first or second progression of glioblastoma. Eligible patients were randomly assigned to APG101 + radiotherapy (RT) or RT alone in a 2:1 allocation ratio. All patients received radio therapy (one cycle) from baseline visit (Day 0) to Day 17 (18 treatment days). Only patients randomised to APG101 + RT received additionally 400 mg APG101 weekly by i.v. administration beginning with the baseline visit (Day 0). Patients were observed (if randomised to the single treatment arm) or received APG101 until disease progression, death or withdrawal from the study, i.e., patients continued in the study as long as sustained clinical benefit was considered by the treating physician.

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	A pharmacokinetic (PK) analysis was performed only for patients receiving APG101. For the first four male and the first four female patients randomised to APG101, PK blood samples were taken at certain fixed times before and after dosing of every infusion. For these eight patients, an additional sample was taken once every day during the radiotherapy. For all other patients receiving APG101, two PK samples were taken every time on the day of dosing, the first sample randomly before dosing and a second sample at any time (randomly) after dosing. For all patients receiving APG101, a PK sample was drawn at the 28- and the 90-day follow-up visits. For pharmacodynamic (PD) assessments, a fluorescent-activated cell sorting (FACS) analysis was performed for patients at selected sites. An analysis for lymphocyte subpopulations and activation markers was performed every six weeks after the end of RT. Additionally, a test to detect antidrug antibodies (ADAs) was performed. Only samples from patients receiving APG101 were analysed. If ADAs to APG101 were detected in individual patients, quarterly follow-up visits were performed until no ADAs were detectable. Only patients randomised to the combination of APG101 + RT attended the weekly visits during the study and completed all scheduled examinations. The patients receiving radiotherapy as a single treatment modality attended only the 6-weekly visits and completed all scheduled examinations of these visits. If the investigator assessed a disease progression (not a pseudoprogression) which was confirmed by the central review board, the patient was required to attend an end-of-study visit and to complete all scheduled assessments. A first follow-up visit had to occur 28 days after a patient had been discontinued and a second follow-up visit had to occur 90 days after a patient had been discontinued. If the patient was unable to attend this visit, a follow-up telephone call had to occur. All patients were subsequently contacted by telephone every eight weeks until death and survival information was collected. The screening and baseline visit as well as the end-of-study, early withdrawal, 28-day follow-up and 90-day follow-up visits and the 8-weekly follow-up telephone calls were mandatory for all patients in the study. Optional follow-up visits could be scheduled on a case-by-case basis for adverse events or other reasons (e.g., relevant safety parameters which had not normalised at the end-of-study visit) until any issue was resolved. A PK blood sample was taken in these cases. To further evaluate the safety of APG101 combined with radiotherapy, the study started with a cohort of nine patients (six patients on APG101 + RT; three patients receiving RT only) to avoid unexpected toxicity. Two weeks after the last of these nine patients completed the reirradiation, an interim safety analysis was performed. Recruitment was not stopped until the DSMB meeting took place. Thereafter, additional patients would have only been included if the DSMB decided to proceed after reviewing the data from this analysis.
Number of patients (planned and analysed):	Planned: 83 Enrolled: 91 Randomised: 91 Drop-outs (before treatment): 7 Treated: 84 Withdrawn: 17 Deaths: 77 Analysed (safety + efficacy): 84
Diagnosis and main criteria for inclusion:	The patients were male or female aged at least 18 years with first or second relapse/progression of glioblastoma who were either not eligible for tumour resection or who had macroscopic residual tumour after resection of the recurrence. The diagnosis of glioblastoma had to be proven histologically and progress had to be documented by magnetic resonance imaging. The patients could have had no more than two prior therapy regimens including one or two resections, one or two chemotherapies of which one had to be temozolomide-containing. All patients had to have one previous radiotherapy of the primary tumour with a maximal dose of 60 Gy administered at least eight months before the end of preirradiation and had to be a candidate for reirradiation with recurrent tumour visible on MRI-T1 (Gd) and with the largest diameter measuring 1 to 4 cm. They had to have a Karnofsky Performance Index of ≥ 60%.
Test products, dose and mode of administration, batch number:	Formulation: APG101 is a clear colourless solution of approximately 10 mg/ml in vials of 5 ml total volume each. Batch no.: The following eight batches were used: 080415-06; 080611-07; 090526-10; 090514-09; 090716-11; 100309-12; 100310-13; F10176

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	Mode of Administration: Patients received 400 mg APG101 once weekly as intravenous administration over 30 minutes beginning with the baseline visit (Day 0). They received treatment until disease progression, death or withdrawal from the study.
Duration of treatment:	Patients were observed (if randomised to the single treatment arm) or received APG101 until disease progression, death or withdrawal from the study.
Reference therapy, dose and mode of administration:	Not applicable.
Baseline therapy	Radiotherapy was considered the standard of care and not a study procedure and is therefore not described in detail. A dummy run was required at by each site. It was carried out with a total dose of 36 Gy, 2 Gy/d, on consecutive working days, 5/week, without interruptions of more than four days from Day 0 to Day 17 (18 treatment days).
Criteria for evaluation:	
- Efficacy:	The efficacy criteria to evaluated the primary and secondary objectives were: - Magnetic resonance image (MRI) - Neurological status - Steroid use - Mini-mental state examination - EORTC Quality of Life Questionnaire (QLQ-C15 PAL) and brain module (QLQ-BN20) Another efficacy criterion was the assessment of the Karnofsky Performance Index (KPI).
- Safety:	The safety criteria were the safety and tolerability of APG101 measured in terms of adverse events, clinical laboratory evaluations (haematology, biochemistry, coagulation and urinalysis), vital signs, electrocardiograms, neurological examinations and abdominal ultrasounds.
- Other	Other criteria: - Recurrence pattern - Antidrug antibody assessments were performed for selected subgroups - Pharmacodynamic assessments - Pharmacokinetic assessments These investigations are not the scope of this clinical study report and will be reported separately.
Statistical methods:	Descriptive summaries were provided where appropriate for each of the primary and secondary variables. Continuous quantitative variable summaries included the number of patients (with non-missing values), mean, standard deviation, median, minimum and maximum and first and third quartile. Categorical qualitative variable summaries included the frequency and percentage of patients who were in the particular category. Time course was described by sample statistics by treatment and visit based on the planned visit structure until the number of evaluable values by visit dropped below six. Missing values were not replaced except for quality of life summary scores.
	Analysis of Efficacy: The primary analysis was performed on the full analysis set and contained the second step of the two-stage design of Simon that tested the hypotheses H_0: $p \leq 15\%$ versus H_1: $p \geq 30\%$, where p is the rate of confirmed PFS at six months in treatment group APG101 + RT. If among the required $n_2 = 36$ patients in the APG101 + reirradiation group there are less than 13 responders overall, H_0 is not rejected. If there are 13 or more responders overall, H_0 is rejected in favour of H_1.

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	In addition, exact 95% confidence intervals were calculated for the rates within treatment groups and asymptotic 95% confidence intervals were presented for the difference of rates between treatment groups. In a secondary efficacy analysis, progression-free survival and overall survival were analysed by using the Kaplan-Meier analysis and a Cox regression model (both with a 95% confidence interval). Sample statistics by treatment group and visit were presented for all other secondary endpoints. All explorative analyses were performed for the full analysis set and the per protocol population. The analysis of safety assessments included summaries of occurrences of treatment-emergent adverse events, clinical laboratory evaluations, vital sign values, electrocardiogram assessments, neurological examinations and abdominal ultrasound examinations. All safety assessments were presented for the Safety Population.
SUMMARY OF RESULTS	
EFFICACY RESULTS:	The results for the primary efficacy parameter, the rate of patients with PFS after six months determined by site and central response assessment were similar. In the APG101 + RT group, PFS6 was determined by central response assessment for 12 patients (20.7%) compared with a PFS6 determined by the site response assessment for 11 patients (19.0%). In the RT group PFS6 was observed for one patient (3.8%) determined by central and site assessment. With 12 patients in the APG101 + RT group achieving PFS6, the decision criterion of Stage 2 of the Simon design was not met. Hence, the null hypothesis could not be rejected. However, the number of patients with PFS6 is remarkably higher in the APG101 + RT group than in the RT group (95% CI of 4.1 to 29 regarding the treatment difference). Patients with a maximum tumour diameter $\leq$ 2.5 cm showed a higher PFS6 rate as compared with patients with a maximum tumour diameter > 2.5 cm when receiving APG101 + RT (27.6% vs. 13.8%, respectively). Also an increased rate of patients with PFS6 was observed in the APG101 + RT group with increasing numbers of previous relapses: 17.1% with one previous relapse (included with the first relapse in the trial), 26.7% with two previous relapses (included with the second relapse in the trial) and 50% when included with three previous relapses (included mistakenly with the third relapse in the trial). A total of three patients had three relapses (two patients in the APG101 + RT group and one patient in the RT group). Patients in the APG101 + RT group had a longer PFS time compared with the RT group indicated by all quartiles independent from kind of response assessment (central/site). The median value determined by central (site) response assessment was 138 days (77 days) in the APG101 + RT group compared with 76 days (76 days) in the RT group. Strong treatment effects on PFS in favour of the APG101 + RT group were shown by the results of the first Cox regression analysis including a maximum tumour diameter with a hazard ratio of 0.49 ($p = 0.0162$) and in the second analysis including the impact of histological features (MIB 1 proliferation rate, GFAP-positive tumour cells and CD95 and CD95L status) with a hazard ratio of 0.52 ($p = 0.0403$). Also, a favourable effect of moderate and high CD95L status ($p = 0.0217$) with a hazard ratio of 0.96 was observed. Although the results were not statistically significant, a small size of the tumour tended to be associated with an increased PFS ($p = 0.0744$, hazard ratio = 0.61). Overall survival was analysed taking into account data collected until the study cut off. The median OS values were similar, with 355 days in the APG101 + RT group and 363 days in the RT group. In the APG101 + RT group, 75% of the patients experienced an OS of more than 218 days and less than 648 days compared with more than 185 days and less than 538 days for 75% of the patients in the RT group. In the Cox regression analysis including the maximum tumour diameter, a small tumour size was shown to have a strong effect on OS ($p = 0.0043$) with a hazard ratio of 0.50. Although not statistically significant, the treatment with APG101 + RT tended to be associated with a longer OS ($p = 0.0725$, hazard ratio = 0.63). Regarding the objective response rate as defined according the modified MacDonald response criteria until database closure, it was shown that three patients in the APG101 + RT group showed a partial response after 73 to 115 days (week 11 to week 17) since randomisation with a maximum duration of maximal 12 to 21 weeks.

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A remarkable higher rate of patients was assessed as having stable disease (defined as PFS of more than 90 days) in the APG101 + RT treatment group (32 patients (55.2%)) compared with the RT group (seven patients (26.9%)). On the basis of the comparison of the group of patients having small tumour sizes (≤ 2.5 cm) with the group of patient with larger sizes (> 2.5cm) with regard to stable disease, small tumour sizes seem to have a favourable effect on stable disease. When receiving APG101 + RT, 62.1% of the patients with a maximal tumour diameter ≤ 2.5 cm and 48.3% of the patients with a maximal tumour diameter > 2.5 cm were assessed with stable disease. In the RT group, 30% of the patients with a maximal tumour diameter ≤ 2.5 cm and 16.7% of the patients with a maximal tumour diameter > 2.5 cm were assessed as having stable disease.

Regarding MMSE, similarly small decreases in mean values were observed in both treatment groups with a 95% CI for the treatment differences of -3.5 to 2.6. For the last value available during the clinical part of the trial (EOS visit or last value available before EOS), most patients showed a total score of at least 25, corresponding to the absence of symptoms of dementia with a similar rate of patients in both treatment groups (42 patients (76.4%) in the APG101 + RT group; 16 patients (76.2%) in the RT group).

With respect to the European Organisation for Research and Treatment of Cancer questionnaires (QLQ-C15 and QLQ-BN20) regarding the primary scales for the assessment of quality of life (overall quality of life, physical functioning, fatigue and QLQ-BN20), the comparison of the data of the last value available during the clinical part of the trial (EOS visit or last value available before EOS) with the screening visit revealed nearly no changes or only a slight worsening in all categories. In the APG101 + RT group, nearly no changes (-10 to 10) were most frequently observed in the categories 'physical functioning' (30 patients (56.6%)) and QLQ-BN20 (36 patients (67.9%)). The rate of patients with nearly no changes or a worsening (changes of ≤ -10) is similar for the category 'overall quality of life' (16 patients (32.0%) with nearly no changes and 19 patients (38.0%) with a worsening). Only for the parameter 'fatigue', a worsening (changes of ≥ 10) was most frequently observed (20 patients (40.0%)).

In the RT group, a worsening was most frequently observed in the categories 'overall quality of life' (change of ≤ -10) (14 patients (66.7%)), 'physical functioning' (change of ≤ -10) (15 patients (68.2%)) and 'fatigue' (change of ≥ 10) (nine patients (42.9%)). Only for the QLQ-BN20 for most patients nearly no changes (-10 to 10) (12 patients (54.5%)) were reported. The 95% confidence intervals showed no remarkable differences for patients showing improvement between both treatment groups for all assessed primary scales.

Regarding the secondary scales of the EORTC questionnaire QLQ-C15 in terms of emotional functioning, nausea/vomiting, pain, dyspnoea, insomnia, appetite loss and constipation, only slight changes in the mean values and no changes or also slight changes in the median scores were observed in both treatment groups comparing the screening visit (considered as baseline) with the last value available during the clinical part of the trial (EOS visit or last value available before EOS). A median change from 33.33 to 0.0 (corresponding to an improvement of judgement from 'a little' to no symptoms) for the symptom of insomnia was observed in the APG101 + RT group. For emotional functioning, a median change from 83.33 to 66.67 (corresponding to a worsening of symptoms) was observed in the APG101 + RT group. In the RT group more considerable changes were observed for the symptom of pain, in which a median change from 16.67 to 0.0 (corresponding to an improvement of judgement from 'a little' to no symptoms) occurred. With regard to constipation, an increase of the median value from 0.00 to 16.67 in the RT group was shown (corresponding to a worsening of symptoms). However, because of to the high variability based on high standard deviation values for each parameter, no major conclusions can be drawn.

With respect to the KPI for the last value available during the clinical part of the trial (EOS visit or last value available before EOS), the mean change from baseline value was higher in the RT group (-15.4%) compared with the APG101 + RT group (-9.1%) with a 95% CI for the treatment differences of 1.78 to 14.33. For the last value available, the mean and median values in both treatment groups were between 70% and 80% and represented a range between performing normal activity with effort (including some signs or symptoms of disease) and being able to care for oneself but being unable to carry on normal activity or to do active work.

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SAFETY RESULTS:	The safety was determined in terms of adverse events, routine laboratory examination, vital signs, electrocardiograms, neurologic examinations and abdominal sonography. At the time of database lock, 77 patients have died altogether. The information of the death of an additional patient (patient No. 1002, 06 May 2014) was not available to the database in terms of collection of survival contact sheets to be entered. Of these 77 patients, 69 patients died because of underlying disease, five patients died for other reasons than the underlying disease, and for three patients, the reason was unknown. A total of 14 patients experienced 16 AEs (including disease progression) leading to death at the time of database lock. Seven patients were in the APG101 + RT group, and the 9 AEs (intestinal obstruction, venous thrombosis of the limb, myocardial infarction and pulmonary embolism) occurred after the treatment period before EOS (EOS was not performed for various reasons) and disease progression and glioblastoma after treatment/before EOS and during the 90-day Follow-up, respectively. Seven of the patients belonged to the RT group, and 3 AEs (neurological decompensation for all patients) occurred during the 90-day follow-up period and 4 AEs (disease progression) during the 90-day Follow-up, respectively. None of these adverse events was considered to be related to the study treatment. Overall, 83 patients (98.8%) experienced at least one treatment-emergent AE at the time of database lock. Similar percentages were observed in both treatment groups. Most of these AEs were related to nervous system disorders, general disorders and administration site conditions and gastrointestinal disorders. Over the entire trial, the most frequently reported treatment-emergent AEs (by MedDRA Preferred Term) were headache, fatigue, brain oedema and hemiparesis. These AEs were considered to be expected in patients with glioblastoma as underlying disease. There were no major differences between the treatment groups apart from a higher incidence of headache in the APG101 + RT group and a higher incidence of brain oedema in the RT group. It should be noted that patients in the combination arm attended weekly visits during the study whereas patients receiving RT as a single treatment only attended 6-weekly visits. Thus, it cannot be excluded that there are further AEs experienced by patients in the RT group which were not reported. In 17 patients in the APG101 + RT group, treatment-emergent AEs were judged to be study drug related (including three patients with unknown relationship). No event was judged as definitely related to the study medication. The patients in the RT group did not receive APG101 and therefore, they could not experience any AE related to trial medication. A total of 35 patients (41.7%) in both treatment groups experienced treatment-emergent AEs classified as severe in intensity. These included 22 patients (37.9%) in the APG101 + RT group and 13 patients (50%) in the RT group. The severe AEs were mostly associated with nervous system disorders (11 patients (19%) in the APG101 + RT group and 10 patients (38.5%) in the RT group) and general disorders and administration site conditions (seven patients (12.1%) in the APG101 + RT group and seven patients (26.9%) in the RT group). During the study period, 12 patients in the APG101 + RT group experienced AEs requiring an action with the study medication (delay/interruption or discontinuation of trial medication) (relationship of AEs and AEs leading to any action on study treatment/led to discontinuation of study treatment was only specified concerning APG101, not for RT). Seven patients of them discontinued from study treatment, the other five patients had a delay or an interruption of study medication. At the time of the database lock, 22 SAEs were observed in 14 patients (24.1%) in the APG101 + RT group and 12 SAEs were reported for eight patients (30.8%) in the RT group. All were considered not related or unlikely to be related to the study drug. Most of them were moderate and severe in intensity and resolved or resolved with sequelae. For two patients in the APG101 + RT group, the SAEs led to death. These SAEs were judged as severe in intensity but not related to the trial medication. Regarding the laboratory results for all laboratory parameters (including urinalysis parameters), only slight changes in median values with only a few changes to clinically significant values at the time of database lock were observed by comparing the screening visit with the last value available. For the safety parameters of vital signs and ECG measurements, no remarkable differences between the treatment groups were observed.	

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	For abdominal sonography, remarkable higher percentages of patients with a shift from normal sonography to abnormal sonography findings were observed in the APG101 + RT group (eight patients (13.8%)) compared with the RT group (one patient (3.8%)). For three patients, the results were judged to be non-clinically significant. As a result of a high percentage of patients with a missing last value available during the clinical part of the trial (at the EOS visit or before the EOS visit) (25.9% in the APG101 + RT group compared with 34.6% in the RT group), providing reliable statements concerning the shifts to abnormal values and comparing the two groups is difficult. For the neurological examination, remarkably higher frequencies of patients in the RT group compared with the APG101 + RT group experienced a change to abnormal findings (differences of > 10% between the treatment groups) from the randomisation visit to the last value available (at the EOS visit or before the EOS visit) for the sensory examination. For the last value available, differences of > 10% between the treatment groups were observed for the optic systems, sensory examinations, coordination and deep tendon reflexes with remarkably higher percentages in the RT group. Symptomatic seizure assessments revealed no major differences between the treatment groups for the last value available during the clinical part of the trial (EOS visit or last value before the EOS visit). A total of five patients (8.5%) improved in the APG101 + RT group compared with one patient (3.8%) in the RT group. A worsening of signs was observed for eight patients (13.7%) in the APG101 + RT group compared with one patient (3.8%) in the RT group. The MRC neurological status revealed higher frequencies of patients with either no neurological deficit (grade 0) or some neurological deficit but adequate function for useful work (grade 1) in the APG101 + RT group (39 patients (67.2%)) compared with the RT group (15 patients (57.7%)) for the last value available during the clinical part of the trial (EOS visit or last value before EOS). A total of 19 patients (32.7%) in the APG101 + RT group showed higher grades (> 1) regarding the last values available including two patients (3.4%) with an MRC status of grade 4 (corresponding to no useful function and the inability to make conscious response). By contrast, 11 patients (42.3%) showed impairments of grade 2 or 3 in the RT group. In the APG101 + RT group, two patients (3.4%) showed an improvement of the MRC status compared with no patients in the RT group. A worsening of the MRC status was observed for 22 patients (34.8%) in the APG101 + RT group compared with 11 patients (42.3%) in the RT group. Overall, the evaluation of adverse events, routine laboratory examination, vital signs, electrocardiogram, neurologic examination and abdominal sonography revealed that administration of study drug APG101 was generally well tolerated and safe.
CONCLUSION:	• The rate of patients with PFS6 is remarkably higher in the APG101 + RT group (12 patients (20.7%)) compared with the RT alone group (one patient (3.8%)). • Notable treatment effects on PFS until database closure in favour of the APG101 + RT group were shown by the results of two Cox regression analyses including maximum tumour diameter and the impact of histological features. Small tumour sizes and a high proportion of moderate to high CD95L status tended to have a favourable effect on PFS. • The OS rate at the end of the follow-up phase of this study revealed no remarkable treatment differences at this stage of follow-up but considerable differences concerning the tumour size were observed in favour of a maximum tumour size diameter of ≤ 2.5 cm. • Only in the APG101 + RT group, three patients with a partial response (according the modified MacDonald response criteria) were observed from 75 to 115 days (week 11 to week 17) after randomisation with a maximum duration of 12 to 21 weeks. • The rate of patients in the APG101 + RT group with stable disease defined as PFS of greater than 90 days was more than twice as high as the rate of patients in the RT treatment group. • The MMSE showed no remarkable treatment differences with similar slightly decreases in mean values in both groups from screening to the last visit. • The primary scales of EORTC questionnaires, including QoL, physical functioning, and fatigue and the QLQ-BN20 revealed no remarkable treatment differences concerning the improvement rate for all parameters at the last visit.

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	• Overall, the evaluation of AEs, routine laboratory examination, vital signs, electrocardiogram, neurologic examination and abdominal sonography revealed that administration of study drug APG101 was generally well tolerated and safe.	
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