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## CHMP Type II variation assessment report

Invented name: Avastin

International non-proprietary name: bevacizumab

Procedure No. EMEA/H/C/000582/II/0093

Marketing authorisation holder (MAH): Roche Registration Limited

Rapporteur and type of application	
CHMP Rapporteur:	Sinan B. Sarac
PRAC Rapporteur:	N/A
This application is in the area of:	(Non-)Clinical
eCTD sequences related to the procedure:	0230, 0231



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# 1. Background information on the procedure

## 1.1. Requested type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration Limited submitted to the European Medicines Agency on 10 November 2016 an application for a variation.

The following changes were proposed:

Variation requested		Type	Annexes affected
C.I.4	Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2 Posology and method of administration, 4.8 Undesirable effects, 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties of the SmPC in order to include the paediatric results from the HERBY (BO25041) study. Study BO25041 (HERBY) is an open-label, randomized, multicenter, comparator Phase II study of the addition of bevacizumab to adjuvant chemoradiation with temozolomide (TMZ) followed by adjuvant TMZ in pediatric patients from  $\geq 3$  years to  $< 18$  years of age with newly diagnosed, localized, supratentorial or infratentorial cerebellar or peduncular high-grade glioma. The package leaflet (PIL) is updated accordingly.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

### **GLP/GCP Inspections:**

N/A

### **Information on Paediatric requirements**

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0005/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0005/2014 was completed.

The PDCO issued an opinion on compliance for the PIP P/0005/2014.

## 1.2. Rationale for the proposed change

The MAH submitted paediatric study results performed in compliance with a paediatric investigational plan which does not support a paediatric indication.

The MAH proposed an update of sections 4.2 Posology and method of administration, 4.8 Undesirable effects, 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties of the Avastin SmPC in order to update the safety, efficacy and pharmacokinetic information based on the results from the paediatric HERBY study.

As a consequence to the SmPC updates, section 2 of the package leaflet (PIL) has also been updated in line with the EU SmPC guideline. No updates to the labelling are foreseen.

No updated RMP is included with this submission.

With the inclusion of the study results in the Avastin product information, the present submission will allow the MAH to fulfil the obligations agreed under the Paediatric Investigational Plan EMEA-000056-PIP03-10-MO2 in order to obtain the 6-month extension of the supplementary protection certificate reward as specified in article 36 of the Paediatric Regulation.

## 2. Overall conclusion and impact on the benefit/risk balance

The MAH has provided the CSR for study BO25041 that evaluated the efficacy, safety, tolerability, and PK of bevacizumab when added to RT/T compared with RT/T alone in paediatric patients with newly diagnosed HGG. A previous interim CSR based on the first 60 randomized patients who were followed for 1 year did not meet the protocol-specified threshold of 10% improvement in 1-year EFS rate in the bevacizumab-containing arm, therefore, Study BO25041 was considered futile. However, since patient recruitment was completed and there was no safety concern, the iDMC recommendation was to continue treatment of ongoing patients as per protocol. The submitted CSR presented the updated analysis of the enrolled 121 patients in the main protocol who were followed for at least 1 year after randomization, unless patient withdrawal or death occurred.

As also concluded by the MAH, the results from the interim analysis, the primary endpoint was not met and the updated analysis of EFS (CRRG-assessed) showed no improvement when bevacizumab was added to the RT/T arm compared with RT/T alone (HR = 1.44; 95% CI: 0.90, 2.30). These results were consistent in various sensitivity analyses and in clinically relevant subgroups. The results for all secondary endpoints (investigator assessed EFS, and ORR and OS) were consistent in showing no improvement associated with the addition of bevacizumab to the RT/T arm compared with the RT/T arm alone. Overall, safety was consistent to that expected with TMZ and RT with the addition of the known safety profile of bevacizumab, and there were no new safety signals identified.

The use of Avastin in high grade glioma, being in the adult or paediatric population, is not an approved indication. At present section 4.2 of the SmPC states that; Avastin should not be used in children aged 3 years to less than 18 years with recurrent or progressive high-grade glioma because of efficacy concerns (see section 5.1 for results of paediatric trials).

The legal requirement to inform in the SmPC about the paediatric development has been noted. With this variation application the MAH proposes updates to SmPC section 4.2, 4.8, 5.1 and 5.2 along with update to section 2 of the PIL in order to appropriately reflect the data. These changes are acceptable. Otherwise the overall benefit risks, in the approved indications remain positive.

### ***Scientific Summary for the EPAR***

#### 4.2 Posology and method of administration

##### Paediatric population

The safety and efficacy of bevacizumab in children less than 18 years old have not been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

There is no relevant use of bevacizumab in the paediatric population in the indications for treatment of cancers of the colon, rectum, breast, lung, ovarian, fallopian tube, peritoneum, cervix and kidney.

#### 4.8 Undesirable effects

##### Paediatric population

The safety and efficacy of Avastin in children less than 18 years old have not been established.

In study BO25041 of Avastin added to postoperative radiation therapy (RT) with concomitant and adjuvant temozolomide in paediatric patients with newly diagnosed supratentorial, infratentorial, cerebellar, or peduncular high-grade glioma, the safety profile was comparable with that observed in other tumour types in adults treated with Avastin.

## 5.1 Pharmacodynamic properties

### High-grade glioma

In a randomized phase II study (BO25041) a total of 121 patients aged  $\geq 3$  years to  $<18$  years with newly diagnosed supratentorial or infratentorial cerebellar or peduncular high-grade glioma (HGG) were treated with post-operative radiation therapy (RT) and adjuvant temozolomide (T) with and without bevacizumab: 10 mg/kg every 2 weeks IV.

The study did not meet its primary endpoint of demonstrating a significant improvement of EFS (Central Radiology Review Committee (CRRC)-assessed) when bevacizumab was added to the RT/T arm compared with RT/T alone (HR = 1.44; 95% CI: 0.90, 2.30). These results were consistent with those from various sensitivity analyses and in clinically relevant subgroups. The results for all secondary endpoints (investigator assessed EFS, and ORR and OS) were consistent in showing no improvement associated with the addition of bevacizumab to the RT/T arm compared with the RT/T arm alone.

Addition of Avastin to RT/T did not demonstrate clinical benefit in study BO25041 in 60 evaluable children patients with newly diagnosed supratentorial or infratentorial cerebellar or peduncular high- grade glioma (HGG) (See section 4.2 for information on paediatric use).

## 5.2 Pharmacokinetic properties

### Paediatric population

The pharmacokinetics of bevacizumab were evaluated in 152 children, adolescents and young adults (7 months to 21 years, 5.9 to 125 kg) across 4 clinical studies using a population pharmacokinetic model. The pharmacokinetic results show that the clearance and volume of distribution of bevacizumab were comparable between paediatric and young adult patients when normalised by body weight, with exposure trending lower as body weight decreased. Age was not associated with the pharmacokinetics of bevacizumab when body weight was taken into account.

The pharmacokinetics of bevacizumab was well characterized by the paediatric population PK model for 70 patients in Study BO20924 ((1.4 to 17.6 years; 11.6 to 77.5 kg) and 59 patients in Study BO25041 (1 to 17 years; 11.2 to 82.3 kg). In Study BO20924, bevacizumab exposure was generally lower compared to a typical adult patient at the same dose. In Study BO25041, bevacizumab exposure was similar compared to a typical adult at the same dose. In both studies, bevacizumb exposure trended lower as body weight decreased.

### 3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		Type	Annexes affected
C.I.4	Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2 Posology and method of administration, 4.8 Undesirable effects, 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties of the SmPC in order to include the paediatric results from the HERBY (BO25041) study. Study BO25041 (HERBY) is an open-label, randomized, multicenter, comparator Phase II study of the addition of bevacizumab to adjuvant chemoradiation with temozolomide (TMZ) followed by adjuvant TMZ in pediatric patients from  $\geq 3$  years to  $< 18$  years of age with newly diagnosed, localized, supratentorial or infratentorial cerebellar or peduncular high-grade glioma. The package leaflet (PIL) is updated accordingly.

is recommended for approval.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet.

### Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0005/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

## 4. Scientific discussion

### 4.1. Introduction

On 23 August 2016, the MAH submitted a completed paediatric study BO25041 (HERBY) for Avastin, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The outcome of that procedure; EMEA/H/C/582/P46 0084, was adopted in November 2016.

Study BO25041 evaluated the efficacy, safety, tolerability, and PK of bevacizumab when added to RT/T compared with RT/T alone in paediatric patients with newly diagnosed HGG. This is not an approved indication for bevacizumab. With this submission the MAH is providing the variation in order to update the SmPC with the legally required information on the paediatric development. With the inclusion of the study results in the Avastin product information, the present submission will allow the MAH to fulfil the obligations agreed under the Paediatric Investigational Plan EMEA-000056-PIP03-10-MO2 in order to obtain the 6-month extension of the supplementary protection certificate reward as specified in article 36 of the Paediatric Regulation.

### 4.2. Clinical aspects

#### 4.2.1. Introduction

The MAH has submitted the study; HERBY (BO25041), as per article 46 of Regulation (EC) No 1901/2006, as a paediatric study post authorization measure since it is included in a PIP (EMEA-C-000056-PIP03-10-MO2). In addition, the results for the Young Patient Cohort substudy are presented. For the Young Patient Cohort, children aged  $\geq 6$  months to  $< 3$  years with localized or metastatic, supratentorial or infratentorial,

non-brainstem WHO Grade III or IV high grade glioma (HGG) recurring or progressing after first-line therapy with surgery and chemotherapy received up to twelve 28-day cycles of TMZ and bevacizumab. Only children who could receive at least four 28-day cycles of combined TMZ and bevacizumab were considered for this substudy.

#### **4.2.2. Clinical study**

##### **Clinical study BO25041 (HERBY) HGG Efficacy and tolerability Research of Bevacizumab in Young children and adolescents.**

###### Study BO25041

Study BO25041 (HERBY: HGG Efficacy and tolerability Research of Bevacizumab in Young children and adolescents) is an open-label, randomized, multicenter, comparator Phase II study of the addition of bevacizumab to adjuvant chemoradiation with temozolomide (TMZ) followed by adjuvant TMZ in pediatric patients from  $\geq 3$  years to  $< 18$  years of age with newly diagnosed, localized, supratentorial or infratentorial cerebellar or peduncular high-grade glioma (HGG).

Eligible patients who fulfilled the inclusion and exclusion criteria and completed the screening assessments were randomized on a 1:1 basis to one of the two treatment arms:

- Arm A (RT/T arm): chemoradiation with TMZ for 6 weeks, then a TMZ treatment break of approximately 4 weeks followed by up to 12 cycles (48 weeks) of TMZ
- Arm B (Bv + RT/T arm): bevacizumab delivered concomitantly with chemoradiation and TMZ for 6 weeks, during the TMZ treatment break of approximately 4 weeks, and thereafter concomitantly with adjuvant TMZ for up to 12 cycles (48 weeks)

Randomization was stratified by age ( $\geq 3$  to  $< 6$  years,  $\geq 6$  to  $< 13$  years,  $\geq 13$  to  $< 18$  years), WHO Grade (Grade III vs. Grade IV) and type of surgery (total/near-total resection vs. others). Patients with diffuse intrinsic pontine glioma (DIPG) were systematically excluded: the inclusion of patients with a peduncular tumor had to be validated by a central radiology review committee (CRRC) before randomization.

The study duration was expected to be approximately 8 years, including a 36-month recruitment period, up to 58 weeks of treatment period, and 5 years of safety follow-up. After randomization, patients were treated with concurrent TMZ and radiation therapy for 6 weeks without (Arm A) or with bevacizumab (Arm B). After chemoradiation, a TMZ treatment break of approximately 4 weeks occurred during which bevacizumab was administered on Day 15 in Arm B. After the TMZ break, patients received adjuvant TMZ for up to 12 cycles of four 28-day cycles each (up to 48 weeks of adjuvant period). Treatment continued until the protocol-defined treatment was completed or until an EFS event was observed, unacceptable toxicity occurred, or consent was withdrawn.

In addition, the results for a Young Patient Cohort substudy were presented in this update analysis. The Young Patient Cohort was not randomized.

Randomized patients are being followed for a minimum of 5 years after randomization or until last patient last visit (LPLV), whichever occurs first.

##### **Overview of Efficacy**

Per the updated analysis, Study BO25041 did not meet its primary endpoint of demonstrating a significant improvement of EFS when bevacizumab was added to the RT/T arm compared with the RT/T arm alone:

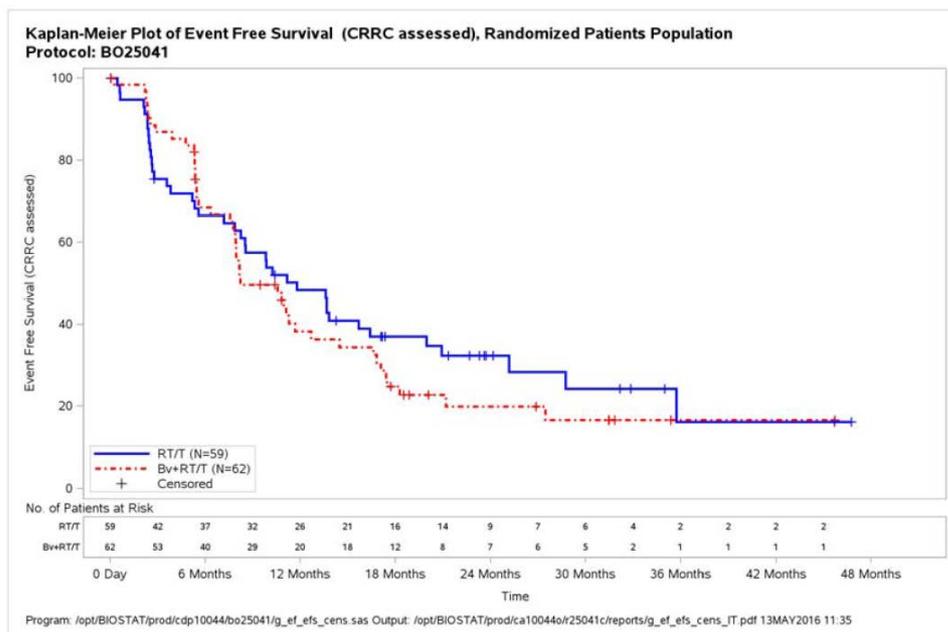
**Table 1 Overview of Efficacy**

	RT/T (N=59)	Bv+RT/T (N=62)
<b>Primary Endpoint:</b>		
<b>EFS (CRRC-assessed)</b>		
Median (months)	11.8	8.2
Stratified HR (95%CI)	1.44 (0.90, 2.30)	
<b>Secondary Endpoints:</b>		
<b>6 month EFS rates (CRRC-assessed)</b>	66.5%	68.4%
<b>1-year EFS rates (CRRC-assessed)</b>	48.4%	38.3%
<b>ORR (CRRC-assessed)</b>	40.0%	41.7%
<b>EFS (investigator-assessed)</b>		
Median (months)	11.8	11.3
Stratified HR (95%CI)	1.49 (0.92, 2.40)	
<b>Overall Survival</b>		
Median (months)	27.0	18.3
Stratified HR (95%CI)	1.23 (0.72, 2.09)	
1-year survival rates	67.7%	74.6%

EFS = event-free survival, HR = hazard ratio

Source: Table 18 of CSR

**Figure 6 Kaplan-Meier Plot of CRRC-Assessed Event-Free Survival (Randomized Patients Population)**



CRRC-assessed EFS: The hazard ratio (HR) was 1.44 (95% CI: 0.90, 2.30) and the Kaplan-Meier-estimated median EFS was 11.8 months (95% CI: 7.85, 16.39) in the RT/T arm and 8.2 months (95% CI: 7.75, 12.68) in the Bv + RT/T arm.

The addition of bevacizumab to RT/T did not show a benefit in the primary endpoint, EFS, compared with RT/T alone.

The results of all secondary endpoints were consistent in showing no improvement associated with the addition of bevacizumab to the RT/T arm compared with the RT/T arm alone:

At 1 year, the Kaplan-Meier estimated event-free rates per CRRC were 48.4% (95% CI: 34.8%, 60.7%) in the RT/T arm and 38.3% (95% CI: 25.8%, 50.6%) in the Bv + RT/T arm

The overall response rate (ORR) was comparable among evaluable patients between the treatment arms (40.0% RT/T [95% CI: 19.1%, 66.8%] vs. 41.7% Bv + RT/T [95% CI: 18.1%, 70.6%]) when structural imaging was used.

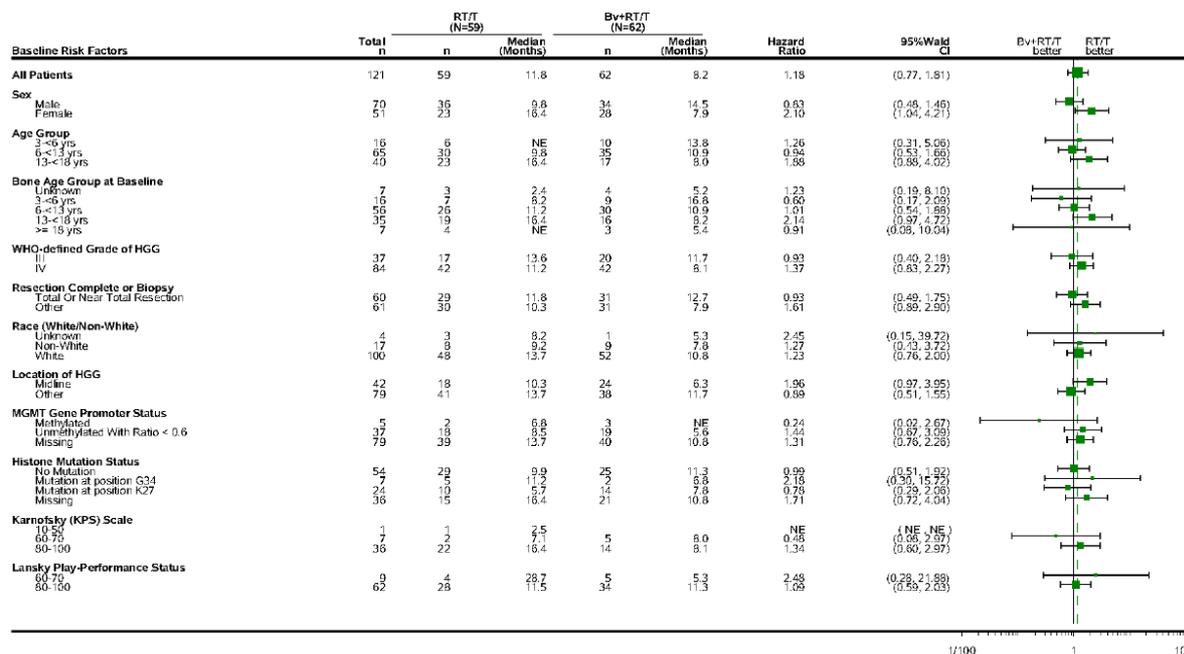
Investigator-assessed EFS: The HR was 1.49 (95% CI: 0.92, 2.40), and the Kaplan-Meier-estimated median EFS was 11.8 months in the RT/T arm and 11.3 months in the Bv + RT/T arm.

The OS HR was 1.23 (95% CI: 0.72, 2.09), with a Kaplan-Meier-estimated median OS of 27 months (95% CI: 14.0, 33.8) in the RT/T arm compared with 18.3 months (95% CI: 16.2, 28.1) in the Bv + RT/T arm.

### Subgroup Analyses

Subgroup analyses were performed for CRRC-assessed EFS using the following factors: sex, age group, race, bone age group at baseline, WHO-defined grade of HGG, complete resection or biopsy, MGMT gene promoter status, histone mutation status, KPS scale score, and Lansky Play-Performance Status score. The results of the subgroup analyses were generally consistent with the results of the randomized patients population (Figure 7). The differences observed in some of the subgroups are most likely due to randomness considering the small number of patients.

Figure 7 Subgroup Analyses of CRRC-Assessed EFS (Randomized Patients Population)



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### Overview of Pharmacokinetics

The pharmacokinetics (PK) of bevacizumab for the PK-evaluable pediatric patients (n = 59) from Study BO25041 were well characterized by a comprehensive pediatric PopPK model that was previously developed with data from 152 pediatric patients across four clinical studies. These 59 PK-evaluable patients included 3 patients in the Young Patient Cohort.

Covariates associated with bevacizumab PK in pediatric patients were similar to those found with adults with body weight (BW), gender, and albumin levels having significant impact on bevacizumab exposure. In addition, pediatric patients with primary central nervous system tumors (e.g., Study AVF3842s/PBTC022 and Study BO25041) were also found to be a specific PK associated covariate in the pediatric PopPK model. No other PK-associated covariates were observed for patients in Study BO25041. Importantly, age was not found to be associated with bevacizumab PK when BW was taken into account.

Bevacizumab exposure in PK-evaluable pediatric patients was found to generally fall within the 90% prediction intervals of adults when administered the same dose regimen (10 mg/kg twice weekly) as in Study BO25041 with a downward trend in exposure as BW (age) decreases. Lower exposure with decreasing BW was expected due to the influence of BW on PK parameters described in the comprehensive pediatric PopPK model.

**Table 38 Key PK Parameter Estimates (Mean (CV%) [Range]) for PK-Evaluable Patients**

Age Subset	No. of PK-Evaluable Patients	CL (mL/day)	V1 (mL)	AUC <sub>ss</sub> (hr • mg/mL)	t <sub>1/2</sub> (days)
All Ages (6 mons to < 18 yr)	59	114 (39.7) [31.4 – 246]	1700 (35.3) [608 – 3170]	81.8 (19.4) [51.5 – 117]	22.4 (27.7) [13.1 – 59.4]
6 months to < 3 year	3	46.4 (31.3) [31.4 – 60.4]	794 (21.6) [608 – 946]	73.3 (14.5) [66.3 – 85.5]	22.3 (8.1) [21.1 – 24.4]
3 to < 6 year	8	67.8 (17.0) [49.0 – 85.8]	958 (14.7) [751 – 1230]	68.6 (23.8) [51.5 – 97.5]	20.0 (11.4) [16.9 – 22.8]
6 to < 13 year	33	111 (31.8) [54.9 – 187]	1680 (23.9) [956 – 2500]	81.4 (15.7) [60.8 – 113]	22.3 (19.6) [13.1 – 34.0]
13 to < 18 year	15	157 (22.9) [105 – 246]	2340 (18.4) [1640 – 3170]	91.4 (19.1) [59.9 – 117]	24.1 (42.9) [14.2 – 59.4]

CL = clearance; V1 = volume of distribution of the central compartment; AUC<sub>ss</sub> = area under the curve at steady-state; t<sub>1/2</sub> = half-life.

Source: [l\\_pkpara001](#), [t\\_pkpara001](#)

## OVERVIEW OF SAFETY

Overall, safety was consistent with that expected of radiotherapy and TMZ use, with the addition of the established safety profile of bevacizumab therapy. No new safety signals were identified for bevacizumab in this pediatric study.

The incidence of Grade  $\geq 3$  AEs was similar between treatment arms, although the incidences of Grade  $\geq 3$  AESIs and SAEs were higher in the Bv + RT/T arm.

**Table 47 Adverse Events of Special Interest to Bevacizumab (Safety-Evaluable Population)**

Body system Adverse Event	RT/T (N=56)	Bv+RT/T (N=60)
Total number of patients with at least one adverse event	4 (7.1%)	16 (26.7%)
Overall total number of events	4	20
<b>PROTEINURIA <math>\geq</math> G3</b>		
Total number of patients with at least one adverse event	0	8 (13.3%)
Total number of events	0	11
PROTEINURIA	0	8 (13.3%)
<b>THROMBOEMBOLIC EVENTS (ARTERIAL) - ANY GRADE</b>		
Total number of patients with at least one adverse event	2 (3.6%)	5 (8.3%)
Total number of events	2	5
HEMIPARESIS	0	2 (3.3%)
CEREBRAL ISCHAEMIA	0	1 (1.7%)
DEVICE OCCLUSION	0	1 (1.7%)
MONOPLÉGIA	1 (1.8%)	0
THROMBOLYSIS	1 (1.8%)	0
THROMBOSIS IN DEVICE	0	1 (1.7%)
<b>HEMORRHAGE <math>\geq</math> G3</b>		
Total number of patients with at least one adverse event	1 (1.8%)	0
Total number of events	1	0
HAEMATURIA TRAUMATIC	1 (1.8%)	0
<b>HYPERTENSION <math>\geq</math> G3</b>		
Total number of patients with at least one adverse event	0	1 (1.7%)
Total number of events	0	1
HYPERTENSION	0	1 (1.7%)
<b>NON GI FISTULA OR ABSCESS <math>\geq</math> G2</b>		
Total number of patients with at least one adverse event	1 (1.8%)	0
Total number of events	1	0
SUBCUTANEOUS ABSCESS	1 (1.8%)	0
<b>PRES (or RPLS) - ANY GRADE</b>		
Total number of patients with at least one adverse event	0	1 (1.7%)
Total number of events	0	1
POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME	0	1 (1.7%)
<b>THROMBOEMBOLIC EVENTS (VENOUS) <math>\geq</math> G3</b>		
Total number of patients with at least one adverse event	0	1 (1.7%)
Total number of events	0	1
DEEP VEIN THROMBOSIS	0	1 (1.7%)
<b>WOUND HEALING COMPLICATIONS <math>\geq</math> G3</b>		
Total number of patients with at least one adverse event	0	1 (1.7%)
Total number of events	0	1
IMPLANT SITE DEHISCENCE	0	1 (1.7%)

Investigator text for AEs encoded using MedDRA version 18.1 . Percentages are based on N in the column headings. For frequency counts by preferred term, multiple occurrences of the same AE in an individual are counted only once. For frequency counts of "Total number of events" rows, multiple occurrences of the same AE in an individual are counted separately.

Program: /opt/BIOSTAT/prod/cdp10044/bo25041/t\_aesi.sas  
 Output: /opt/BIOSTAT/prod/cal0044o/r25041c/reports/t\_aesi\_SE.out  
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AEs leading to withdrawal of study treatment occurred at a higher incidence in the Bv + RT/T arm and were mainly driven by proteinuria, an identified AESI of bevacizumab.

## Young Patient Cohort

The Young Patient Cohort was comprised of children aged  $\geq 6$  months to  $< 3$  years with localized or metastatic, supratentorial or infratentorial, non-brainstem WHO Grade III or IV HGG recurring or progressing after first-line therapy with surgery and chemotherapy received up to twelve 28-day cycles of TMZ and bevacizumab. Only children who could receive at least four 28-day cycles of combined TMZ and bevacizumab were considered for this substudy. Three patients were enrolled. CRRC-assessed time to EFS for the 3 patients were 50 days, 90 days, and 545\* days (\*censored observation), respectively. Among these patients the majority of the AEs reported were of Grade 1 or Grade 2 severity, with the exception of two Grade 3 AEs in two patients: decreased platelet count and decreased neutrophil count.

## Impact on product information

Study BO25041 failed to meet its primary endpoint and no new safety signals have been identified. Therefore, the marketing authorization holder will not seek an indication nor amend existing indications.

The data included in this submission do not affect the benefit-risk balance and therefore do not require further regulatory action on the marketing authorization. However, with this Type II variation the MAH intends to update the SmPC with results from Study BO25041 and fulfill the obligations for the Avastin Paediatric investigation Plan (EMA-000056-PIP03-10-M02).

## Conclusions

Study BO25041 did not meet its primary endpoint of significantly improved CRRC-assessed EFS when bevacizumab was added to the RT/T arm compared with RT/T alone (HR = 1.44; 95% CI: 0.90, 2.30). These results were consistent in various sensitivity analyses and in clinically relevant subgroups.

The results for all secondary endpoints (investigator assessed EFS, and ORR and OS) were consistent in showing no improvement associated with the addition of bevacizumab to the RT/T arm compared with the RT/T arm alone.

Overall, safety in Study BO25041 was consistent with that expected with TMZ and RT with the addition of the known safety profile of bevacizumab, and there were no new safety signals identified.

Pharmacokinetics results indicated that bevacizumab exposure in pediatric patients tends to decrease with decreasing BW, although exposure in pediatric patients from Study BO25041 was similar to adult exposure following a similar dose and regimen. Body weight, sex, and serum albumin concentration were significant covariates associated with bevacizumab PK in pediatric patients in this study, and are in agreement with covariates identified in previous pediatric and adult studies. The presence of primary CNS tumors was found to be a specific covariate associated with pediatric PK. Age was not found to be associated with bevacizumab PK when BW was taken into account.

## 4.2.3. Discussion on clinical aspects

The MAH has provided the CSR for study BO25041 that evaluated the efficacy, safety, tolerability, and PK of bevacizumab when added to RT/T compared with RT/T alone in paediatric patients with newly diagnosed HGG. A previous interim CSR based on the first 60 randomized patients who were followed for 1 year did not meet the protocol-specified threshold of 10% improvement in 1-year EFS rate in the bevacizumab-containing arm, therefore, Study BO25041 was considered futile. However, since patient recruitment was completed and there was no safety concern, the iDMC recommendation was to continue treatment of ongoing patients as per protocol. The submitted CSR presented the updated analysis of the enrolled 121 patients in the main protocol who were followed for at least 1 year after randomization, unless patient withdrawal or death occurred.

As also concluded by the MAH, the results from the interim analysis, the primary endpoint was not met and the updated analysis of EFS (CRRC-assessed) showed no improvement when bevacizumab was added to the RT/T arm compared with RT/T alone (HR = 1.44; 95% CI: 0.90, 2.30). These results were consistent in various sensitivity analyses and in clinically relevant subgroups. The results for all secondary endpoints (investigator assessed EFS, and ORR and OS) were consistent in showing no improvement associated with the addition of bevacizumab to the RT/T arm compared with the RT/T arm alone. Overall, safety was consistent to that expected with TMZ and RT with the addition of the known safety profile of bevacizumab, and there were no new safety signals identified.

The use of Avastin in high grade glioma, being in the adult or paediatric population, is not an approved indication. At present section 4.2 of the SmPC states that; Avastin should not be used in children aged 3 years to less than 18 years with recurrent or progressive high-grade glioma because of efficacy concerns (see section 5.1 for results of paediatric trials).

The legal requirement to inform in the SmPC about the paediatric development has been noted. With this variation application the MAH proposes updates to SmPC section 4.2, 4.8, 5.1 and 5.2 along with update to section 2 of the PIL in order to appropriately reflect the data. These changes are acceptable. Otherwise the overall benefit risk, in the approved indications remain positive.

### **4.3. Changes to the Product Information**

As a result of this variation, section(s) 4.2, 4.8, 5.1 and 5.2 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

Please refer to Attachment 1 which includes all agreed changes to the Product Information.

## **5. Attachments**

1. Product Information (changes highlighted) as adopted by the CHMP on 26 January 2017