20 November 2014
EMA/CHMP/704739/2014 adopted
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invented name: Votrient

International non-proprietary name: PAZOPANIB

Procedure No. EMEA/H/C/001141/II/0026

Marketing authorisation holder (MAH): Glaxo Group Ltd

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Assessment Timetable / Steps taken for the assessment

Timetable	Dates
Start of procedure:	24 August 2014
CHMP Rapporteur Assessment Report	29 September 2014
CHMP comments	13 October 2014
Rapporteur Revised Assessment Report	17 October 2014
Adoption of RSI	23 October 2014
CHMP Rapporteur Assessment Report on Responses	6 November 2014
CHMP comments	11 November 2014
Opinion	20 November 2014

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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, Glaxo Group Ltd submitted to the European Medicines Agency on 31 July 2014 an application for a variation.

The following changes were proposed:

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

Update of section 4.2 of the SmPC further to submission of the results of Study ADVL0815 (PZP114411), a Phase I Study of Pazopanib as a Single Agent for Children with Relapsed or Refractory Solid Tumours, including central nervous system (CNS) tumours.

1.2. Rationale for the proposed change

This Type II variation supports the amendment of the SmPC, Section 4.2, Paediatric population, to delete the sentence “No data are available”.

Results from study ADVL0815/PZP114411, a Phase I Study of Pazopanib as a Single Agent for Children with Relapsed or Refractory Solid Tumours, including central nervous system (CNS) tumours, are available and the statement of “no data are available” is no longer appropriate. The available paediatric data regarding safety and tolerability of pazopanib are limited and therefore the conclusion “that safety and efficacy of pazopanib in children aged 2 to 18 years have not been established” remains unchanged.

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

The MAH for Votrient (pazopanib) has submitted a variation in order to amend the SmPC, Section 4.2, Paediatric population, to delete the sentence “No data are available”.

With the variation results from study ADVL0815/PZP114411, a Phase I Study of Pazopanib as a Single Agent for Children with Relapsed or Refractory Solid Tumours, including central nervous system (CNS) tumours, has been included. The primary purpose of the phase I study ADVL0815 was to identify the maximum tolerated dose (MTD) of pazopanib for administration to children, adolescents and young adults. The primary objectives were to evaluate toxicity and begin the process of characterising pazopanib PK parameters in a paediatric population. Evaluation of clinical activity was a secondary objective. A total of 53 paediatric subjects with a variety of relapsed/refractory solid tumours were evaluated and reported.

The data showed that plasma pazopanib concentrations associated with clinical and biologic effects consistent with VEGFR inhibition (20 µg/mL) were achieved at all dose levels after oral administration of tablets/suspension.

Some clinical activity of pazopanib was observed in a heavily pretreated paediatric population.

Clinical activity included 2 subjects with partial responses in refractory desmoplastic small round cell tumour and hepatoblastoma. Stable disease were seen in 12 subjects (23%) in a variety of tumour types (malignant

melanoma (n=2), synovial sarcoma (n=2), alveolar soft part sarcoma, malignant glioma, osteosarcoma, desmoplastic small round cell tumour, alveolar rhabdomyosarcoma (n=2), alveolar soft part sarcoma, gastrointestinal stromal sarcoma.

Serious adverse events were reported for 25 (47%) subjects. The most common SAEs were anaemia (4 [8%] subjects), increased lipase (4 [8%] subjects), abdominal pain, dyspnoea and hypothyroidism (each in 3 [6%] subjects). No other SAEs were reported for greater than 2 subjects. Decreases in left ventricular ejection fraction were reported for 9 (17%) subjects, 3/17 at the MTD for tablets and none at the MTD for the suspension. All (3) fatal SAEs had the primary cause of death related to their disease. The types of AEs observed was consistent with those seen in the adult population treated with pazopanib.

Overall conclusion

It can be agreed that based on the data from this small paediatric study no firm conclusion can be drawn about activity nor safety in particular tumour types and consequently efficacy of pazopanib in children aged 2 to 18 years of age based on the data from this study has not yet been established. The overall efficacy and safety profile of pazopanib in the approved indications (renal cell carcinoma and soft tissue sarcoma) remains unchanged.

With the provided data the statement currently included in the SmPC section 4.2; “no data are available” is no longer appropriate. It is also endorsed that even though some information is now available the overall paediatric data regarding safety and tolerability of pazopanib are still limited and therefore the conclusion “that safety and efficacy of pazopanib in children aged 2 to 18 years have not been established” should remain unchanged.

It has been considered whether it could be of value to evaluate the data by comparing the PK data/parameters in adults with those in children of the various age categories (2-6, 6-12, 12-18 years and >18 years) taking into account possible differences in formulation and absolute doses and provide some level of paediatric PK data in section 5.2 of the SmPC. This has been addressed by the MAH. As Votrient (pazopanib) is not approved for the use in the paediatric population, and the numbers on which any pharmacokinetic information may be based on and subsequently addressed in section 4.2 is very limited it is considered fully acceptable that nothing further may be included in section 5.2 in the SmPC.

3. Recommendations

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

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

Update of section 4.2 of the SmPC further to submission of the results of Study ADVL0815 (PZP114411), a Phase I Study of Pazopanib as a Single Agent for Children with Relapsed or Refractory Solid Tumours, including central nervous system (CNS) tumours.

The requested variation leads to amendments to the Summary of Product Characteristics.

is recommended for approval.

4. Scientific discussion

4.1. Introduction

Votrient (Pazopanib), a multi-target receptor tyrosine kinase inhibitor of vascular endothelial growth factor receptors (VEGFR) -1, -2 and -3, platelet-derived growth factor receptors (PDGFR) –α and -β, and stem cell factor receptor (c-kit), is approved in the EU for the treatment of patients with advanced renal cell carcinoma (RCC) and also for the treatment of patients with advanced soft tissue sarcoma who have received prior chemotherapy.

At the time of the type II variation to include advanced soft tissue sarcoma as a therapeutic indication (EMEA/H/C/001141/II/007), the MAH agreed to add text regarding the paediatric population to Section 4.2 of the SmPC. The currently approved text is as follows:

Paediatric population

Pazopanib should not be used in children younger than 2 years of age because of safety concerns on organ growth and maturation (see Section 4.4 and 5.3).

The safety and efficacy of pazopanib in children aged 2 to 18 years of age have not yet been established (see Section 5.1). No data are available.

With this type II variation the MAH asks for an amendment of the SmPC, Section 4.2, Paediatric population, in order to delete the sentence "No data are available."

The proposed change is below (proposed deleted text is struck through):

Paediatric population

Pazopanib should not be used in children younger than 2 years of age because of safety concerns on organ growth and maturation (see Section 4.4 and 5.3).

The safety and efficacy of pazopanib in children aged 2 to 18 years of age have not yet been established (see Section 5.1). ~~*No data are available.*~~

The MAH has submitted the results from a Phase I paediatric study and consequently the statement of "no data are available" is no longer appropriate. However, the available paediatric data regarding safety and tolerability of pazopanib are limited and therefore the conclusion "that safety and efficacy of pazopanib in children aged 2 to 18 years have not been established" remains unchanged.

The data submitted with this application relates to the use of pazopanib in the paediatric population from a study in children with relapsed or refractory solid tumours. The study; ADVL0815 (PZP114411), a Phase I Study of Pazopanib as a Single Agent for Children with Relapsed or Refractory Solid Tumours, including central nervous system (CNS) tumours, was conducted by the Children's Oncology Group and the National Cancer Institute (NCI), US.

Table 1 Overview of Study ADVL0815

Study	Features
Critical Design Features	Phase I Open-label; Non-randomized Three-part study (1a Phase I dose escalation, 2a Suspension Formulation component, 2b expanded Imaging Cohort)
Study Population	Paediatric (Aged 2 years to ≤21 years Part 1, 2a; and 2 year to ≤25 years Part 2b) Diagnosis of relapsed or refractory solid tumour Measurable or evaluable disease

	Adequate organ function
Number of subjects	53 Pazopanib tablets 37 (27 subjects , Part 1; 10 subjects , Part 2b) Pazopanib oral suspension 16 (Part 2a)
Endpoints	
Primary	Maximum tolerated dose; toxicities; pharmacokinetics
Secondary	Anti-tumour and biological activity; pharmacogenetics; pharmacodynamics

The details from the study are summarised below

4.2. Clinical aspects

4.2.1. Methods – analysis of data submitted

Study ADVL0815 (PZP114411)

Study Design

Study ADVL0815 was a phase I trial design where pazopanib, as a single agent, was administered orally on a once daily basis. The primary purpose of ADVL0815 was to identify the maximum tolerated dose (MTD) of pazopanib for administration to children, adolescents and young adults with refractory solid tumours, including central nervous system tumours. Other primary objectives were to evaluate toxicity and obtain initial pazopanib pharmacokinetic (PK) parameters in a paediatric patient population. Evaluation of clinical activity was a secondary objective.

This study was a three-part study:

- Part 1 (Phase I Dose Escalation): The starting dose of pazopanib was 275 mg/m2. Pazopanib dosing was escalated in subsequent cohorts in increments of approximately 30%. There was no intrapatient dose escalation. Blood samples were obtained for PK analysis and correlative biology studies including VEGF haplotype, plasma levels of VEGF, P1GF, soluble VEGFR1, and soluble VEGFR2 and measurement of circulating endothelial cells and peripheral blood monocytes. Changes in tumour vascular permeability in response to pazopanib were also explored using dynamic contrast enhanced magnetic resonance imaging (DCE-MRI).
- Part 2a (Suspension Formulation Component): The starting dose was 50% of the MTD as determined in Part 1. Once the MTD or highest dose level was reached, the cohort was expanded in order to obtain additional safety information and PK data for the suspension formulation. PK evaluation was required in all subjects who participated in this component of the study.
- Part 2b (Expanded Imaging Cohort): At the MTD or recommended Phase II dose, a cohort of up to 10 subjects with recurrent or refractory (revised to relapsed or refractory in Protocol Amendment 1A) soft tissue sarcoma (revised to soft tissue sarcoma, desmoplastic small round cell tumour or extra-osseous Ewing sarcoma in Protocol Amendment 2) and a measurable (at least 2 cm) lesion in the head, neck, extremity or fixed within the abdomen or pelvis (revised to thorax, abdomen or pelvis in Protocol Amendment 2) such that it is not sensitive to motion artefact were recruited to further explore changes in tumour vascular permeability using DCE-MRI. Imaging studies and limited PK sampling was required in all subjects who participated in this component of the study.

The *primary objectives* of this study were:

- To estimate the MTD and/or recommended Phase II dose of oral pazopanib administered on a once daily schedule to children with refractory solid tumours.
- To define and describe the toxicities of oral pazopanib administered as either a tablet or suspension.
- To characterise the PK of oral pazopanib in children with refractory solid tumours.

The *secondary objectives* of this study were:

- To preliminarily define the anti-tumour activity of oral pazopanib within the confines of a Phase I study.
- To assess the biological activity of oral pazopanib including changes in peripheral blood monocyte counts, CECs, and plasma angiogenic factors.
- To explore changes in tumour vascular permeability following initiation of pazopanib therapy and to correlate these changes with clinical outcome, as applicable. Specifically, to evaluate changes in (DCE-MRI) scans obtained within 15 ± 2 days after initiation of pazopanib therapy as compared to baseline within a soft tissue sarcoma cohort.
- To preliminarily assess vascular endothelial growth factor (VEGF) haplotype/phenotype relationships in a paediatric cancer patient population.
- To explore pazopanib concentration effect relationships with biomarkers and with clinical outcomes, including hypertension.

Enrollment

Subjects were to be enrolled on the study once all eligibility requirements for the study were met. Subjects who gave informed consent, or whose parents or guardian gave informed consent if the subject was a child, in order to undergo screening for eligibility were not considered enrolled and were not to be enrolled until the screening was completed and they were determined to meet all eligibility criteria. Subjects were not to receive any protocol therapy prior to enrolment. Complete inclusion/exclusion criteria can be found in the clinical pharmacology study report.

Treatment

In all parts of the study, treatment cycles were defined as 28 days in duration. Subjects were to receive up to a total of 24 cycles of therapy with pazopanib in the absence of progressive disease or unacceptable toxicity. A maximum of 55 subjects were anticipated (increased from 46 subjects in Protocol Amendment 3).

Part 1: Phase I Dose Escalation

Subjects with recurrent or refractory (revised to relapsed or refractory in Protocol Amendment 1A) solid or CNS tumours were enrolled. Two to six evaluable subjects were entered at each dose level for determination of MTD. A minimum of 9 and a maximum of 24 evaluable subjects were expected to be enrolled in Part 1 of the study. In Protocol Amendment 3, this was increased to a maximum of 27 subjects.

Part 2a: Suspension Formulation Component

Once the MTD or Phase II recommended dose had been defined, up to 12 additional subjects with relapsed or refractory solid tumours were to be enrolled to acquire PK data using the powder for suspension formulation. In Protocol Amendment 3, the maximum number of subjects in this strata was increased to 18 subjects, to ensure 12 subjects with PK at the MTD with at least 6 subjects <12 years of age in this expanded cohort.

Part 2b: Expanded Imaging Cohort

Once the MTD or Phase II recommended dose had been defined, up to 10 additional subjects with recurrent or refractory (revised to relapsed or refractory in Protocol Amendment 1A) soft tissue sarcomas were to be enrolled to evaluate changes in vascular permeability using DCE-MRI.

Statistical Methods

Efficacy was a secondary objective of this study, best defined by the preliminary anti-tumour activity as assessed by disease response. Summary statistics were produced to describe best response.

Disease response was assessed using the Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.0 for measureable disease. Each subject was classified according to their "best response" for the purposes of analysis of treatment effect. Two objective status determinations of disease status, by computer tomography (CT) or magnetic resonance imaging (MRI), obtained on two consecutive determinations, separated by at least a 4-week time period, were required to determine the subject's overall best response.

Demographic and Other Characteristics of Study Population

In total, 53 subjects entered the study.

Summary of Demographic Characteristics

	Part 1 Pazopanib tablets				Part 2b Pazopanib tablets)		Part 1 Pazopanib tablets	
	275 mg/m^2 (N=7)	350 mg/m^2 (N=6)	450 mg/m^2 (N=7)	600 mg/m^2 (N=7)	160 mg/m^2 (N=12)	225 mg/m^2 (N=4)	450 mg/m^2 (N=10)	Total (N=53)
Age (years)								
Mean	13.9	10.0	15.0	13.6	12.8	7.0	15.5	13.1
Standard deviation	4.88	3.22	3.96	5.13	4.73	3.56	4.60	4.84
Median (Minimum-maximum)	15.0 (7-20)	9.0 (7-16)	14.0 (10-20)	14.0 (4-21)	11.0 (7-19)	7.5 (3-10)	17.0 (8-23)	13.0 (3-23)
Age Group (years), n (%)								
2 to <12 years	2 (29)	5 (83)	1 (14)	1 (14)	6 (50)	4 (100)	3 (30)	22 (42)
12 to 18 years	4 (57)	1 (17)	4 (57)	5 (71)	4 (33)	0	4 (40)	22 (42)
>18 years	1 (14)	0	2 (29)	1 (14)	2 (17)	0	3 (30)	9 (17)
Sex, n (%)								
Female	3 (43)	3 (50)	3 (43)	4 (57)	6 (50)	2 (50)	5 (50)	26 (49)
Male	4 (57)	3 (50)	4 (57)	3 (43)	6 (50)	2 (50)	5 (50)	27 (51)
Race n (%)								
White	5 (71)	4 (67)	6 (86)	5 (71)	10 (83)	3 (75)	9 (90)	42 (79)
Black	2 (29)	1 (17)	1 (14)	0	2 (17)	1 (25)	0	7 (13)
Korean	0	1 (17)	0	0	0	0	0	1 (2)
Other Asian	0	0	0	1 (14)	0	0	0	1 (2)
Unknown	0	0	0	1 (14)	0	0	1 (10)	2 (4)
Body Surface Area (m^2)								
Mean	1.39	1.04	1.53	1.39	1.44	0.99	1.50	1.37
Standard deviation	0.401	0.235	0.274	0.344	0.437	0.265	0.420	0.391
Median	1.46	1.01	1.46	1.32	1.58	0.94	1.59	1.34
Minimum-maximum	0.8-1.8	0.8-1.4	1.3-2.0	0.8-1.9	0.8-2.1	0.8-1.3	0.9-2.1	0.8-2.1

Source: m5.3.3.2 CPSR Table 7

4.2.2. Pharmacology results

Part 1 and Part 2a were the dose escalation parts of the ADVL0815 (PZP114411) study.

The starting pazopanib tablet dose in Part 1 was 275 mg/m^2 and 2 to 6 evaluable subjects were enrolled at each dose level. Part 2a investigated the safety and PK of pazopanib after administration as the suspension formulation. The starting dose of the pazopanib suspension in Part 2a was 50% of the MTD or highest dose investigated in Part 1. Once the MTD or recommended Phase II dose of pazopanib tablets was defined, up

to 10 additional subjects were enrolled in Part 2b (imaging cohort) to explore changes in vascular permeability using DCE-MRI.

Serial blood samples for the determination of plasma pazopanib concentrations were collected over 24 h after a single dose (Day 1), and over 8 h after repeated oral doses on Day 15 or Day 22 in a subset of subjects (PK population). Blood samples were collected at predose (trough) at the Days 15, 22, and 27 clinic visits, and just prior to starting subsequent odd-numbered cycles.

The mean (range) age of subjects enrolled in Study ADVL0815 (PZP114411) was 13.1 (3 – 23) years. A total of 22 (42%) subjects were aged between 2 and <12 years.

Mean (range) body surface area was 1.37 (0.8 – 2.1) m^2. Oral pazopanib doses of 275 mg/m^2, 350 mg/m^2, 450 mg/m^2, and 600 mg/m^2 as tablets were investigated. Oral suspension doses of 160 mg/m^2 and 225 mg/m^2 also were investigated.

The pharmacokinetics of pazopanib in subjects in Study ADVL0815 (PZP114411) are summarized in Table 1. Predose (trough) plasma pazopanib concentration are summarized in Table 2.

Table 2 Geometric Mean (95% CI) [CVb%] Pazopanib PK Parameters After Single and Repeated Daily Doses in Subjects in Study ADVL0815 (PZP114411) (PK Population)

Cohort	Dose Level (mg/m^2)	Day	N	tmax (h)	Cmax (µg/mL)	AUC(0-8) (µg*h/mL)	AUC(0-24) (µg*h/mL)
Tablet (Part 1)	275	1	5	4.0 (1.9, 22.0)[a]	33.0 (17.0, 63.8) [45.2]	164 (81.7, 331) [47.8]	431 (217, 859) [50.4]
		15/22	5	2.0 (1.0 - 4.0)[a]	47.3 (32.7, 68.4) [26.9]	304 (238, 389) [18.9]	NC
	350	1	2	1.0, 6.0	8.18, 61.3	35.9, 362	60.9, 962
		15/22	1	2.0	11.6	61.4	NC
	450	1	2	2.1, 6.0	20.9, 112	115, 594	253, 1750
		15/22	2	1.0, 6.0	40.7, 79.0	246, 541	NC
	600	1	3	6.0 (4.1 - 8.1)[a]	36.2 (32.3, 98.2)[a]	188 (149 - 605)[a]	561 (531, 1400)[a]
		15/22	3	6.0 (2.1- 6.5)[a]	90.6 (63.5, 105)[a]	603 (449 - 751)[a]	NC
Suspension (Part 2a)	225	1	4	2.0 (2.0 - 6.0)[a]	27.8 (11.3, 67.9) [46.0]	164 (70.4, 384) [44.4]	376 (155, 919) [47.7]
		15/22	2	2.0, 2.1	40.0, 52.0	247, 344	NC
	160	1	12	2.0 (2.0 - 10.0)[a]	19.7 (13.8, 28.1) [60.2]	113 (81.7, 158) [53.9]	342 (227, 515) [65.7][b]
		15/22	10	2.0 (0.5 – 8.0)[a]	37.4 (27.8, 50.3) [33.7]	241 (170, 341) [35.8]	NC
Imaging (Part 2b)	450	1	3	4.0 (2.0 - 10.1)[a]	21.5 (13.8 - 29.0)[a]	139 (80, 540)[a]	378 (208, 540) [a]
		15/22	3	1.0 (1.0 – 4.0)[a]	50.6 (24.0 – 63.1)[a]	374 (170 – 449)[a]	NC

Source:; m5.3.3.2 CPSR Table 22
Data reported as min, max when n=2.
a Data reported as median (range)
b n=10
AUC = area under concentration-time curve; CI = confidence interval; Cmax = maximum observed concentration; CVb = coefficient of variation; NC = not calculated, tmax = time of occurrence of Cmax.

Table 3 Mean (SD) Trough Plasma Pazopanib Concentrations after Repeated Daily Doses (PK Population)

Formulation	Dose (mg/m^2)	Day 15 (µg/mL)	Day 22 (µg/mL)	Day 27 (µg/mL)
Tablet	275	32.7 (12.6)	34.5 (21.2)	31.4 (16.8)

(Part 1)	350	32.4 (20.1)	28.8 (18.4)	31.4 (24.3)
	450	25.7 (15.5)	19.1 (12.6)	26.0 (14.1)
	600	42.9 (16.6)	49.1 (16.6)	36.4 (25.9)
Suspension (Part 2a)	160	23.0 (9.3)	25.2 (7.9)	25.2 (8.7)
	225	27.3 (11.4)	23.9 (14.4)	40.7
Imaging (Part 2b)	450	41.5 (13.0)	46.4 (16.8)	49.8 (18.7)

Source m5.3.3.2 CPSR Table 24:.
N: 160 mg/m^2 level: Day 15 (N=10); Day 22 (N=8); Day 27 (N=8)
225 mg/m^2 level: Day 15 (N=3); Day 22 (N=2); Day 27 (N=1)
275 mg/m^2 level: Day 15 (N=6); Day 22 (N=6); Day 27 (N=5)
350 mg/m^2 level: Day 15 (N=6); Day 22 (N=6); Day 27 (N=4)
450 mg/m^2 level: Day 15 (N=5); Day 22 (N=4); Day 27 (N=5)
600 mg/m^2 level: Day 15 (N=5); Day 22 (N=4); Day 27 (N=4).
450 mg/m^2 (Part 2b) level: Day 15 (N=7); Day 22 (N=7); Day 27 (N=7)

4.2.3. Efficacy Results

Two (4%) subjects achieved a PR (Table 3). Subject 794200, with desmoplastic small round cell tumour, achieved a PR after 5.5 months, which was sustained for 24 months. Subject 774572, with hepatoblastoma and embryonal hepatoma, had a PR after 5.5 months and maintained this response for a further 5.5 months; however, they were removed from the study because of an AE.

Twelve (23%) subjects had a best response of stable disease, and had the following diagnoses:

- In Part 1: malignant melanoma (n=2), synovial sarcoma (n=2), alveolar soft part sarcoma, malignant glioma, osteosarcoma
- In Part 2a: desmoplastic small round cell tumour
- In Part 2b: alveolar rhabdomyosarcoma (n=2), alveolar soft part sarcoma, gastrointestinal stromal sarcoma. (All subjects in Part 2b had sarcoma.)

Table 3 Summary of Investigator-assessed Best Response (with confirmation) RECIST 1.0 (Safety Population)

	Part 1 (Pazopanib tablets) (n=27)	Part 2a (Pazopanib suspension) (n=16)	Part 2b (Pazopanib tablets) (n=10)	Total (n=53)
Best Response, n (%)				
Complete Response	0	0	0	0
Partial Response	1 (4)	0	1 (10)	2 (4)
Stable Disease	7 (26)	1 (6)	4 (40)	12 (23)
Non-CR/Non-PD	0	0	0	0
Progressive Disease	3 (11)	2 (13)	5 (50)	10 (19)
Not evaluable	16 (59)	13 (81)	0	29 (55)
Response Rate				
CR+PR, n (%)	1 (4)	0	1 (10)	2 (4)
95% Confidence Interval, %	(0.7, 18.3)	(0, 19.4)	(1.8, 40.4)	(1.0, 12.8)

Source: m5.3.3.2 CSPR Table 27
Abbreviations: CR=complete response; PD=Progressive disease PR=partial response

4.2.4. Safety Results

The primary objective of this study included defining the maximum tolerated dose (MTD), evaluate toxicity and obtain initial pazopanib pharmacokinetic (PK) parameters in a paediatric patient population. In addition to monitoring of AEs, monitoring of specific toxicities was performed for growth plate, thyroid and cardiac toxicity.

In total, 53 subjects entered the study. All were included in the safety population and were evaluable for the analysis of safety. Of the 53 subjects entered into the study, 27 subjects received pazopanib tablets in Part 1, 16 subjects received a pazopanib suspension in Part 2a, and 10 subjects received pazopanib tablets (at the MTD) in Part 2b. All subjects discontinued study treatment. The most common primary reason for discontinuation from study treatment was disease progression (35 [66%] subjects), followed by AEs (11 [21%] subjects).

The planned duration of the protocol therapy was 24 cycles, with each cycle defined as 28 days in duration. Median exposure was 3.0 months (range: 1 to 23 months) across all groups. One subject in Part 2b received the maximum of 24 cycles of study treatment.

Analysis of Adverse Events

All subjects had at least one AE during the study and at least one AE that was considered by the investigator related to study treatment (Table 4). AEs led to withdrawal for 11 (21%) subjects.

Table 4 Adverse Event Overview (Safety Population)

	Part 1 Pazopanib tablets				Part 2a Pazopanib suspension		Part 2b Pazopanib tablets	Total (N=53)
	275 mg/m^2 (N=7)	350 mg/m^2 (N=6)	450 mg/m^2 (N=7)	600 mg/m^2 (N=7)	160 mg/m^2 (N=12)	225 mg/m^2 (N=4)	450 mg/m^2 (N=10)	
Any AE[a], n (%)	7 (100)	6 (100)	7 (100)	7 (100)	12 (100)	4 (100)	10 (100)	53 (100)
AEs related to protocol therapy	7 (100)	6 (100)	7 (100)	7 (100)	12 (100)	4 (100)	10 (100)	53 (100)
AE leading to dose interruption	0	0	0	1 (14)	0	0	1 (10)	2 (4)
Any SAE, n(%)	4 (57)	2 (33)	3 (43)	5 (71)	4 (33)	2 (50)	5 (50)	25 (47)
SAEs related to protocol therapy	4 (57)	2 (33)	3 (43)	5 (71)	3 (25)	2 (50)	4 (40)	23 (43)
Fatal SAEs	0	0	0	1 (14)	1 (8)	0	1 (10)	3 (6)
Fatal SAEs related to study treatment	0	0	0	0	0	0	0	0

Source: m5.3.3.2 CPSR Table 12
AE: adverse event, SAE: serious adverse event
Information on AEs leading to discontinuation of treatment is included in **Error! Reference source not found.**. The data collected about each AE did not provide a record of the AEs leading to discontinuation.

Common Adverse Events

The most common AEs are summarised in table 5.

Table 5 Summary of Adverse Events in >= 30% Subjects (Safety Population)

System Organ Class Preferred Term, n (%)	Part 1 Pazopanib tablets				Part 2a Pazopanib suspension		Part 2b Pazopanib tablets	Total (N=53)
	275 mg/m^2 (N=7)	350 mg/m^2 (N=6)	450 mg/m^2 (N=7)	600 mg/m^2 (N=7)	160 mg/m^2 (N=12)	225 mg/m^2 (N=4)	450 mg/m^2 (N=10)	
Any event	7 (100)	6 (100)	7 (100)	7 (100)	12 (100)	4 (100)	10 (100)	53 (100)
White blood cell decreased	4 (57)	4 (67)	5 (71)	3 (43)	6 (50)	2 (50)	8 (80)	32 (60)
Fatigue	4 (57)	3 (50)	4 (57)	5 (71)	4 (33)	2 (50)	9 (90)	31 (58)
Diarrhoea	6 (86)	2 (33)	6 (86)	3 (43)	4 (33)	1 (25)	7 (70)	29 (55)
Vomiting	5 (71)	3 (50)	4 (57)	4 (57)	4 (33)	2 (50)	6 (60)	28 (53)
Hypertension	3 (43)	5 (83)	2 (29)	3 (43)	4 (33)	3 (75)	6 (60)	26 (49)
Lymphocyte count decreased	2 (29)	3 (50)	2 (29)	4 (57)	6 (50)	1 (25)	7 (70)	25 (47)
Neutrophil count	3 (43)	4 (67)	3 (43)	2 (29)	3 (25)	2 (50)	8 (80)	25 (47)

decreased								
ALT increased	3 (43)	0	6 (86)	4 (57)	5 (42)	3 (75)	3 (30)	24 (45)
AST increased	4 (57)	2 (33)	5 (71)	2 (29)	2 (17)	3 (75)	6 (60)	24 (45)
Headache	2 (29)	3 (50)	4 (57)	4 (57)	3 (25)	1 (25)	7 (70)	24 (45)
Hyperglycemia	2 (29)	3 (50)	3 (43)	3 (43)	4 (33)	2 (50)	7 (70)	24 (45)
Nausea	3 (43)	2 (33)	3 (43)	4 (57)	4 (33)	1 (25)	7 (70)	24 (45)
Proteinuria	3 (43)	2 (33)	4 (57)	3 (43)	5 (42)	2 (50)	5 (50)	24 (45)
Platelet count decreased	2 (29)	4 (67)	3 (43)	2 (29)	3 (25)	3 (75)	6 (60)	23 (43)
Anaemia	1 (14)	1 (17)	4 (57)	4 (57)	3 (25)	2 (50)	7 (70)	22 (42)
Hyponatremia	2 (29)	2 (33)	3 (43)	1 (14)	5 (42)	3 (75)	5 (50)	21 (40)
Abdominal pain	2 (29)	2 (33)	3 (43)	3 (43)	3 (25)	1 (25)	4 (40)	18 (34)
Hypoalbuminemia	1 (14)	1 (17)	3 (43)	2 (29)	4 (33)	2 (50)	5 (50)	18 (34)
Constipation	1 (14)	1 (17)	2 (29)	3 (43)	3 (25)	2 (50)	5 (50)	17 (32)
Anorexia	1 (14)	1 (17)	2 (29)	2 (29)	3 (25)	2 (50)	5 (50)	16 (30)
Hypophosphatemia	2 (29)	1 (17)	2 (29)	3 (43)	4 (33)	2 (50)	2 (20)	16 (30)

Source: m5.3.3.2 CPSR Table 14

AEs with a maximum grade of Grade 3 or higher, reported for more than 1 subject overall, are presented in Table 6.

Table 6 Summary of Adverse Events of Grade 3 or 4 in Greater than 1 Subject Overall (Safety Population)

	Part 1 Pazopanib tablets				**Part 2a Pazopanib suspension**		**Part 2b Pazopanib tablets**
System Organ Class Preferred Term[a], n (%)	**275 mg/m^2 (N=7)**	**350 mg/m^2 (N=6)**	**450 mg/m^2 (N=7)**	**600 mg/m^2 (N=7)**	**160 mg/m^2 (N=12)**	**225 mg/m^2 (N=4)**	**450 mg/m^2 (N=10)**
Any event of Grade 3 or 4	4 (57)	3 (50)	4 (57)	3 (43)	5 (42)	4 (100)	6 (60)
Neutrophil count decreased	1 (14)	2 (33)	1 (14)	0	0	1 (25)	2 (20)
Lymphocyte count decreased	0	0	0	0	3 (25)	1 (25)	2 (20)
Anaemia	0	0	0	1 (14)	0	1 (25)	3 (30)
Anorexia	0	0	0	2 (29)	1 (8)	0	1 (10)
Dyspnoea	0	0	0	2 (29)	0	0	2 (20)
Abdominal pain	0	0	0	0	1 (8)	0	2 (20)
ALT increased	0	0	1 (14)	0	0	2 (50)	0
Back pain	0	0	0	0	1 (8)	0	2 (20)
Headache	0	0	0	1 (14)	0	0	2 (20)
Hypokalemia	0	0	1 (14)	0	1 (8)	1 (25)	0
Hypertension	0	0	1 (14)	1 (14)	0	0	0
Activated PTT prolonged	1 (14)	1 (17)	0	0	0	0	0
Ataxia	0	1 (17)	0	1 (14)	0	0	0
Depressed level of consciousness	0	0	0	0	1 (8)	0	1 (10)
Diarrhoea	0	0	0	0	0	0	2 (20)
Hyponatremia	0	0	0	0	1 (8)	0	1 (10)
Hypophosphatemia	0	0	0	1 (14)	1 (8)	0	0
Lipase increased	1 (14)	0	0	0	0	0	1 (10)
Pain in extremity	0	0	1 (14)	0	0	0	1 (10)
Serum amylase increased	0	0	0	1 (14)	1 (8)	0	0
Tumour pain	1 (14)	0	0	0	0	0	1 (10)
White blood cell decreased	1 (14)	1 (17)	1 (14)	0	0	0	0

Pain	0	0	0	0	1 (8)	0	1 (10)

Source: m5.3.3.2 CPSR Table 15 ALT= Alanine aminotransferase; PTT = Partial thromboplastin time
Ordered by frequency overall and then by alphabetical order.

AEs were also analysed by age group (2 to <12 years, 12 to <19 [i.e., up to and including 18] years, >18 years [i.e. 19 years and above]), although interpretation is limited by the small number of subjects (n=22, 22 and 12, respectively).

- Of the most common AEs, AST increased and hyponatremia were the only AEs reported at a higher incidence in the 2 to <12 years group compared with the 12 to <19 or >18 years age groups (59%, compared with 41% and 33% , respectively, and 50% compared with 32% and 42%, respectively).
- Of the most common AEs, those reported at a higher incidence in the 12 to <19 years group compared with the 2 to <12 or >18 years age groups included fatigue (64% compared with 50% and 58%, respectively), headache (55% compared with 36% and 42%, respectively), and hyperglycemia (55% compared with 41% and 42%, respectively)
- Of the most common AEs, a number were reported at a higher incidence in the >18 years group compared with the 2 to <12 or 12 to <19 years age groups (>15% difference). These included ALT increased (75% compared with 41% and 41%, respectively), diarrhoea (83% compared with 41% and 55%, respectively), lymphocyte count decreased (67% compared with 41% and 41%, respectively), platelet count decreased (67% compared with 36% and 41%, respectively), and white blood cell decreased (75% compared with 59% and 50%, respectively).

Seven (13%) subjects died and all had the primary cause of death reported as disease under study Table 7. Only one primary cause of death was given for each subject and the 7 deaths includes the 3 subjects considered to have fatal SAEs.

Table 7 Summary of Deaths (Safety Population)

	Part 1 Pazopanib tablets				Part 2a Pazopanib suspension		Part 2b Pazopanib tablets	
	275 mg/m^2 (N=7)	350 mg/m^2 (N=6)	450 mg/m^2 (N=7)	600 mg/m^2 (N=7)	160 mg/m^2 (N=12)	225 mg/m^2 (N=4)	450 mg/m^2 (N=10)	Total (N =53)
Subject status								
Dead	0	0	0	2 (29)	3 (25)	1 (25)	1 (10)	7 (13)
Alive at last contact	7 (100)	6 (100)	7 (100)	5 (71)	9 (75)	3 (75)	9 (90)	46 (87)
Primary cause of death								
Due to disease under study	0	0	0	2 (29)	3 (25)	1 (25)	1 (10)	7 (13)
Contributing cause(s) of death								
None	0	0	0	2 (29)	3 (25)	1 (25)	1 (10)	7 (13)

Source: m5.3.3.2 CPSR Table 18
Note: Only one primary cause of death was given. If there were other reasons for the death then these were captured under the contributing causes.

Table 8 presents the clinical laboratory grade changes from baseline grade for ALT and bilirubin. Other clinical chemistry values of Grade 3 included: alkaline phosphatase (1 subject), amylase (1 subject) and lipase (1 subject). These findings were reported as AEs. There were no Grade 4 values reported for any parameter.

Table 8 Summary of ALT and Bilirubin Laboratory Grade Changes from Baseline (Safety Population)

Protocol Therapy	Planned Time	N[a]	Any Grade Increase n (%)	Increase to Grade 1 n (%)	Increase to Grade 2 n (%)	Increase to Grade 3 n (%)
ALT						

Pazopanib tablets (Part 1)						
275 mg/m²	Worst-case post baseline	7	2 (29)	2 (29)	0	0
350 mg/m²	Worst-case post baseline	6	0	0	0	0
450 mg/m²	Worst-case post baseline	7	3 (43)	3 (43)	0	0
600 mg/m²	Worst-case post baseline	7	4 (57)	4 (57)	0	0
Pazopanib suspension (Part 2a)						
160 mg/m²	Worst-case post baseline	12	2 (17)	2 (17)	0	0
225 mg/m²	Worst-case post baseline	4	3 (75)	1 (25)	0	2 (50)
Pazopanib tablet (Part 2b)						
450 mg/m²	Worst-case post baseline	10	2 (20)	1 (10)	1 (10)	0
Total						
	Worst-case post baseline	53	16 (30)	13 (25)	1 (2)	2 (4)
Bilirubin						
Pazopanib tablets (Part 1)						
275 mg/m²	Worst-case post baseline	7	1 (14)	1 (14)	0	0
350 mg/m²	Worst-case post baseline	6	1 (17)	0	1 (17)	0
450 mg/m²	Worst-case post baseline	7	1 (14)	1 (14)	0	0
600 mg/m²	Worst-case post baseline	7	0	0	0	0
Pazopanib suspension (Part 2a)						
160 mg/m²	Worst-case post baseline	12	0	0	0	0
225 mg/m²	Worst-case post baseline	4	0	0	0	0
Pazopanib tablet (Part 2b)						
450 mg/m²	Worst-case post baseline	10	0	0	0	0
Total						
	Worst-case post baseline	53	3 (6)	2 (4)	1 (2)	0

Source: m5.3.3.2 CPSR Table 20
N is defined as the number of subjects with values at the specified planned time.

Vital Signs, Physical Findings, and Other Observations Related to Safety

Five subjects had an increase to Grade 2 diastolic blood pressure (DBP), 2 subjects had an increase to Grade 3 DBP and 2 subjects had increase to Grade 2 systolic blood pressure (SBP). In addition 3 subjects had decreases in left ventricular ejection fraction or shortening fraction as noted on echocardiograms, and one subject had an AE of "cardiac disorder – other" reported.

Growth plate toxicity was also monitored. A total of 36 (68%) subjects had an open tibial growth plate at screening. At least two knee radiographs were obtained and centrally reviewed for 27 subjects. One subject had a closed growth plate on central review, and the second was ineligible for the study. Of the 26 subjects with open physes (median age, 11 years; range, 4 to 17 years), one 11-year old subject had thickening of the growth plate. This was confirmed by MRI, and a decrease in height velocity. Three additional subjects aged 11, 8 and 4 years-old each had growth plate widening radiographically after 4 cycles of treatment, but were discontinued because of progressive disease. The remaining 22 subjects had normal radiographs, including 3 subjects receiving 8, 12, and 13 cycles.

4.2.5. Discussion & conclusion

The MAH for Votrient (pazopanib) has submitted a variation in order to amend the SmPC, Section 4.2, Paediatric population, to delete the sentence "No data are available".

With the variation results from study ADVL0815/PZP114411), a Phase I Study of Pazopanib as a Single Agent for Children with Relapsed or Refractory Solid Tumours, including central nervous system (CNS) tumours, has been included. The primary purpose of the phase I study ADVL0815 was to identify the MTD of pazopanib for administration to children, adolescents and young adults. The primary objectives were to evaluate toxicity and begin the process of characterising pazopanib PK parameters in a paediatric population. Evaluation of clinical activity was a secondary objective. A total of 53 paediatric subjects with a variety of relapsed/refractory solid tumours were evaluated and reported.

The data showed that plasma pazopanib concentrations associated with clinical and biologic effects consistent with VEGFR inhibition (20 μg/mL) were achieved at all dose levels after oral administration of tablets/suspension.

Some clinical activity of pazopanib was observed in a heavily pretreated paediatric population.
Clinical activity included 2 subjects with partial responses in refractory desmoplastic small round cell tumour and hepatoblastoma. Stable disease were seen in 12 subjects (23%) in a variety of tumour types (malignant melanoma (n=2), synovial sarcoma (n=2), alveolar soft part sarcoma, malignant glioma, osteosarcoma, desmoplastic small round cell tumour, alveolar rhabdomyosarcoma (n=2), alveolar soft part sarcoma, gastrointestinal stromal sarcoma.

Serious adverse events were reported for 25 (47%) subjects. The most common SAEs were anaemia (4 [8%] subjects), increased lipase (4 [8%] subjects), abdominal pain, dyspnoea and hypothyroidism (each in 3 [6%] subjects). No other SAEs were reported for greater than 2 subjects. Decreases in left ventricular ejection fraction were reported for 9 (17%) subjects, 3/17 at the MTD for tablets and none at the MTD for the suspension. All (3) fatal SAEs had the primary cause of death related to their disease. The types of AEs observed was consistent with those seen in the adult population treated with pazopanib.

Overall conclusion

It can be agreed that based on the data from this small paediatric study no firm conclusion can be drawn about activity nor safety in particular tumour types and consequently efficacy of pazopanib in children aged 2 to 18 years of age based on the data from this study has not yet been established. The overall efficacy and safety profile of pazopanib remains unchanged.

With the provided data the statement currently included in the SmPC section 4.2; “no data are available” is no longer appropriate. It is also endorsed that even though some information is now available the overall paediatric data regarding safety and tolerability of pazopanib are still limited and therefore the conclusion “that safety and efficacy of pazopanib in children aged 2 to 18 years have not been established” remains unchanged.

However, it could be considered of value to evaluate the data by comparing the PK data/parameters in adults with those in children of the various age categories (2-6, 6-12, 12-18 years and >18 years) taking into account possible differences in formulation and absolute doses and provide some level of paediatric PK data in section 5.2 of the SmPC.

4.3. Changes to the Product Information

As a result of this variation, section 4.2 of the SmPC is updated. The proposal is considered appropriate. Please refer to Attachment 1 which includes all agreed changes to the Product Information.

5. Request for supplementary information

1. It could be considered of value to evaluate the data by comparing the PK data/parameters in adults with those in children of the various age categories (2-6, 6-12, 12-18 years and >18 years) taking into account possible differences in formulation and absolute doses and provide some level of paediatric PK data in section 5.2 of the SmPC.

6. Assessment of the responses to the request for supplementary information

Question 1

It could be considered of value to evaluate the data by comparing the PK data/parameters in adults with those in children of the various age categories (2-6, 6-12, 12-18 years and >18 years) taking into account possible differences in formulation and absolute doses and provide some level of paediatric PK data in section 5.2 of the SmPC.

Response:

VOTRIENT does not currently have an indication in the paediatric population; however, GSK agrees that paediatric pharmacokinetic data could be of value. To that end, the available data were reviewed.

The breakdown of the pharmacokinetic results of the children by age categories, formulation, and dose from Study ADVL0815/PZP114411 (a phase I study of pazopanib as a single agent for children with relapsed or refractory solid tumours, including central nervous system (CNS) tumours) is shown in Table 1. As can be observed from the information in the table, the sample size for each age category is very small therefore the data are not amenable for a summary in the SmPC to provide relevant pharmacokinetic data to a prescriber at this time.

GSK will continue to collect and review data from ongoing paediatric studies and will inform the EMA of relevant data in this population as they become available.

Table 1 Summary of Demographic Characteristics with Available Pharmacokinetic Data (Study ADVL0815/PZP114411)

Demographics	Number of subjects							
	Part 1 (Pazopanib tablets)				Part 2a (Pazopanib suspension)		Part 2b (Pazopanib tablets)	Total
	275 mg/m² (N=5)	350 mg/m² (N=2)	450 mg/m² (N=2)	600 mg/m² (N=3)	160 mg/m² (N=12)	225 mg/m² (N=4)	450 mg/m² (N=3)	(N=31)
Age Group (years)								
2 to ≤6	0	0	0	1	0	2	0	3
6 ≤ 12	2	2	0	0	6	2	1	13
12 to 18 years	2	0	2	1	4	0	0	9
>18 years	1	0	0	1	2	0	2	6

Conclusion

The MAH as provided their response to the one outstanding issue. As highlighted by the MAH Votrient (pazopanib) is not approved for the use in the paediatric population, and the numbers on which any pharmacokinetic information may be based on and subsequently addressed in section 4.2 is very limited. Thus the conclusion of the MAH, that nothing further may be included in section 5.2 in the SmPC is endorsed.

X Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐ No need to update overall conclusion and impact on benefit-risk balance