EMA/CHMP/28241/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sutent

International non-proprietary name: sunitinib

Procedure No. EMEA/H/C/000687/II/0070

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 5555
Send a question via our website www.ema.europa.eu/contact

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure:	30 Jul 2018	30 Jul 2018	☐
☐	CHMP Rapporteur Assessment Report	03 Sep 2018	04 Sep 2018	☐
☐	CHMP members comments	17 Sep 2018	17 Sep 2018	☐
☐	Updated CHMP Rapporteur Assessment Report	20 Sep 2018	n/a	☐
☐	Start of written procedure	25 Sep 2018	25 Sep 2018	☐
☐	Request for supplementary information	27 Sep 2018	27 Sep 2018	☐
	Submission of MAH's responses	9 Oct 2018	8 Oct 2018	
☐	Re-start of procedure:	10 Oct 2018	10 Oct 2018	☐
☐	CHMP Rapporteur Assessment Report	24 Oct 2018	24 Oct 2018	☐
☐	CHMP members comments	29 Oct 2018	29 Oct 2018	☐
☐	Updated CHMP Rapporteur Assessment Report	31 Oct 2018	n/a	☐
☐	Start of written procedure	6 Nov 2018	6 Nov 2018	☐
☐	2nd Request for supplementary information	8 Nov 2018	8 Nov 2018	☐
	Submission of MAH's responses	13 Nov 2018		
☐	Re-start of procedure:	14 Nov 2018	14 Nov 2018	☐
☐	CHMP Rapporteur Assessment Report	28 Nov 2018	28 Nov 2018	☐
☐	CHMP members comments	3 Dec 2018	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	6 Dec 2018	6 Dec 2018	☐
☐	Start of written procedure	n/a	n/a	☐
☒	Opinion	13 Dec 2018	13 Dec 2018	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for PRAC plenary discussion: proposal for update of SmPC/PL, introduction of or changes to imposed conditions or additional risk minimisation measures (except for generics aligning with the originator medicinal product), substantial changes to the pharmacovigilance plan (relating to additional pharmacovigilance activities, except for generics adapting aligning with the originator medicinal product), substantial disagreement between the Rapporteur and other PRAC members, at the request of the Rapporteur, any other PRAC member, the Chair or EMA.

Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair.

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Pfizer Europe MA EEIG submitted to the European Medicines Agency on 5 July 2018 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 sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to include paediatric study results (from studies A6181196 and ACNS1021) performed in compliance with a paediatric investigation plan (PIP). In addition the MAH took the opportunity to introduce editorial changes in the PL.

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

Information on paediatric requirements

The application included an EMA Decision P/0147/2018 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0147/2018 was completed.

The PDCO issued an opinion on compliance for the PIP P/0147/2018.

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

The aim of the variation is to update Sutent SmPC to include paediatric study results from studies A6181196 and ACNS1021 performed in compliance with a paediatric investigation plan (PIP), in order to provide physicians with the available information (dosing, administration, adverse reactions, pharmacokinetics, and clinical activity) in paediatric cancer patients, including those with gastrointestinal stromal tumour (GIST). The MAH is not seeking an indication in the paediatric population, as the clinical pharmacology, efficacy, and safety of sunitinib in children and young adults with GIST do not conclusively support a sufficiently favourable benefit/risk profile.

The data (clinical pharmacology, efficacy and safety) included in this submission were collected from 3 clinical studies: ADVL0612, ACNS1021, and A6181196. They were conducted globally to determine the maximum tolerated dose (MTD) of sunitinib in paediatric patients with refractory solid tumors (Study ADVL0612), to estimate the objective response rate (ORR) to sunitinib in recurrent/progressive/refractory high-grade glioma (HGG) or ependymoma in pediatric (aged 18 months to 17 years) and young adult (aged 18 to 22 years) patients (Study ACNS1021), and to evaluate the PK, safety, and preliminary anti-tumor efficacy of sunitinib in pediatric and young adult patients diagnosed with advanced, unresectable GIST (Study A6181196). Furthermore, results from 3 modeling analysis reports, which provide additional sunitinib PK data, have been included in the submission.

According to the MAH, based on the clinical pharmacology results, a starting dose of 20 mg/m^2/day on Schedule 4/2 is predicted to provide comparable systemic sunitinib exposures to those observed in adult patients with GIST treated at 50 mg/day on Schedule 4/2.

However, data from the phase I study ADVL0612 identified the 15 mg/m2/day as the sunitinib MTD in paediatric subjects without previous exposure to anthracyclines or cardiac irradiation. As stated by the MAH in the RSI, the MTD projection in ADVL0612 study was done in heavily pretreated pediatric patients mainly with CNS tumors. In addition, the starting dose in both clinical trial A6181196 and ACNS1021 was 15 mg/m^2 (based on the MTD) with the option to escalate the dose based on toxicity. Further, the MAH noted that in the majority of the patients on the published case studies, the dose was higher than 20 mg/m^2. The information that children treated in clinical trials/in case series received starting or average daily doses of 20 mg/m^2 is not emerging from the SmPC, therefore it appeared somewhat misleading to report that the MTD is 15 mg/m^2, and that 20 mg/m^2 is the dose in paediatric patients expected to provide exposures similar to that obtained in adult patients with GIST. As per CHMP request, the MAH modified the SmPC section 5.2 to describe the dosages of Sutent received by pediatric patients in the clinical experience, in order to clarify the apparent contradiction between MTD and wording on 20 mg/m^2.

Based on the clinical data provided in paediatric patients with GIST (i.e. study A6181196 and 3 case series from literature), due to the lack of objective confirmed radiological responses, the limited number of patients in the clinical trial, the intrinsic limitations of retrospective case series, along with the indolent nature of GIST in paediatric patients, it is agreed that the available evidence does not conclusively support the clinical activity of sunitinib in children with GIST.

The benefit-risk balance of Sutent remains positive.

3. Recommendations

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

Variation accepted		**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 sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to include paediatric study results (from studies A6181196 and ACNS1021) performed in compliance with a paediatric investigation plan (PIP). In addition the MAH took the opportunity to introduce editorial changes in the PL.

☒ is recommended for approval.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0147/2018 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB are recommended.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Please refer to Scientific Discussion "EMEA/H/C/000687/II/0070"

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Sunitinib is an orally active small molecule multiple RTKs (PDGFRα-β, VEGFR1-2-3, KIT, FLT3, CSF-1R, RET) inhibitor, currently approved for metastatic RCC, GIST and pNET in adults.

This application relates to the submission of paediatric study results with Sutent, performed in compliance with a PIP. The following data are included in the dossier:

- Study A6181196 "A Phase I Study of Sunitinib (SU11248), an Oral Multi-Targeted Tyrosine Kinase Inhibitor, in Children With Refractory Solid Tumours";

- Study ACNS1021 "A Phase II Study of Sunitinib in Recurrent, Refractory or Progressive High-Grade Glioma and Ependymoma Tumours in Paediatric and Young Adult Patients";

- Retrospective analyses of medical records from paediatric and young adult patients with GIST treated with sunitinib from 3 case-series publications;

- Population Modeling Analysis Report.

The scope of this Type II variation is to support the inclusion of relevant paediatric data in the sunitinib SmPC (dosing, administration, adverse reactions, pharmacokinetics, and clinical activity) to inform physicians of the available information in paediatric cancer patients, including those with gastrointestinal stromal tumour (GIST). The MAH is not seeking an indication in the paediatric population, as the clinical pharmacology, efficacy, and safety of sunitinib in children and young adults with GIST do not conclusively support a sufficiently favorable benefit/risk profile.

The PDCO adopted on 29 June 2018 an opinion confirming the compliance of all studies in the agreed PIP (P/0147/2018). The PDCO positive opinion has been included by the MAH in the dossier (EMA/PDCO/255740/2018).

The MAH stated that an updated RMP will be provided by 3Q2018.

6. Clinical Pharmacology aspects

Results from 3 modeling analysis reports, which provide additional sunitinib PK data have been provided:

• Population Modeling Analysis Report (PMAR-EQDD-A618w-Other-366) entitled 'Population Pharmacokinetics-Pharmacodynamics of Sunitinib in Patients with GIST and Solid Tumors' describes key safety and efficacy endpoints of sunitinib and its active metabolite, SU012662, using pooled PK data from all studies in adult and paediatric patients with GIST or solid tumours. Two-compartment models with lag time were successfully used to describe the PK of sunitinib and SU012662. Mechanism-based and semi-mechanistic PK-Pharmacodynamics (PD) models were successfully built to describe key safety and efficacy endpoints of sunitinib.

• Population Modeling Analysis Report (PMAR-EQDD-A618b-DP4-846) entitled 'Population Pharmacokinetics of Sunitinib in Paediatric Patients with GIST and Other Solid Tumors' presents the results of a population PK model for sunitinib and SU012662 using pooled PK data from studies in paediatric patients with GIST or other solid tumours (ie, Studies ADVL0612, ACNS1021, and A6181196).

• Physiologically based (PB) population PK Report (PBPK SimCYP Report) entitled 'SIMCYP Prediction of Sunitinib Exposure in Paediatrics' presents the analysis of the prediction of sunitinib and SU012662 exposures in paediatric patients using PBPK simulations with SimCYP

According to the MAH, based on the clinical pharmacology results, a starting dose of 20 mg/m2/day on Schedule 4/2 in paediatric patients with GIST (within age ranges from 6 years to 11 years and from 12 years to 17 years) is predicted to provide comparable systemic sunitinib exposures to those observed in adult patients with GIST treated at 50 mg/day on Schedule 4/2.

Following discussions with the EMA's Paediatric Committee (PDCO), the MAH agreed to conduct the single-arm, open-label, multicenter, multinational, Phase 1/2 clinical trial of single-agent sunitinib (Study A6181196) to investigate the use of sunitinib for the treatment of paediatric GIST, collecting safety, PK, and efficacy data in children aged 6 years to less than 18 years. The PDCO recommended a primary endpoint of PK parameters of sunitinib and its active metabolite SU012662.

The PDCO accepted the MAH's proposal to conduct population PK and PK-PD analyses to help extrapolate the PK and key safety and efficacy endpoints of sunitinib to paediatric GIST patients based on the available data in adult patients with GIST or non-GIST solid tumours and paediatric patients with non-GIST solid tumours. The analysis results were compared to the available safety and efficacy data in paediatric GIST patients from available literature to confirm the predictability of the models in paediatric GIST patients (PMAR-EQDD-A618w- Other-366).

In addition, the MAH was requested to perform an integrated population PK analysis of the data from 3 paediatric studies of sunitinib (PMAR-EQDD-A618b-DP4-846). The MAH was also requested to build a PBPK model for sunitinib in which the predicted PK concentrations were compared to the observed concentrations in paediatric patients with GIST or solid tumours (Measure 5 of the PIP). The results of the former analysis are presented in the PMAR-EQDD-A618b-DP4-846, and the results of the PBPK analysis are presented in the PBPK SimCYP report (PBPK SimCYP Report).

6.1. Methods – analysis of data submitted

One of the main objective of the present application is to provide supportive PK data for the administration of sunitinib in pediatric patients. Clinical studies included in this package were conducted globally to determine the maximum tolerated dose (MTD) of sunitinib in pediatric patients with refractory solid tumors (Study ADVL0612), to estimate the objective response rate (ORR) to sunitinib in recurrent/progressive/refractory high-grade glioma (HGG) or ependymoma in pediatric (aged 18 months to 17 years) and young adult (aged 18 to 22 years) patients (Study ACNS1021), and to evaluate the PK, safety, and preliminary anti-tumor efficacy of sunitinib in pediatric and young adult patients diagnosed with advanced, unresectable GIST (Study A6181196).

The PK data included in this summary of clinical pharmacology were collected from 3 studies: ADVL0612, ACNS1021, and A6181196:

Table 1. Overview of Pediatric Clinical Studies With Subjects Evaluable for PK

Protocol No. (Study Type)	Design and Objectives	Starting Dose/ Formulation/ Schedule	PK-Evaluable Subjects* (n)	Full PK Profile Sampling	Trough Concentration Sampling	Non-compartmental PK Analysis
ADVL0612	Open-label, Phase I dose escalation sequential-cohort study of oral sunitinib in children with refractory solid tumors. The aim of the study was to determine the MTD of sunitinib when given on the recommended adult schedule of QD for 28 days followed by 14 days off-treatment.	Part A: 15 and 20 mg/m^2; Capsules; QD; Schedule 4/2 Part B: 15 and 20 mg/m^2; Capsules; QD; Schedule 4/2 Part C: 15 mg/m^2; Sprinkled Capsules[a]; QD; Schedule 4/2	Refractory solid tumors (Part A: 12; Part B: 11; Part C: 12)	X[b]	X	X
ACNS1021	Open-label, Phase II study to estimate the ORR to sunitinib in 2 strata of recurrent/progressive/refractory HGG and ependymoma in pediatric (aged 18 months to 17 years) and young adult (aged 18 to 22 years) patients.	15 mg/m^2; capsules; QD for 28 days followed by a 14-day off-period	Recurrent/progressive/refractory HGG and ependymoma tumors (24)	X[b]	X	X
A6181196	Single-arm, multi-center, multi-national, Phase I/II study evaluating the PK, safety, and preliminary anti-tumor efficacy of sunitinib in children and young adults diagnosed with advanced, unresectable GIST.	15 mg/m^2; capsules; Schedule 4/2	GIST (6)	X	X	X

Source: CSRs ADVL0612, ACNS1021, and A6181196.
*The total number of subjects enrolled was the same as PK-evaluable subjects in Studies ADVL0612 and A6181196; for Study ACNS1021, the total number of subjects enrolled was 29.
GIST=gastrointestinal stromal tumor; HGG=high-grade glioma; MTD=maximum tolerated dose; ORR=objective response rate; PK=pharmacokinetic(s); QD=once daily; X=study had PK sampling.
a. Sprinkled capsule contents on yogurt or applesauce.
b. Full PK profile was collected from selected number of patients.

The demographic characteristics of subjects who were enrolled in each study are provided in the table below:

Table 2. Summary Demographics for Pediatric Clinical Studies With Subjects Evaluable for PK

Protocol No. (Dose Level, if applicable)	N	Age (years)		Weight (kg)		n (%)						
		Mean (±SD)	Min-Max	Mean (±SD)	Min-Max	Sex		Race				
						Male (%)	Female (%)	White	Black	Asian	NA/ Others	Unspec-ified
ADVL0612	Part A: 12	14.6 (3.1)	10-20	53.7 (14.3)	28.6-74.5	8 (66.7)	4 (33.3)	5 (41.7)	5 (41.7)	0	1 (8.3)	1 (8.3)
	Part B: 11	10.3 (4.7)	3-18	45.3 (23.5)	17.1-78.9	3 (27.3)	8 (72.7)	6 (54.5)	1 (9.1)	2 (18.2)	0	2 (18.2)
	Part C: 12	12.1 (5.2)	4-21	53.0 (25.4)	21.0-100.0	5 (41.7)	7 (58.3)	9 (75.0)	1 (8.3)	1 (8.3)	1 (8.3)	0
ACNS1021	24	11.0 (4.6)	3-18	NA	NA	15 (62.5)	9 (37.5)	21 (87.5)	3 (12.5)	0	0	0
A6181196	6	14.3 (1.4)	13-16	47.3 (9.9)	39.2-66.8	1 (16.7)	5 (83.3)	5 (83.3)	0	1 (16.7)	0	0

Source: CSRs ADVL0612, ACNS1021, and A6181196.
%=n/N × 100; Max=maximum; Min=minimum; N=total number of subjects; NA=not available; PK=pharmacokinetic(s); SD=standard deviation.

Study A6181196

Study A6181196 was a single-arm, open-label, multicenter, multinational, Phase 1/2 clinical trial evaluating the PK, safety, and preliminary anti-tumour efficacy of sunitinib in children diagnosed with advanced unresectable GIST. The starting dose of sunitinib was 15 mg/m^2 per day administered orally on Schedule 4/2. The primary objective of this study was to characterize the plasma PK profile of sunitinib and SU012662 in children and young adults with advanced unresectable GIST. The primary study endpoints were the PK parameters of sunitinib and SU012662, including AUC24 (total plasma exposure [AUC from 0 to 24 hrs]) and oral clearance (CL/F).

Table 2. Summary of Sunitinib, SU012662, and Total Drug Single-Dose Pharmacokinetic Parameters and Multiple-Dose Trough Concentrations Following Sunitinib Oral Doses of 15 mg/m^2 in Paediatric Patients with GIST - Study A6181196

PK Parameter	Sunitinib Mean (CV%) [Median]	SU012662 Mean (CV%) [Median]	Total Drug Mean (CV%) [Median]
Observed (n=6)			
T_{max} (hr)	8.0 (4.0–8.0)[a]	8.0 (4.0–8.0)[a]	NC
C_{max} (ng/mL)	18.4 (34) [16.1]	2.37 (17) [2.44]	NC
AUC_8 (ng·hr/mL)	82.7 (39) [80.0]	10.7 (35) [9.82]	NC
C_{trough} C1D15 (ng/mL)	24.4 (42) [20.8]	11.7 (15) [11.7]	36.0 (31) [32.4]
C_{trough} C1D28 (ng/mL)	29.1 (46) [29.3]	13.0 (36) [12.8]	42.1 (42) [42.1]
C_{trough} C2D28 (ng/mL)	44.7 (90) [30.9]	20.9 (63) [15.9]	65.6 (80) [48.7]
C_{trough} C3D28 (ng/mL)	31.3 (49) [27.8]	20.5 (46) [19.5]	51.8 (46) [43.5]
Dose-Corrected (n=6)			
C_{trough} C1D15 (ng/mL)	24.4 (42) [20.8]	11.7 (15) [11.7]	36.0 (31) [32.4]
C_{trough} C1D28 (ng/mL)	29.1 (46) [29.3]	13.0 (36) [12.8]	42.1 (42) [42.1]
C_{trough} C2D28 (ng/mL)	32.5 (69) [24.9]	15.2 (45) [14.8]	47.7 (61) [38.9]
C_{trough} C3D28 (ng/mL)	19.9 (36) [18.6]	13.1 (31) [13.8]	32.9 (31) [29.8]

Sources: Study A6181196 CSR Tables 14.4.3.1, 14.4.3.2, 14.4.3.3, 14.4.3.4, 14.4.3.5, 14.4.3.6, 16.2.5.3.2.
Abbreviations: AUC_8=area under plasma concentration-time curve from time zero to 8 hours post-dose; C_{max}=maximum concentration; C_{trough}=trough concentration; CV=coefficient of variation; D=Day; GIST=gastrointestinal stromal tumour; NC=not calculated; Dose-corrected=dose-corrected to the starting dose by multiplying observed concentration by correction factor starting dose/current dose; hr=hour; T_{max}=time to maximum concentration; Total Drug=sunitinib+SU012662.

[a] Median (minimum-maximum).

The assessment of the paediatric study for Sutent (A6181196) was already done and the conclusion was that the number of patients enrolled do not allow to draw any sound conclusion about pharmacokinetic (PK), safety, and efficacy of sunitinib in children and young adults diagnosed with advanced unresectable gastrointestinal stromal tumour (GIST).

Study ADVL0612

Study ADVL0612 was an open-label, dose-escalation, sequential-cohort, Phase 1 clinical study of oral sunitinib in children with refractory solid tumours. Of note, children and young adults were included in this study as 3, 7, and 6 patients ⩽12 years of age in Part A, Part B, and Part C, respectively, and as 2 and 1 patients >18 years of age in Part A and Part C, respectively. The aim of this study was to determine the MTD of sunitinib when given on the recommended adult Schedule 4/2. The clinical pharmacology objectives of this study were to characterize the PK of oral sunitinib in children with refractory solid tumours and to evaluate the tolerability and PK profile of sunitinib capsule contents sprinkled over apple sauce or yogurt using the recommended Phase 2 dose (RP2D) determined from the dose-escalation part of this study. This study included 3 parts:

- Part A (12 patients - full analysis population) (interpatient dose escalation): The starting dose of sunitinib was 20 mg/m^2 QD with dose levels for subsequent groups of patients of 30 mg/m^2 QD and 40 mg/m^2 QD. If the MTD had been exceeded at the first dose level, then the subsequent cohort of patients were treated at the 15 mg/m2 QD dose level.

- Part B (11 patients - full analysis population) (interpatient dose escalation): After observing cardiac-related dose-limiting toxicities (DLTs) in Part A of the study, the protocol was amended to exclude

patients with previous anthracycline or cardiac radiation exposure. Part B was initiated to determine the MTD in the revised study population. The starting dose of sunitinib was 15 mg/m^2 QD with dose levels for subsequent groups of patients of 20 mg/m2 QD or 30 mg/m2 QD. Patients in Part B of the study had not received prior anthracycline treatment or cardiac radiation exposure.

- Part C (12 patients - full analysis population): All patients treated in Part C received the RP2D determined in Part B. Patients in Part C took each sunitinib dose using the powder contained within sunitinib capsules sprinkled onto 5 mL of apple sauce or yogurt per capsule.

Table 8. Summary of Dose-Corrected (15 mg/m^2) Sunitinib, SU012662 and Total Drug Single-Dose PK Parameters and Multiple-Dose Trough Concentrations Following Sunitinib Oral Doses of 15 and 20 mg/m^2 as Intact Capsule

PK Parameter	Study Parts A and B Combined (15 mg/m^2) Mean (CV%) [Median] n	Study Parts A and B Combined (20 mg/m^2) Mean (CV%) [Median] n
Sunitinib		
t_{max} (h)	7.0 (2.0–48.0) 8[a]	8.0 (8.0–8.0) 1[a]
C_{max} (ng/mL)	21.7 (61) [17.2] 8	22.6 (NA) [22.6] 1
AUC_{24} (ng•h/mL)	329 (46) [268] 8	371 (NA) [371] 1
AUC_{48} (ng•h/mL)	554 (36) [528] 8	570 (NA) [570] 1
C_{trough} D7 (ng/mL)	30.9 (40) [28.9] 14	31.7 (31) [33.2] 9
C_{trough} D14 (ng/mL)	34.5 (50) [28.4] 13	30.3 (34) [27.9] 7
C_{trough} D21 (ng/mL)	31.9 (53) [35.1] 12	30.8 (30) [28.2] 7
C_{trough} D28 (ng/mL)	38.2 (61) [22.9] 9	38.8 (37) [34.9] 6
SU012662		
t_{max} (h)	8.0 (4.0–48.0) 8[a]	8.0 (8.0–8.0) 1[a]
C_{max} (ng/mL)	3.60 (62) [2.61] 8	4.50 (NA) [4.50] 1
AUC_{24} (ng•h/mL)	57.0 (65) [40.9] 8	88.5 (NA) [88.5] 1
AUC_{48} (ng•h/mL)	117 (58) [84.5] 8	173 (NA) [173] 1
C_{trough} D7 (ng/mL)	12.4 (37) [10.9] 14	13.0 (41) [10.9] 9
C_{trough} D14 (ng/mL)	16.6 (49) [13.7] 13	14.8 (53) [12.8] 7
C_{trough} D21 (ng/mL)	17.1 (55) [15.0] 12	16.2 (55) [12.7] 7
C_{trough} D28 (ng/mL)	17.1 (34) [13.9] 9	21.0 (64) [17.3] 6
Total Drug		
t_{max} (h)	7.0 (2.0–48.0) 8[a]	8.0 (8.0–8.0) 1[a]
C_{max} (ng/mL)	25.2 (59) [20.2] 8	27.1 (NA) [27.1] 1
AUC_{24} (ng•h/mL)	386 (48) [307] 8	461 (NA) [461] 1
AUC_{48} (ng•h/mL)	671 (38) [651] 8	746 (NA) [746] 1
C_{trough} D7 (ng/mL)	43.3 (34) [38.2] 14	44.7 (31) [43.8] 9
C_{trough} D14 (ng/mL)	51.1 (43) [40.6] 13	45.1 (40) [40.7] 7
C_{trough} D21 (ng/mL)	49.0 (49) [50.6] 12	47.0 (37) [40.0] 7
C_{trough} D28 (ng/mL)	55.2 (49) [36.7] 9	59.9 (45) [56.1] 6

Source: ADVL0612 CSR Table 15.

AUC_{24}=area under plasma concentration-time curve from time 0 to 24 hours postdose; AUC_{48}=area under plasma concentration-time curve from time 0 to 48 hours postdose; C_{max}=maximum plasma concentration; C_{trough}=trough plasma concentration; CV%=coefficient of variation percent; D=day; NA=not applicable or not available; PK=pharmacokinetic; t_{max}=time to maximum plasma concentration; Total Drug=sunitinib+SU012662.

a. Median (minimum-maximum).

This study was evaluated during the procedure n. EMA/H/C/687/P46-048. Overall, pharmacokinetic/pharmacodynamics analyses appeared to be adequate. However, Pk modelling have been encouraged (PopPK, PBPK).

In comparison to adults, the single-dose maximum and 0–24 hours concentrations exposures as well as the steady state trough plasma exposures in children with solid tumours appear to be higher for both sunitinib and its active metabolite SU012662. The correlative analyses with respect to the effect

of body size and age supported dosing based on body surface area to ensure uniform total plasma exposures across different body sizes and age ranges in children.

The pharmacokinetic/pharmacodynamic correlative analyses performed to assess the relationships between soluble, CEC- or CEP-related biomarkers and sunitinib, SU012662, and Total Drug steady state trough concentrations, supported concentration dependent modulation of soluble as well as CEC- and CEP-related sunitinib pharmacological targets following multiple dosing with sunitinib in children.

Study ACNS1021

Study ACNS1021 was an open-label Phase 2 clinical trial designed to estimate the ORR for sunitinib in 2 strata of recurrent/progressive/refractory HGG and ependymoma in paediatric (ages 18 months to 17 years) and young adult (ages 18 years to 22 years) patients. Patients received sunitinib 15 mg/m2 as capsules in 6-week cycles. The clinical pharmacology objective (secondary) of the study was to describe the PK profile of paediatric and young adult patients taking sunitinib. The summary of PK parameters for each study group is provided in the table below:

Table 19. Summary of Sunitinib, SU012662 and Total Drug Single-Dose Pharmacokinetic Parameters and Multiple-Dose Trough Concentrations Following Sunitinib Oral Doses of 15 mg/m^2

Dose PK Parameter	Recurrent/Progressive/ Refractory High Grade Glioma Mean (%CV) [Median] n	Recurrent/Progressive/ Refractory High Grade Ependymoma Mean (%CV) [Median] n	Both Groups Combined Mean (%CV) [Median] n
Sunitinib			
T_{max} (h)	7.0 (7.0-24.0) 3[a]	5.5 (4.0-7.0) 2[a]	7.0 (4.0-24.0) 5[a]
C_{max} (ng/mL)	20.1 (5) [20.6] 3	22.0 (NC) [22.0] 2	20.9 (7) [20.7] 5
AUC_{24} (ng•h/mL)	377 (11) [369] 3	370 (NC) [370] 2	374 (8) [370] 5
C_{trough} D7 (ng/mL)	41.0 (41) [35.3] 12	36.0 (49) [35.9] 10	38.8 (44) [35.9] 22
C_{trough} D14 (ng/mL)	41.3 (55) [42.4] 10	38.1 (33) [37.3] 10	39.7 (45) [40.1] 20
C_{trough} D28 (ng/mL)	37.0 (56) [31.8] 10	36.4 (40) [40.0] 11	36.7 (47) [35.3] 21
SU012662			
T_{max} (h)	24.0 (7.0–24.0) 3[a]	15.5 (47.0–24.0) 2[a]	24.0 (7.0–24.0) 5[a]
C_{max} (ng/mL)	2.62 (48) [2.54] 3	2.95 (NC) [2.95] 2	2.75 (33) [2.93] 5
AUC_{24} (ng•h/mL)	48.7 (53) [42.7] 3	63.3 (NC) [63.3] 3	54.5 (20) [62.9] 5
C_{trough} D7 (ng/mL)	15.1 (65) [10.7] 12	14.4 (39) [15.8] 10	14.8 (54) [13.6] 22
C_{trough} D14 (ng/mL)	16.4 (84) [11.5] 10	16.1 (35) [17.5] 10	16.2 (63) [16.2] 20
C_{trough} D28 (ng/mL)	20.6 (68) [15.1] 10	15.1 (35) [17.3] 11	17.7 (59) [17.0] 21
Total Drug			
C_{trough} D7 (ng/mL)	56.1 (42) [43.9] 12	50.5 (43) [50.9] 10	53.5 (42) [47.9] 22
C_{trough} D14 (ng/mL)	57.7 (56) [55.6] 10	54.2 (33) [55.6] 10	55.9 (45) [55.6] 20
C_{trough} D28 (ng/mL)	57.6 (53) [47.4] 10	51.5 (37) [57.4] 11	54.4 (46) [53.4] 21

Source: Tables 14.4.3.1.1-3 and 14.4.4.1.1-2

Abbreviations: %CV=percent coefficient of variation; AUC_{24}=area under plasma concentration-time curve from time 0 to 24 hours postdose; C_{max}=maximum plasma concentration; C_{trough}=trough plasma concentration; D=Day; h=hour; n=number of patients; NC=not calculated since n<3; PK=pharmacokinetic; T_{max}=time to maximum plasma concentration; total drug=sunitinib+SU012662.

a. Median (minimum-maximum).

Based on the PK results of Study ACNS1021, both sunitinib and its active metabolite appeared to reach steady state by Day 14 of Cycle 1. The Day 14 mean steady-state trough plasma exposures to

sunitinib (39.7 ng/mL), SU012662 (16.2 ng/mL), and total drug (55.9 ng/mL) appeared to be slightly higher than those observed in the Phase 1 Study ADVL0612 by 20.3%, 1.25%, and 14.1%, respectively. The plasma exposures to sunitinib and its active metabolite appeared to be similar between patients in the HGG group and those in the ependymoma group. The dose-corrected plasma exposures to sunitinib and SU012662 appeared to be higher in children in this study as compared to adults in Study ADVL0612, indicating potentially lower CL/F per BSA in children as compared to adults.

A total of 12 patients consented and had blood samples drawn for pharmacodynamic studies, of these samples for only 9 patients (2 in the glioma group and 7 in the ependymoma group) resulted in sufficient quality of protein in the plasma for analyses. Profile plots of VEGF and VEGFR2 levels were analysed: the mean plasma VEGF level did not significantly change from Day 1 (106.9 pg/mL) to Day 14 (142.8 pg/mL) or to Day 28 (128.2 pg/mL). However, there was a decrease in mean VEGFR2 levels from 12379 pg/mL on Day 1 to 10103 pg/mL on Day 14 and 9676 pg/mL on Day 28.

No other correlative analyses were performed and PBMCs were not analyzed. No tumor tissue evaluations (genotyping and protein expression) were performed.

Population Pharmacokinetics-Pharmacodynamics of Sunitinib in Patients with GIST and Solid Tumors (PMAREQDD-A618w-Other-366)

Dataset: The PK and PD (safety and efficacy) data collected during Studies 248-ONC-0511-002, RTKC-0511-005, RTKC-0511-016, RTKC-0511-018 in adult patients with solid tumors, ADVL0612 in pediatric patients with solid tumors, A6181004, A6181045, A6181047, RTKC-0511-013 in adult patients with GIST were pooled for the population PK and PK-PD analyses. For the population PK and safety PK-PD analyses, only the studies in patients with solid tumors and GIST were used whereas for efficacy PK-PD analyses only studies of patients with GIST were used.

All the available safety data from Study ADVL0612 were included in the PK-PD analyses for safety endpoints. However, for efficacy, the PK-PD modeling for the Sum of the Longest Diameters (SLD) only included adult GIST data.

Demographic characteristics of ADVL0612 study population are reported below:

Table 7. Demographic Characteristics - Full Analysis Population

Number (%) of Subjects	Sunitinib							
	Part A			Part B			Total	Part C
	15 mg/m^2	20 mg/m^2	Total	15 mg/m^2	20 mg/m^2	Total	Part A+Part B	15 mg/m^2
	N=6	N=6	N=12	N=8	N=3	N=11	N=23	N=12
Gender								
Male	4 (66.7)	4 (66.7)	8 (66.7)	3 (37.5)	0	3 (27.3)	11 (47.8)	5 (41.7)
Female	2 (33.3)	2 (33.3)	4 (33.3)	5 (62.5)	3 (100.0)	8 (72.7)	12 (52.2)	7 (58.3)
Age (years)								
≤2	0	0	0	0	0	0	0	0
>2-12	1 (16.7)	2 (33.3)	3 (25.0)	5 (62.5)	2 (66.7)	7 (63.6)	10 (43.5)	6 (50.0)
>12-18	3 (50.0)	4 (66.7)	7 (58.3)	3 (37.5)	1 (33.3)	4 (36.4)	11 (47.8)	5 (41.7)
>18	2 (33.3)	0	2 (16.7)	0	0	0	2 (8.7)	1 (8.3)
Mean	16.3	12.8	14.6	10.5	9.7	10.3	12.5	12.1
Standard deviation	3.3	1.9	3.1	5.3	3.5	4.7	4.5	5.2
Range	12-20	10-15	10-20	3-18	6-13	3-18	3-20	4-21
Race								
White	4 (66.7)	1 (16.7)	5 (41.7)	4 (50.0)	2 (66.7)	6 (54.5)	11 (47.8)	9 (75.0)
Black	1 (16.7)	4 (66.7)	5 (41.7)	1 (12.5)	0	1 (9.1)	6 (26.1)	1 (8.3)
Asian	0	0	0	2 (25.0)	0	2 (18.2)	2 (8.7)	1 (8.3)
Other	0	1 (16.7)	1 (8.3)	0	0	0	1 (4.3)	1 (8.3)
Unspecified	1 (16.7)	0	1 (8.3)	1 (12.5)	1 (33.3)	2 (18.2)	3 (13.0)	
Weight (kg)								
Mean	61.7	45.7	53.7	46.6	41.7	45.3	49.7	53.0
Standard deviation	12.2	12.1	14.3	26.4	16.7	23.5	19.2	25.4
Range	46.3-74.5	28.6-63.7	28.6-74.5	17.1-78.9	23.0-55.2	17.1-78.9	17.1-78.9	21.0-100.0
Height (cm)								
Mean	167.8	153.4	160.6	140.0	130.0	137.3	149.4	148.8
Standard deviation	9.5	10.8	12.3	26.4	11.9	23.2	21.5	25.3
Range	149.9-175.0	136.8-165.9	136.8-175.0	102.0-171.5	116.4-138.4	102.0-171.5	102.0-175.0	110.0-188.2

Source: Table 14.1.2.1a, Table 14.1.2.1b, Table 14.1.2.1c.
N=Total number of subjects in respective cohort.

Table 1. Characteristics of Phase 1-3 Studies Used for Population PK and PK-PD Analyses

Study number	Study design/Tumor	Age Category	n[a]	Dosing schedule: dose
248-ONC-0511-002	Phase I/Solid tumors	Adults	27	4/2: 25, 50, 75, or 100 mg QD or QOD
RTKC-0511-005	Phase I/Solid Tumors	Adults	41	4/2 or 2/2: 50 and 75 mg QD or QOD
RTKC-0511-016	Phase I/Solid Tumors	Adults	12	2/1: 50 mg
RTKC-0511-018	Phase I/Solid Tumors	Adults	26	2/1: 50 mg (loading dose of 50-175 mg only on Day 1 of Cycle 1)
ADVL0612	Phase I/Solid Tumors	Children	35	4/2: 15 mg/m^2 (Parts A, B, and C) and 20 mg/m^2 (Parts A and B)
RTKC-0511-013	Phase I/II/GIST	Adults	86	2/1: 50 mg 2/2: 25, 50, 75 mg 4/2: 50 mg
A6181004	Phase III/GIST	Adults	217	4/2: 50 mg
A6181045	Phase I/II/GIST	Adults	36	4/2: 25, 50, 75 mg
A6181047	Phase II/GIST	Adults	26	CDD: 37.5 mg

[a] Number of PK-evaluable subjects.

The analysis was performed using nonlinear mixed effects modeling methodology as implemented in NONMEM (Version 7.2, University of California at San Francisco, California). Analyses were performed using the first order conditional estimation method with interaction (FOCE INTERACTION) approximation method in NONMEM. Additional softwares used in the analyses of the data were S-Plus® Version 8.0, Xpose Version 4 and PsN Version 3.1.2.

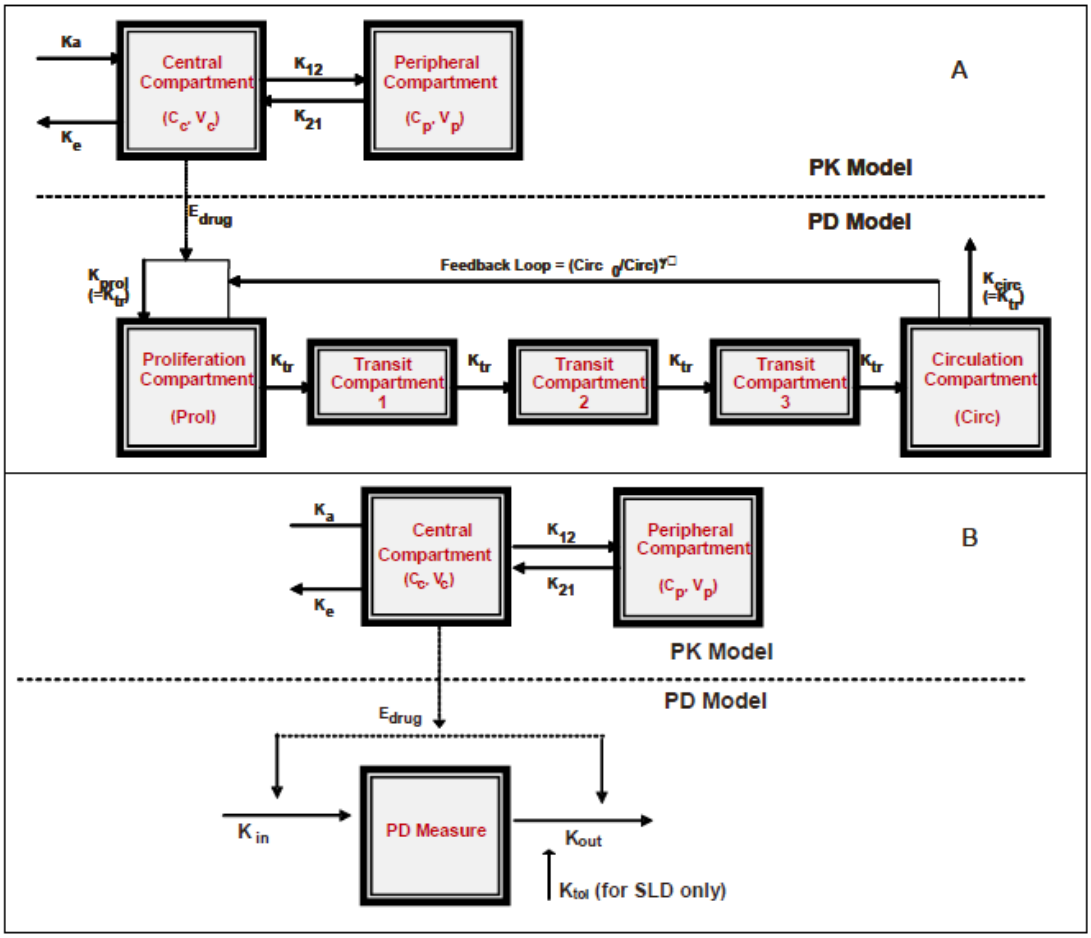
Based on the prior knowledge, a 2-compartment model with first-order absorption (NONMEM subroutine ADVAN4) was used as the initial model to fit to sunitinib and SU012662 concentrations. The disposition kinetics were modeled using a parameterization involving apparent clearance (CL/F),

central compartment apparent volume of distribution (Vc/F), apparent inter-compartmental clearance (Q/F), and peripheral compartment apparent volume of distribution (Vp/F). In addition, a first order absorption rate constant (ka) and a lag-time parameter (tlag) were used to characterize the absorption process.

During the sequential PK-PD modeling portion, safety endpoints such as absolute neutrophil count, platelet count, LVEF, BP, lymphocyte count, ALT, and AST as well as efficacy endpoint SLD were used.

The type of base models tested were transit compartments in series with feedback loop model, the indirect response model, the indirect response tumor model with tolerance function, and Gompertz tumor model.

Figure 1. Schematics of (A) the Semi-Mechanistic PK-PD Model with Transit Compartments in Series plus a Rebound Feedback Loop and (B) the Mechanism-Based PK-PD Model, an Indirect Response Model



C_c = drug concentration in the central compartment; C_p = drug concentration in the peripheral compartment; Circ = effect concentration in the circulation compartment; E_{drug} = drug effect calculated using a basic or sigmoidal E_{max} model; γ_f = feedback loop power function; K_a = drug absorption rate constant; K_e = drug elimination rate constant; K_{in} = input rate constant; K_{out} = output (elimination) rate constant; K_{circ}: elimination rate constant of the endpoint from the circulation compartment; K_{tr} = transit rate constant; K_{prol} = proliferation rate constant of the end point in the proliferation compartment (e.g., stem cells);K_{tol}=tolerance function; K_{12} = drug distribution rate constant from central to peripheral compartment; K_{21} = drug redistribution rate constant from peripheral to central compartment; Prol = effect concentration in proliferation compartment; V_c = drug central compartment volume of distribution; V_p = drug peripheral compartment volume of distribution.

Initially, attempts were made to incorporate the sum of predicted concentrations of sunitinib and its active metabolite, instead of sunitinib alone, into the sequential PK-PD base models for selected endpoints (ie, SLD, platelet count, ANC, hemoglobin, and lymphocyte count); however, this approach did not lead to any noticeable improvements in the model objective function value and performance and was associated with significantly longer run times, and in some instances led to model instability or run terminations. Therefore, only the predicted sunitinib concentrations, based on its final PK model, were used to produce the drug effects while building the base and final sequential PK-PD models for different endpoints.

The estimate of intersubject variability was provided as 95% confidence interval calculated as mean - 1.96·standard error and mean + 1.96·standard error. The within-individual variability was modeled as an additive term on the logtransformed concentration following both-sides log-transformed approach for both PK and PD.

Covariates investigation was performed using the basic model. The covariates were subjected to a stepwise forward selection algorithm using a likelihood ratio test based on the change in the extended least squares minimum objective function (ΔMOF). The significance level (α) chosen for covariate entry into a PK or PK-PD parameter sub-model was 0.01 (ΔMOF of 6.63). Covariates were systematically entered into the sub-models in steps, where the covariate with the greatest ΔMOF for each step was entered into the sub-model unless the addition of the covariate into the model resulted in instability of the model. This process was continued until the final step, where no covariates could meet the criterion for entry. This model was considered the full model. The full model obtained from the forward selection procedure was subjected to a backward elimination algorithm using a significance level of α =0.001 (ΔMOF=10.83). This process was repeated until all of the remaining covariate parameters, when excluded one at a time, resulted in significant likelihood ratio tests ($p \leq 0.001$). This model was considered the final model. The covariates examined during building the final PK and PK-PD models are listed below:

Table 4. Covariates Examined in PK and PK-PD Base Models

Type	PK Parameter	Covariates
PK	CL/F	AGE, SEX, BWT, BBSA, RAC, BEC, TUM
	V_c/F	AGE, SEX, BWT, BBSA, TUM
	K_a	FORM
PK-PD	BASE	AGE, SEX, BWT, BBSA, RAC, BEC, TUM, SCH
	K_{out}	AGE, SEX, BWT, BBSA, RAC, BEC, TUM, SCH, Baseline PD
	EC_{50}	AGE, SEX, BWT, BBSA, RAC, BEC, TUM, SCH, Baseline PD
	K_{PD}(Slope)	AGE, SEX, BWT, BBSA, RAC, BEC, TUM, SCH, Baseline PD
	Emax	AGE, SEX, BWT, BBSA, RAC, BEC, TUM, SCH, Baseline PD
	K_{tol}	AGE, SEX, BWT, BBSA, RAC, BEC, TUM, SCH, Baseline PD

For continuous PK-PD endpoints, the covariates indentified following the initial screening using GAM were subjected to the stepwise covariate selection procedure described above.

For continuous PK-PD endpoints, the covariates identified following the initial screening using GAM were subjected to the stepwise covariate selection procedure described above.
AGE=baseline age; BASE=baseline value; Baseline PD=baseline value for the pharmacodynamic end point; BBSA=baseline body surface area; BEC=baseline performance status (0 for ECOG 0 or Karnofski Score >90, and 1 for ECOG ≥1 or Karnofski score ≤90); BWT=baseline total body weight; EC_{50}=concentration of sunitinib producing 50% of maximum effect; ECOG=Eastern Cooperative Oncology Group; E_{max}=maximum effect; GAM=generalized additive models; GIST=gastrointestinal stromal tumor; K_{PD}=effect first-order rate constant (ie, slope); K_{out}= output rate constant; K_{tol}=tolerance rate constant; PD=pharmacodynamic(s); PK=pharmacokinetic(s); RAC=race (0 for Non-Asian and 1 for Asian); SCH=dosing schedule (0 for intermittent dosing schedule and 1 for continuous dosing schedule); SEX=gender (0 for males and 1 for females); TUM=tumor type (0 for solid tumors and 1 for GIST).

Descriptive statistics for the subjects baseline characteristics and covariates considered in building the population PK model are displayed below:

Table 5. Subject Baseline Characteristics: Continuous Variables

Variable	N	Mean ± SD	Median	Range
AGE, Years	506	53 ± 16.2	55	3 - 84
BWT, kg	500	71.8 ± 19.7	38.8	14.8 - 150
BHT, kg	488	168 ± 12.8	143	102 - 185
BBSA, kg	486	1.8 ± 0.287	1.26	0.66 - 2.58

Variable	N	Mean ± SD	Median	Range
BAST, U/L	469	27.4 ± 18.3	24.0	12 - 45
BALT, U/L	502	25.5 ± 19.7	19.0	9 - 67
BCRCL,mL/min	496	103 ± 39.8	12.0	4 - 16
BBP, mmHg	500	72.4 ± 11.2	38.8	14.8 - 150
BANC, 10^9/L	501	5.27± 2.9	4.55	1.15 – 21.8
BPLA, 10^9/L	500	319 ± 132	290	87 – 939
BLYM, 10^9/L	466	1.48 ± 0.86	1.34	0.13 – 12.7
BHGB, g/dL	501	11.9 ± 1.67	11.8	7.8 – 18.5
BLVEF, %	377	63.3 ± 7.21	63	35.6 - 84

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Table 6. Subject Baseline Characteristics: Categorical Variables

Variable	Categories	Subject Count (%)
DOSE	12.5 mg	9 (1.78)
	25 mg	37 (7.3)
	37.5 mg	26 (5.1)
	50 mg	381 (75.3)
	75 mg	23 (4.5)
	150 mg	17 (3.4)
	Other	13 (2.6)
RACE	Caucasian	394 (77.9)
	Black	25 (4.9)
	Asian	57 (11.3)
	Hispanic	23 (4.5)
	Unknown	7 (1.4)
SEX	Male	308 (60.9)
	Female	198 (39.1)
ECOG	Status 0	224 (44.2)
	Status 1	264 (52.1)
	Status 2	6 (1.2)
	Unknown	12 (2.4)
TUM	Solid Tumor:	134 (26.5)
	GIST:	372 (73.5)
SCHD	Intermittent dosing	
	4/2 (4 wks on, 2 wks off)	379 (74.9)
	2/1 (2 wks on, 1 wk off)	56 (11.1)
	2/2 (2 wks on, 2 wks off)	45 (8.9)
	Continuous dosing	
	CDD	26 (5.1)
FORM	Intact Capsule	494 (97.4)
	Sprinkled Capsule	12 (2.3)

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The effect of extreme outliers (|CWRES|>6) on the population PK parameter estimates and on the diagnostic plots were tested and based on each extreme outlier observation assessment, 20 observations with |CWRES|>6 were excluded from the dataset.

Population Modeling Analysis Report (PMAR-EQDD-A618b-DP4-846)

For the integrated population PK (popPK) analyses in pediatric patients with GIST and solid tumors, the PK data collected from Studies ADVL0612, ACNS1021, and A6181196 in pediatric patients with GIST and other solid tumors were pooled (PMAR-EQDD-A618b-DP4-846). The objectives of the popPK analysis were to identify covariates which account for the inter-individual variability in the PK of sunitinib and its active metabolite and to make predictions pediatric patients with GIST within age ranges 6-11 and 12-17 years of age.

The analysis was performed using nonlinear mixed effects modeling methodology as implemented in NONMEM (Version 7.1.2, University of California at San Francisco, California). Analyses were performed using FOCEI. Additional software used in the analyses of the data were S-Plus Version 8.0, RStudio, Xpose Version 4 and Perl-speaks-NONMEM (PsN) Version 3.2.12.

Based on the prior knowledge, a 2 compartment model with first-order absorption (NONMEM subroutine ADVAN4) was used as the initial model to fit to sunitinib and SU012662 concentrations. The disposition kinetics were modeled using a parameterization involving apparent clearance (CL/F), central compartment apparent volume of distribution (Vc/F), apparent inter-compartmental clearance (Q/F), and peripheral compartment apparent volume of distribution (Vp/F). In addition, a first-order absorption rate constant (ka) and a tlag were used to characterize the absorption process. The FOCEI estimation method was used to estimate all the parameters. The models used in this study were mainly adopted from the study of Population Pharmacokinetics-Pharmacodynamics of Sunitinib in Patients with GIST and Solid Tumors (PMAR-EQDD-A618w-Other-366).

Intersubject variability was included on the mean pharmacokinetic parameters for parent and metabolite SU012662, including CL/F, Vc/F, and ka. The within-individual variability was modeled as an additive term on the log-transformed concentration following both-sides log-transformed approach for PK:

$$ln(Y_{ij}) = ln(F_{ij}) + W \times \varepsilon_{ij}$$

where ln(Yij) denotes the observed concentration for the ith patient at time tj on logarithm scale, the ln(Fij) denotes the corresponding model-predicted concentration on logarithm scale, and εi j denotes the intraindividual random effect, assumed to have a mean of zero and variance σ2 of 1. W was the estimated variance of the residual variability that was one of the θs to be estimated.

Based on prior experience, the following group of potential covariates were predefined in the PMAP:

Table 3. Covariates Considered in the Population PK Analysis

PK Parameters	Covariates
CL/F	Body Weight or BSA, Sex, RAC, Tumor Type, BEC, Age
Vc/F	Body Weight or BSA, Sex, Tumor Type, Age
PK Parameters	Covariates
k_a	Form

CL/F=apparent clearance; VC/F=apparent central volume of distribution; k_a=absorption rate constant; Body weight= baseline body weight; BSA=baseline body surface area; BEC=baseline Eastern Cooperative Oncology Group (Eastern Cooperative Oncology Group (ECOG)=0 or >0); FORM=formulation (0=Intact capsule and 1= Sprinkle capsules on yogurt or applesauce); PK=pharmacokinetic; RAC=Race (Asian or Non-Asian).

Potential covariates were initially graphically plotted against ETAs to identify any relationships. Subsequently, identified covariates were tested for significance in a stepwise manner using the stepwise covariate model building procedure (SCM) application in PSN with statistical criteria of α=0.01 for forward inclusion step, which corresponds to an objective function value (OFV) change of 6.63 based on a Chi-square (χ2) distribution with degrees of freedom (df)=1. The full model was then subjected to a backward elimination step with a statistical criteria of α=0.001, which corresponds to an OFV change of 10.84 based on a χ2 distribution with df=1. The full model obtained from the forward selection procedure was subjected to a backward elimination algorithm using a significance level of α=0.001 (ΔMOF=10.83). This model was considered the final model.

The percentage of post-baseline observations which were BLQ was only 5.8% (27/466) and 10.5% (49/466) for sunitinib and SU012662, respectively. Therefore, the effect of BLQ data on modeling was not evaluated.

The dataset for the pooled analysis comprised 439 sunitinib and 417 SU012662 post-baseline measurable plasma observations from 65 patients treated with sunitinib. Descriptive statistics for the subjects baseline characteristics and covariates considered in building the population PK model are displayed below:

Table 4. Subject Baseline Characteristics by Age

Age, Year	No	Sex (M/F)	Race (Asian/Non Asian)	Tumor Type (GIST/Other)	ECOG (=0/>0)	Body Weight, Kg Median (Range)	BSA, m^2 Median (Range)
2-5	6	3/3	1/5	0/6	2/1	18.3 (16.2-28.7)	0.69 (0.66-0.98)
6-11	20	9/11	0/18	0/20	8/4	28.4 (17.1-56.3)	1.1 (0.72-1.48)
12-17	33	17/16	2/30	6/27	18/15	56 (37.1-100)	1.6 (1.26-2.14)
18-21	6	3/3	1/5	0/6	1/5	71.2 (62.5-74.5)	1.87 (1.62-1.92)
Total (6-17)	53	26/27	2/48	6/47	26/19	49.1 (17.1-100)	1.44 (0.72-2.14)
Total (2-21)	65	32/33	4/58	6/59	29/25	49.1 (16.2-100)	1.44 (0.66-2.14)

No= number; GIST=Gastrointestinal stromal tumors; Other=Other solid tumors; Race was unknown for 3 patients; ECOG was unknown for 11 patients. ePharmacology artifact ID RA14272552.

Sutent model

A 2-compartmental model with first order absorption including tlag for absorption and elimination rates was used as initial model for sunitinib. This model has been previously used to describe the pharmacokinetics of sunitinib. The correlation between the eta values for CL/F and Vc/F, CL/F and ka, and Vc/F and ka was estimated and appeared to be weak (0.57, -0.07, and -0.07, respectively); hence, a full or partial omega block was not included in the base model for sunitinib. In addition, the diagnostic plots appear to be satisfactory and the model appeared to be very stable, as indicated by the condition number. Subsequently, the effect of extreme outliers (|CWRES|>6) on the population PK parameter estimates and on the diagnostic plots was tested and based on each extreme outlier observation assessment, four observations with |CWRES|>6 were excluded from the dataset. They were considered influential outlier observations as their exclusion led to greater than 15% changes in the ω of CL/F, Vc/F and Ka. The magnitude of the spread for observations versus IPRED was small around the line of identity, indicating that the model predicted the individual concentrations well. In the base model, η estimates appeared normally distributed and displayed mean near zero for the PK parameters.

Table 5. Sunitinib Base and Final Population Pharmacokinetic Model Building

Model	Description	OFV	Reference Model	ΔOFV	ePharmacology Artifact ID	Note
Model 1	2-cmpt	74.33	NA	NA	14272553	439 observations in 65 patients
Model 2	2-cmpt	-92.08	NA	NA	14272656	Extreme outlier observations with |CWRES|>6 (n=2) was excluded.
Model 3	2-cmpt (Base Model)	-253.3	NA	NA	14272923	Extreme outlier observations with |CWRES|>6 (n=2) was excluded.
Model 4	Base Model Tested For Covariates using PsN (SCM)	NA	NA	NA	14287525	Forward Selection (α=0.01); backward elimination (α=0.001); Full Model= Base Model + CL/F with BSA (POW), Vc/F with BSA(POW), KA with FORM.
Model 5	Final Model	-301.6	Model 3	-48.3	14287763	Final Model= Base Model + CL/F with BSA (POW), Vc/F with BSA(POW).

ΔOFV=difference between OFV of 2 nested models.

A summary of PK parameters from the base model and also following bootstrapping is listed below:

Table 6. Sunitinib Base and Final Model Pharmacokinetic Parameters Summary

Parameter	Base Model Results Mean (RSE %)	Base Model Bootstrap Median (95% CI)	Final Model Results Mean (RSE %)	Final Model Bootstrap Median (95% CI)
CL/F (ϑ1), L/hr	23.1 (6.8)	22.9 (17.8-25.7)	24.0 (5.8)	23.8 (15.4-26.7)
Vc/F (ϑ2), L	1000 (12.8)	972 (775-1183)	1030 (9.8)	1006 (845-1164)
k_a (ϑ3), 1/hr	0.349 (31.8)	0.33 (0.21-0.54)	0.374 (28.3)	0.35 (0.23-0.62)
tlag (ϑ4), hr	0.77 (3.2)	0.76 (0.59-0.88)	0.759 (3.6)	0.75 (0.57-0.88)
Vp/F (ϑ5), L	98.9 (40.8)	113 (72.1-159190)	81.3 (22.9)	95.4 (64.3-425327)
Q/F (ϑ6), L/hr	0.682 (108.4)	0.69 (0.30-13.8)	0.387 (79.6)	0.46 (0.26-11.4)
BSA on CL/F (ϑ9)	NA	NA	0.733 (25.6)	0.75 (0.41-1.34)
BSA on Vc/F (ϑ8)	NA	NA	1.46 (19.9)	1.47 (0.99-1.83)
ω(CL/F), %	37.9 (29)	38 (30.1-50.5)	33 (35.4)	32.7 (26.5-51.2)
ω(Vc/F), %	52.3 (42.7)	50.3 (33.9-66.1)	25.3 (45.2)	21.8 (0.25-40.8)
ω(Ka), %	119.5 (47)	114.5 (72-164.5)	103.4 (41.5)	100.6 (67.2-148)
σ (ϑ7) , %	31.8 (2.3)	31.3 (25.5-37.6)	32.2 (2.3)	31.7 (26-38)

CI=confidence interval; IIV=inter-individual variability; CL/F=Apparent clearance; k_a= first order absorption rate constant; Q/F=intercompartmental clearance; Vc/F=central volume of distribution; Vp/F=peripheral volume of distribution; RSE= relative standard error; σ=Residual variability; ω=Inter-individual variability.
ePharmacology Artifact ID RA14272923, 14281236, 14287763 and 14299617.

To evaluate model stability and the CI of the final parameter estimates, a nonparametric bootstrapping approach was used (1000 replicates). The median values from 1,000 bootstrapping analysis runs were similar to the parameter estimates of the dataset, and the bootstrapped 95% CIs overlapped with those of the final dataset, suggesting that the model parameters were stable with the exception of Vp/F. The η-shrinkage was only 7.8% and 32% for CL/F and Vc/F, respectively.

The typical value for CL/F was estimated to be 24 L/h, Vc/F was estimated to be 1030 L. The key PK parameters in the final model with significant (α=0.001) covariate effect are shown below:

$CL/F = 24L/hr \cdot (BSA/1.44)^{0.733}$

During the SCM analysis, the effect of BSA was statistically significant on CL/F using a power function as above. This effect is consistent with graphical plots that showed a trend with BSA and this PK parameter. The inclusion of BSA on CL/F was statistically significant (α=0.001). The inclusion of BSA on CL/F in the final model corrected for the previously observed trend in plots of η on CL/F versus BSA in the base model.

$V\ c/F = 1030L \cdot (BSA/1.44)^{1.46}$

During the SCM analysis, the effect of BSA was statistically significant on Vc/F using a power function. This effect is consistent with graphical plots that showed a trend with BSA and this PK parameter. The inclusion of BSA on Vc/F was statistically significant (α=0.001). The inclusion of BSA on Vc/F in the final model corrected for the previously observed trend in plots of η on Vc/F versus BSA in the base model.

Figure 11. Goodness-of-Fit Diagnostic Plots for Plasma Sunitinib Concentrations (Final Model)

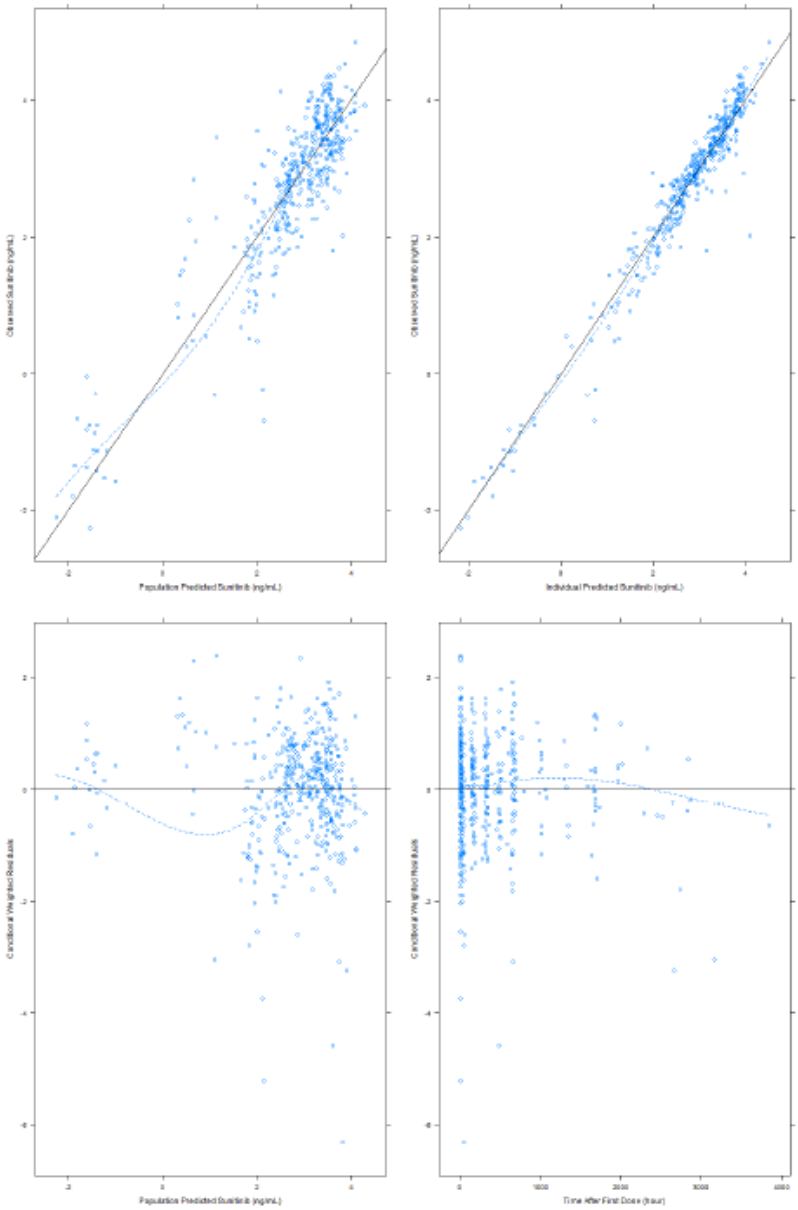
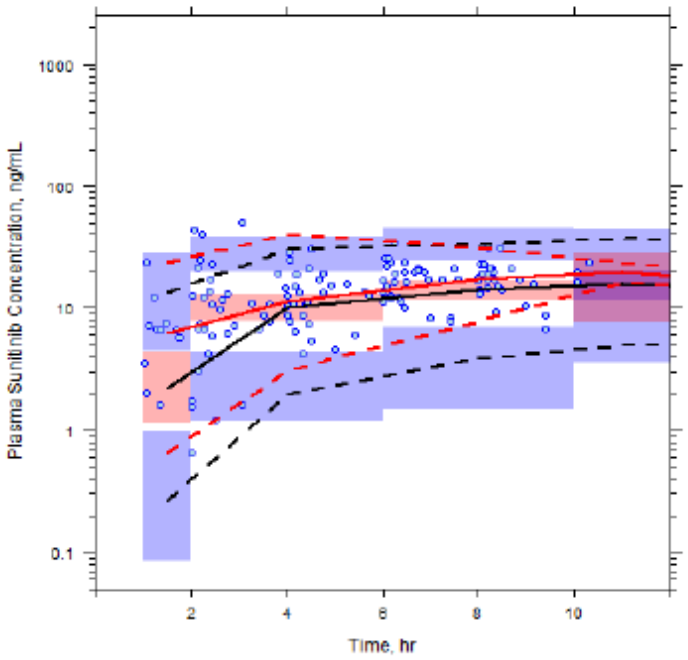


Figure 12. VPC Plot for Plasma Sunitinib Concentrations in 12 Hours Post-dose (Final Model)



ePharmacology artifact ID RA14643257.
Blue circles represent the observed data and the red lines represent the median (solid line), 2.5th and 97.5th percentile (dash line) of the observed data. The 95% confidence intervals for simulated median and each percentile are shown by pink and blue shaded areas, respectively.
VPC=visual predictive check.

A summary of PK parameters from the final model and also following bootstrapping procedures is listed in the table below:

Table 7. Omega Decreases from Sunitinib Base Model to Final Model

Parameter	Base Model	Final Model	Change[a]
CL/F ω^2	0.144	0.11	0.034 (23.6%)
Vc/F ω^2	0.274	0.064	0.21 (76.6%)

CL/F=Apparent clearance; Vc/F=central volume of distribution; ω=Inter-individual variability. [a]Change = ω^2 Final Model – ω^2 Base Model; % change =100% – 100%(ω^2 Final Model / ω^2 Base Model). ePharmacology Artifact ID: RA14272923 and 14287763.

The bootstrap results were consistent with the population parameters estimates indicating that the final model was stable and that the population parameter estimates from the final model represented the final dataset adequately.

Inclusion of baseline BSA as a covariate into the final mode reduced interpatient variability of CL/F and Vc/F by 23.6% and 76.6%.

SU012662 Model

A 2-compartmental model with first order absorption including tlag for absorption and elimination rates was used as initial model for SU012662. Based upon pre-clinical observations, a conversion of 21 % of the total parent to metabolite was assumed to bring the magnitude of the parameters to a more physiologically relevant level. This model has been widely used for previous sunitinib and SU012662 reports. The correlation between the eta values for CL/F and Vc/F, CL/F and ka, and Vc/F and ka was estimated and appeared to be weak (0.453, -0.131, and -0.123, respectively); hence, a full or partial omega block was not included in the base model for SU012662. In addition, the diagnostic plots appear to be satisfactory and the model appeared to be very stable, as indicated by the condition number. Subsequently, the effect of extreme outliers (|CWRES|>6) on the PK parameter estimates and on the diagnostic plots was tested and based on each extreme outlier observation assessment, two observations with |CWRES|>6 were excluded from the dataset. They were considered influential outlier observations as their exclusion led to greater than 15% changes in intraindividual random effects. Therefore, Model 2 was carried forward. The magnitude of the spread for observations versus IPRED was small around the line of identity, indicating that the model predicted the individual concentrations well. In the base model, η estimates appeared normally distributed and displayed mean near zero for the PK parameters.

Table 8. SU012662 Base and Final Population Pharmacokinetic Model Building

Model	Description	OFV	Reference Model	ΔOFV	ePharmacology Artifact ID	Note
Model 1	2-cmpt	-113.33	NA	NA	14299549	417 observations in 65 patients
Model 2	2-cmpt	-307	Model 1	NA	14307701	Extreme outlier observations with |CWRES|>6 (n=2) was excluded.
Model	Description	OFV	Reference Model	ΔOFV	ePharmacology Artifact ID	Note
Model 3	Base Model Tested For Covariates using PsN (SCM)	NA	NA	NA	14335658	Forward Selection (α=0.01); backward elimination (α=0.001);Full Model= Base Model + CL/F with SEX + BSA (POW), Vc/F with BSA(POW).
Model 4	Final Model	-357	Model 2	-50	14311767	Final Model= Base Model + CL/F with BSA (POW), Vc/F with BSA(POW).

ΔOFV=difference between OFV of 2 nested models.

A summary of PK parameters from the base model and also following bootstrapping has been listed in the table below:

Table 9. SU012662 Base and Final Model Pharmacokinetic Parameters Summary

Parameter	Base Model Results Mean (RSE %)	Base Model Bootstrap Median (95% CI)	Final Model Results Mean (RSE %)	Final Model Bootstrap Median (95% CI)
CL/F (ϑ1), L/hr	10.2 (7.3)	10.1 (8.65-11.6)	11.1 (6.9)	11.1 (9.35-12.6)
Vc/F (ϑ2), L	999 (13.9)	926 (607-1211)	1060 (14)	975 (543-1193)
k_a (ϑ3), 1/hr	0.287 (18.3)	0.266 (0.18-0.38)	0.275 (36.7)	0.26 (0.15-0.37)
tlag (ϑ4), hr	0.645 (10.7)	0.65 (0.46-0.77)	0.638 (26.3)	0.65 (0.44-0.76)
Vp/F (ϑ5), L	47.9 (143)	99 (0.48-4160)	63.1 (141)	113 (0.63-4902)
Q/F (ϑ6), L/hr	4.72 (151)	7.21 (0.06-1855)	6.7 (319)	9.75 (0.09-50575)
BSA on CL/F (ϑ9)	NA	NA	0.87 (26)	0.87 (0.48-1.27)
BSA on Vc/F (ϑ8)	NA	NA	1.61 (20)	1.82 (1.23-3.52)
ω(CL/F), %	53 (26)	52.5 (39.5-66.4)	44 (19.8)	42.5 (30.9-55.2)
ω(Vc/F), %	64.7 (27.7)	68.8 (52.7-93)	42 (37.6)	43.7 (27.2-64.4)
ω(Ka), %	98.7 (29)	95.1 (58.7-133)	95.7 (42.4)	90 (52.3-122)
σ (ϑ7) , %	25.7 (8.3)	25.4 (22-30)	26 (3.24)	25.8 (22-31)

CI=confidence interval; IIV=inter-individual variability; CL/F=Apparent clearance; k_a= first order absorption rate constant; Q/F=intercompartmental clearance; Vc/F=central volume of distribution; Vp/F=peripheral volume of distribution; RSE= relative standard error; σ=Residual variability; ω=Inter-individual variability.
ePharmacology Artifact ID RA14307701, 14331757, 14311767 and 14316356.

To evaluate model stability and the CIs of the final parameter estimates, a nonparametric bootstrapping approach was used (1000 replicates; 91.8% successful). The median values from 1,000 bootstrapping analysis runs were similar to the parameter estimates of the base model, and the bootstrapped 95% CIs overlapped with those of the original dataset, suggesting that the model was stable with the exception of Vp/F and Q/F. The large relative standard errors of Vp/F and Q/F may be related to the sampling schedule. The η-shrinkage was only 8.15% and 15.6% for CL/F and Vc/F, respectively.

The effects of different covariates (Model 3) on CL/F and Vc/F were examined following initial screening using SCM to identify significant covariates to be tested and subsequently by applying forward selection and backward elimination procedure until the final model was identified (Model 4). The typical value for CL/F was estimated to be 11.1 L/h, Vc/F was estimated to be 1060 L. The key PK parameters in the final model with significant (α=0.001) covariate effect are shown below

$CL/F = 11.1L/hr \cdot (BSA/1.44)^{0.87}$

During the SCM analysis, the effect of BSA was statistically significant on CL/F using a power function. This effect is consistent with graphical plots that showed a trend with BSA and this PK parameter. The inclusion of BSA on CL/F was statistically significant (α=0.001).

$c/F = 1060L \cdot (BSA/1.44)^{1.61}$

During the SCM analysis, the effect of BSA was statistically significant on Vc/F using a power function as above. This effect is consistent with graphical plots that showed a trend with BSA and this PK parameter. The inclusion of BSA on Vc/F was statistically significant (α=0.001).

Figure 22. Goodness-of-Fit Diagnostic Plots for Plasma SU012662 Concentrations (Final Model)

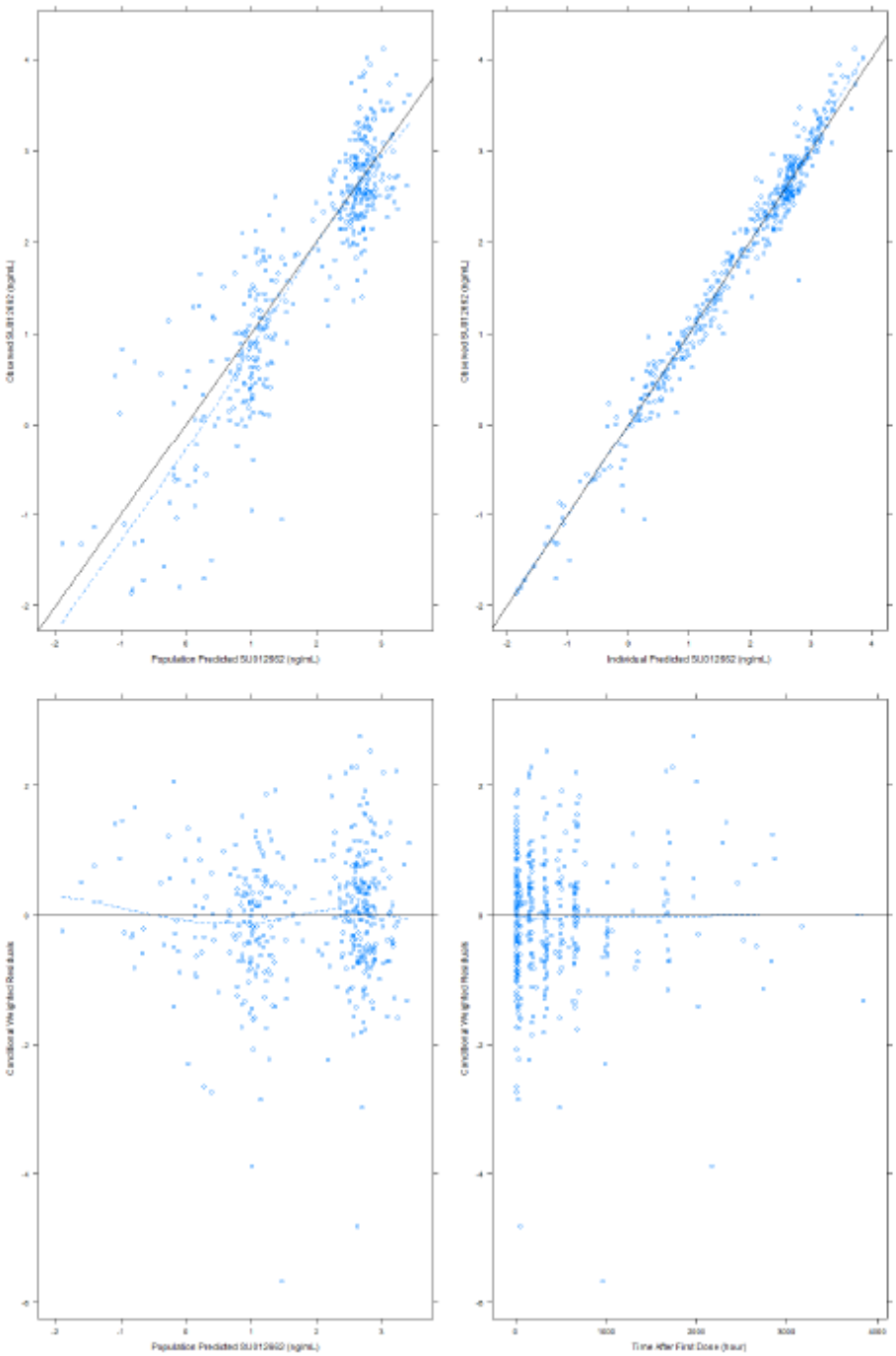
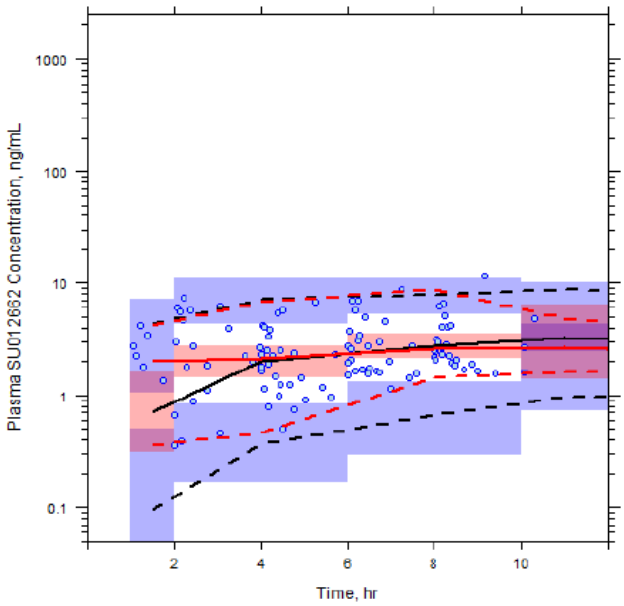


Figure 23. VPC Plot for Plasma SU012662 Concentrations in 12 Hours Post-dose (Final Model)



ePharmacology artifact ID RA14311911.
Blue circles represent the observed data and the red lines represent the median (solid line), 2.5th and 97.5th percentile (dash line) of the observed data. The 95% confidence intervals for simulated median and each percentile are shown by pink and blue shaded areas, respectively.
VPC=visual predictive check.

A summary of PK parameters from the final model and also following bootstrapping procedures is listed in the table below:

Table 10. Omega Decreases from SU012662 Base Model to Final Model

Parameter	Base Model	Final Model	Change[a]
CL/F ω^2	0.281	0.194	0.091 (32.4%)
Vc/F ω^2	0.419	0.177	0.243 (58%)

CL/F=Apparent clearance; Vc/F=central volume of distribution; ω=Inter-individual variability. [a]Change = ω^2 Final Model – ω^2 Base Model; % change =100% – 100%(ω^2 Final Model / ω^2 Base Model). ePharmacology Artifact ID: RA14307701 and 14311767.

The bootstrap results were consistent with the population parameters estimates indicating that the final model was stable and that the population parameter estimates from the final model represented the final dataset adequately. Inclusion of baseline BSA as a covariate into the final mode reduced interpatient variability of CL/F and Vc/F by 32.4% and 58%.

PBPK SimCYP

The objective of this analysis was to predict the exposure of sunitinib (SU011248) and its active metabolite SU012662 in paediatrics using physiologically-based pharmacokinetic (PBPK) simulations with SimCYP (version 16, release 1).

Sunitinib has been studied in 3 paediatric studies: in children (target age: 2 to 21 years; actually enrolled from 3 to 21 years) with refractory solid tumours in Study ADVL0612; in children (target age: 18 months to 22 years; actually enrolled from 3 to 19 years) with recurrent, refractory, or progressive high grade glioma and ependymoma tumours in Study ACNS1021; and in children (target age: 6 to 18 years; actually enrolled from 13 to 16 years) with gastrointestinal stromal tumour (GIST) in Study A6181196.

The results of the clinical studies, including the mass-balance study and the 3 paediatric studies, were used to validate the performance of the PBPK model for sunitinib and SU012662. The sunitinib and SU012662 compound files were developed in-house and verified using available clinical data. The compound files for sunitinib and SU012662 were created in SimCYP based on physico-chemical properties and human PK data, as summarised below:

Table 2. Sunitinib (SU011248) Input Parameters for SimCYP Simulation

Parameters	Value	Note	Source
Molecular weight (g/mol)	398.48	--	Reference 5
LogP	3.1	--	Reference 6
Compound type	Monoprotic base	--	Pfizer internal data
pK_a	8.5	--	Reference 6
Fu_{plasma}	0.05	--	Reference 5
B/P ratio	1.17	--	Reference 7
Fa[a]	0.791	--	Reference 2
k_a (h^{-1})	0.236	--	Reference 4
T_{lag} (h)	0.527	--	Reference 4
Fu_{gut}	0.05	Assume the same as Fu_{plasma}	
Q_{gut} (L/h)[b]	4.26	SimCYP predicted	
V_{ss} (L/kg)	22.9	Projected from population PK analysis estimated V_{ss} 22.9 L/kg; K_p Scalar adjusted to 3.29	Reference 5
CL_{int} (rhCYP3A4) ($\mu L \cdot min^{-1} \cdot pmol^{-1}$)	0.603	Retrograde model back-calculated from CL/F 37.2 L/h from popPK model, and corresponding $F_{m,CYP3A4}$ 66.5%, $F_{m,other\ HLM}$ 33.5%, respectively	Reference 2,4
CL_{int} (Other HLM) ($\mu L \cdot min^{-1} \cdot mg^{-1}$)	41.6	Retrograde model back-calculated from CL/F 37.2 L/h from popPK model, and corresponding $F_{m,CYP3A4}$ 66.5%, $F_{m,other\ HLM}$ 33.5%, respectively	Reference 2,4
CL_r (L/h)[c]	4.05	--	Reference 2

AUC_{inf}=area under the concentration-time curve from time 0 to infinity; B/P ratio=blood/plasma ratio; CL_{int}=intrinsic clearance; CL_r=renal clearance; CL/F=apparent oral clearance; CYP=cytochrome P450; Fa=fraction of administered dose absorbed; $F_{m,CYP3A4}$=fraction metabolised by CYP3A4; $F_{m,other\ HLM}$=fraction metabolised by other metabolising enzymes; Fu_{gut}=fraction unbound in the gut; Fu_{plasma}=fraction unbound in plasma; HLM=human liver microsomes; k_a=absorption rate constant; K_p=tissue:plasma partition coefficients; LogP=partition coefficient; PK=pharmacokinetics; pKa=acid dissociation constant; Q_{gut}=gut blood flow; rhCYP3A4=recombinant human CYP3A4; SimCYP=physiologically-based pharmacokinetic modelling software; T_{lag}=lag time; V_{ss}=volume of distribution at steady state; --=no notes were recorded.

a. Fa was assumed to be 0.791 based on human [14C]SU011248 human mass-balance study.[2]

b. Q_{gut} was predicted by SimCYP based on Caco-2 cell permeability of 3×10-6 cm/s at pH 6.5/7.4 (apical/basolateral).[8]

c. CL_r was calculated from the amount of sunitinib recovered in urine divided by AUC_{inf} of sunitinib in the mass-balance study.[2]

Table 3. SU012662 Input Parameters for SimCYP Simulation

Parameters	Value	Note	Source
Molecular weight (g/mol)	370.42	--	Reference 5
LogP[a]	1.88	--	Pfizer internal data
Compound type	Monoprotic base	--	Pfizer internal data
pK_a[a]	10.96	--	Pfizer internal data
Fu_{plasma}	0.1	--	Reference 5
B/P ratio	1.17	Assume the same as sunitinib	Reference 7
Fu_{gut}	0.1	Assume the same as Fu_{plasma}	
V_{ss} (L/kg)	42.3	Projected from population PK analysis estimated V_{ss} 42.3 L/kg; K_p Scalar adjusted to 6.41	Reference 2
CL[b] (L/h)	36.8	--	Reference 2

AUC_{inf}=area under the concentration-time curve from time 0 to infinity; B/P ratio=blood/plasma ratio; CL=clearance; CL_{po}=oral clearance; Fu_{gut}=fraction unbound in the gut; Fu_{plasma}=fraction unbound in plasma; K_p=tissue:plasma partition coefficients; LogP=partition coefficient; PK=pharmacokinetics; pK_a=acid dissociation constant; SimCYP=physiologically-based pharmacokinetic modelling software; V_{ss}=volume of distribution at steady state; --=no notes were recorded.

a. Calculated value.

b. CL was derived from the amount of SU012662 recovered in the mass-balance study divided by AUC_{inf} of SU012662 and entered as CL_{po} in SimCYP.[2]

Sunitinib

The model development employed a combined "bottom-up" and "top-down" approach to fully utilise the available in vitro or in silico experimental data and in vivo observed clinical data. The first-order absorption model parameterised with a fraction of administered dose absorbed (Fa), first order absorption rate constant [time-1] (ka), and lag time for absorption (Tlag) was selected to describe the absorption process of sunitinib in humans. Ka and Tlag were set as 0.236 h-1 and 0.527 h, respectively, based on the popPK analysis for the adults. The full PBPK distribution model was selected. The tissue composition-based model implemented in SimCYP (Method 2), proposed by Rodgers and Rowland, was selected to predict the steady-state volumes of distribution (= CL•MRT) (Vss), with the tissue:plasma partition coefficients (Kp) scalar adjusted to make the Vss/F as 29 L/kg, which was the Vss/F of sunitinib estimated from the population PK analysis for the adults. The retrograde model implemented in the SimCYP was used to back-calculate the hepatic intrinsic clearance (CLint,hep) from the population PK analysis for the adults estimated plasma clearance (apparent oral clearance [CL/F] of 37.2 L/h). Based on the [14C]sunitinib human mass-balance study, the Fa value was estimated to be 79.1% since 60.9% of the dose was ascribed to be metabolites of sunitinib, which are considered to be formed following oral absorption or drug-related entities (including sunitinib) excreted renally. After correction with the total recovery of 77%, Fa was 79.1%. Furthermore, based on the mass-balance study, the renal clearance (CLr) of sunitinib was set to 4.05 L/h. The transformation of sunitinib to SU012662 was primarily through CYP3A4. The fraction metabolised by CYP3A4 (Fm,CYP3A4) was

determined by dividing the total amount of SU012662 recovered in the faeces and urine by the total amount of sunitinib absorbed minus the amount of sunitinib excreted renally. The Fm,CYP3A4 was calculated as 66.5%. After entering the values for CLr, Fa, fraction of drug remaining after first-pass through the intestinal wall (Fg), and Fm,CYP3A4 information in the retrograde model, CYP3A4 intrinsic clearance (CLint) and the additional microsomal CLint,hep were estimated to be 0.603 µL/min/pmol and 41.6 µL/min/mg protein, respectively.

SU012662

The CYP3A4 mediated metabolism of sunitinib was used as the input of SU012662. The full PBPK distribution model was selected. The tissue composition-based model implemented in SimCYP (Method 2), proposed by Rodgers and Rowland, was selected to predict the Vss. The Kp scalar was adjusted to make the Vss/F as 42.3 L/kg, which was the Vss/F of SU012662 estimated from the population PK analysis for the adults. In vivo clearance (CL) was derived based on the amount of SU012662 recovered divided by the area under the concentration-time curve (AUC) from time 0 to infinity (AUCinf) of SU012662 in the mass-balance study, and was calculated to be 36.8 L/h.

6.2. Results

Population Pharmacokinetics-Pharmacodynamics of Sunitinib in Patients with GIST and Solid Tumors (PMAREQDD-A618w-Other-366)

Sutent Model

The key PK parameters in the final model with significant (α=0.001) covariate effect are shown below:

$$CL/F = 50.7*(1-0.00578*(AGE-55)-0.000269*(AGE-55)^2)*(1-0.0973*BEC_0)*(1-0.185*RAC_{Asian})*(1-0.169*SEX_F)*(1-0.274*TUM_{Solid})$$

$$V_c/F = 3160*(AGE/55)^{0.295}*(BBSA/1.81)^{1.05}*(1-0.299*TUM_{Solid})$$

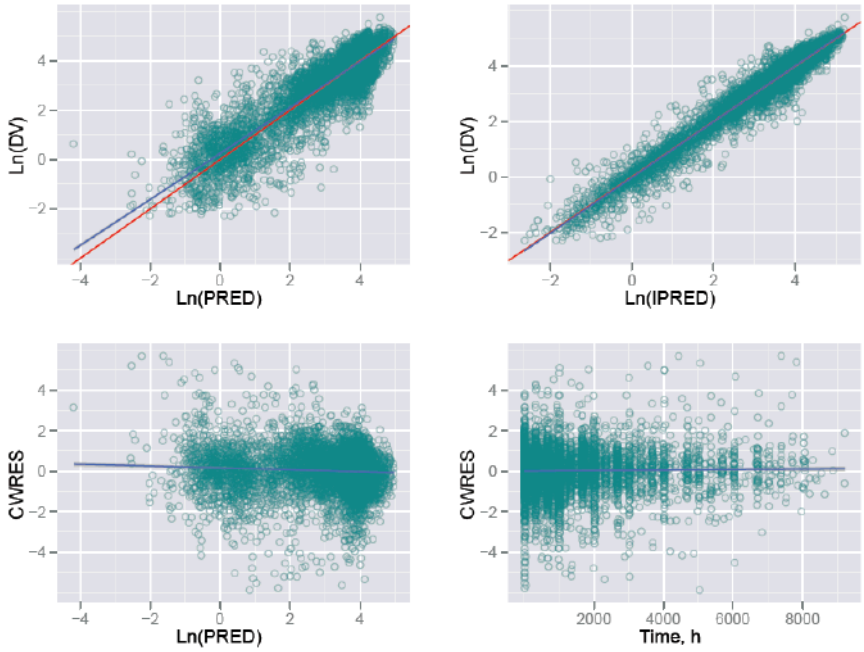
Table 8. Sunitinib Mean and 95% Confidence Interval Results for Base and Final Model

Parameter	Base Model		Final Model	
	Model Results[a]	Bootstrap Results[b]	Model Results[a]	Bootstrap Results[c]
Population Mean Estimates (95% CI)				
CL/F (θ_1), L/hr	37.2 (35.6–38.8)	37.1 (35.5–38.9)	50.7 (46.6–54.8)	50.6 (46.8–54.3)
V_c/F (θ_2), L	2610 (2435–2785)	2610 (2420–2780)	3160 (2952–3367)	3140 (2870–3380)
K_a (θ_3), hr^{-1}	0.236 (0.193–0.279)	0.256(0.199–0.446)	0.232 (0.174–0.290)	0.246 (0.196–0.441)
t_{lag} (θ_4), hr	0.527 (0.522–0.532)	0.527 (0.522–0.882)	0.527 (0.522–0.532)	0.527 (0.522–0.897)
V_p/F (θ_5), L	349 (289–409)	356 (293–453)	348 (274–422)	357(287–475)
Q/F (θ_6), L/hr	1.15 (0.658–1.64)	1.14 (0.808–1.83)	1.05 (0.678–1.42)	1.05 (0.743–1.64)
$\theta_{AGE1(CL/F)}$ (θ_8)			-0.00578 (-0.00796 – -0.00360)	-0.00578 (-0.00793 – -0.00362)
$\theta_{AGE2(CL/F)}$ (θ_9)			-0.000269 (-0.000340 – -0.000198)	-0.00027 (-0.00033 – -0.00019)
$\theta_{BEC(CL/F)}$ (θ_{10})			-0.0973 (-0.180 – -0.0142)	-0.0968 (-0.16 – -0.0283)
$\theta_{RAC(CL/F)}$ (θ_{11})			-0.185 (-0.267– -0.103)	-0.184 (-0.261– -0.0819)
$\theta_{SEX(CL/F)}$ (θ_{12})			-0.169 (-0.228– -0.103)	-0.169 (-0.233– -0.105)
$\theta_{TUM(CL/F)}$ (θ_{13})			-0.274 (-0.354– -0.194)	-0.274 (-0.349– -0.188)
$\theta_{AGE(Vc/F)}$ (θ_{14})			0.295 (0.170–0.420)	0.292 (0.161–0.392)
$\theta_{BBSA(Vc/F)}$ (θ_{15})			1.05 (0.746–1.35)	1.05 (0.71–1.45)
$\theta_{TUM(Vc/F)}$ (θ_{16})			-0.299 (-0.366– -0.232)	-0.287 (-0.357– -0.189)
Residual Variability CV (95% CI)				
$\sigma(\theta_7)$, %	34.2 (32.2–36.2)	33.7 (31.4–35.9)	34.3 (32.3–36.2)	33.7 (31.5–36)
Inter-Subject Variability CV (95% CI)				
$\omega_{\eta(CL/F)}$	43.1 (39.1–46.8)	42.9 (39–46.6)	36.9 (33.2–40.3)	36.4 (33.2–40.3)
$\omega_{\eta(Vc/F)}$	50.0 (43.4–55.8)	49.7 (43.5–55.2)	35.4 (29.9–40.1)	35.6 (30–42.1)
$\omega_{\eta(ka)}$	152 (136–166)	156 (140–190)	148 (136–158)	152 (136–186)

[a] 95% confidence interval was estimated as (mean-1.96*SE–mean+1.96*SE)
[b] 20% Run Failure (rounding error) with a single attempt; all runs were included. The numbers represent median (2.5%ile, 97.5%ile).
[c] 22% Run Failure (rounding error) with a single attempt; all runs were included. The numbers represent median (2.5%ile, 97.5%ile).
ePharm Folder ID 669170: Runs 20, 117, 141, and 178

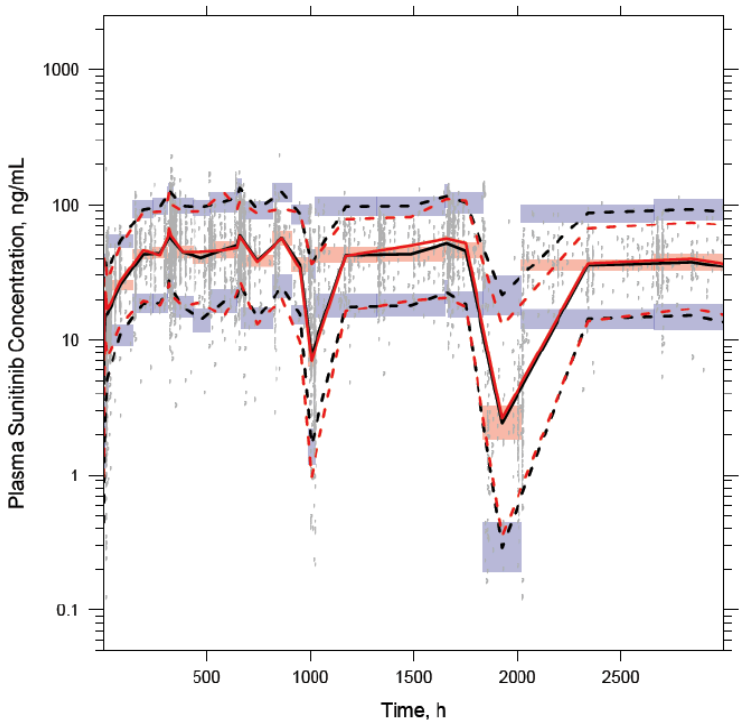
Some of the key diagnostic plots for the base model are displayed below:

Figure 4. Goodness-of-Fit Diagnostic Plots for Plasma Sunitinib Concentrations (Final Model)



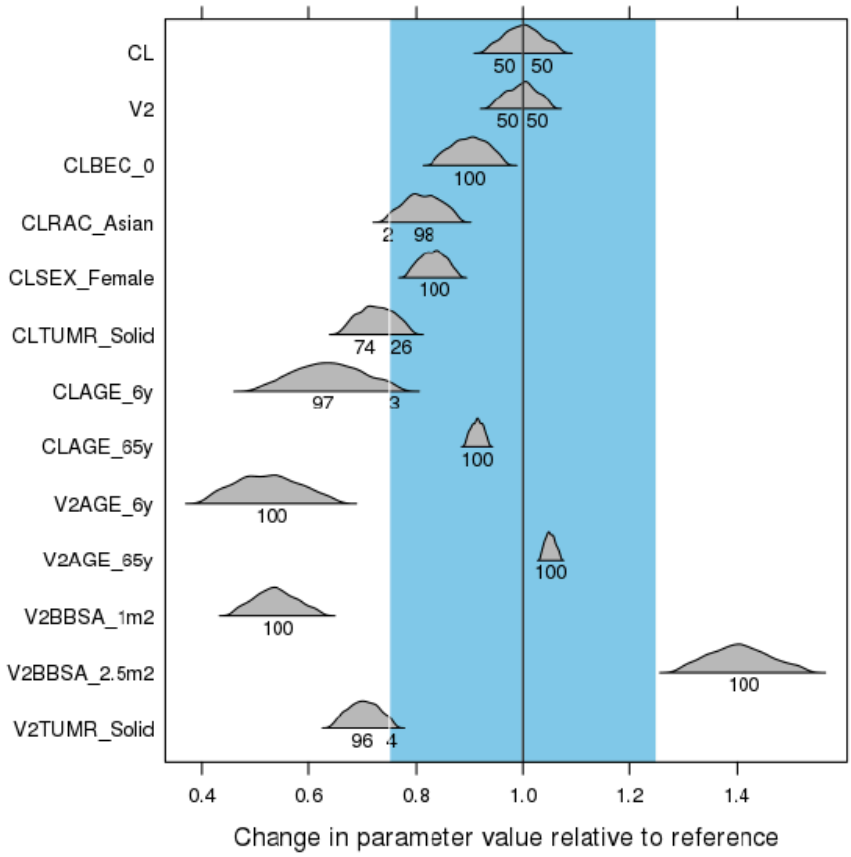
Solid red lines in observations (DV) versus population predictions (PRED) and individual predictions (IPRED) plots are lines of unity. Solid blue lines are the predictions regression lines (ePharm Folder ID 669170: Run # 179).

Figure 5. Prediction and Variance Corrected (PVC) Visual Predictive Check (VPC) Plot for Plasma Sunitinib Concentrations (Final Model)



Red and black solid lines represent observed and predicted median lines and the dotted lines the upper and lower bounds of the 95% confidence intervals (CI). The red shaded areas represent 90% CI for the median predictions and the blue shaded area for the upper and lower bounds of the 95% CI (ePharm Folder ID 669170: Run #174).

Figure 6. Effect of Significant (α=0.001) Covariates on CL/F (CL) and V_c/F (V2) Values Relative to the Reference Based on Sunitinib Final PK Model



Reference: a 55 year old male non-Asian GIST patient with BBSA=1.81 m^2 and ECOG=1; ePharm Folder ID 669170: Run # 132; CLBEC_0: effect of ECOG (0 vs. ≥1) on CL/F; CLRAC_Asian: effect of RACE (Asian vs.non-Asian) on CL/F; CLSEX_Female: effect of SEX (female vs.male) on CL/F; CLTUMR_Solid: effect of TUM (solid tumors vs. GIST) on CL/F; CLAGE_6y: effect of age (6 yrs vs.55 yrs) on CL/F; CLAGE_65y: effect of AGE (65 yrs vs. 55 yrs) on CL/F; V2AGE_6y: effect of AGE (6 yrs vs. 55 yrs) on V_c/F; V2AGE_6y: effect of AGE (6 yrs vs. 55 yrs) on V_c/F; V2AGE_65y: effect of AGE (65 yrs vs. 55 yrs) on V_c/F; V2BBSA_1m2: effect of BBSA (1 m^2 vs. 1.81 m^2) on V_c/F; V2BBSA_2.5m2: effect of BBSA (2.5 m^2 vs. 1.81 m^2) on V_c/F; V2TUMR_Solid: effect of TUM (solid tumors vs. GIST) on V_c/F.

SU012662 Model

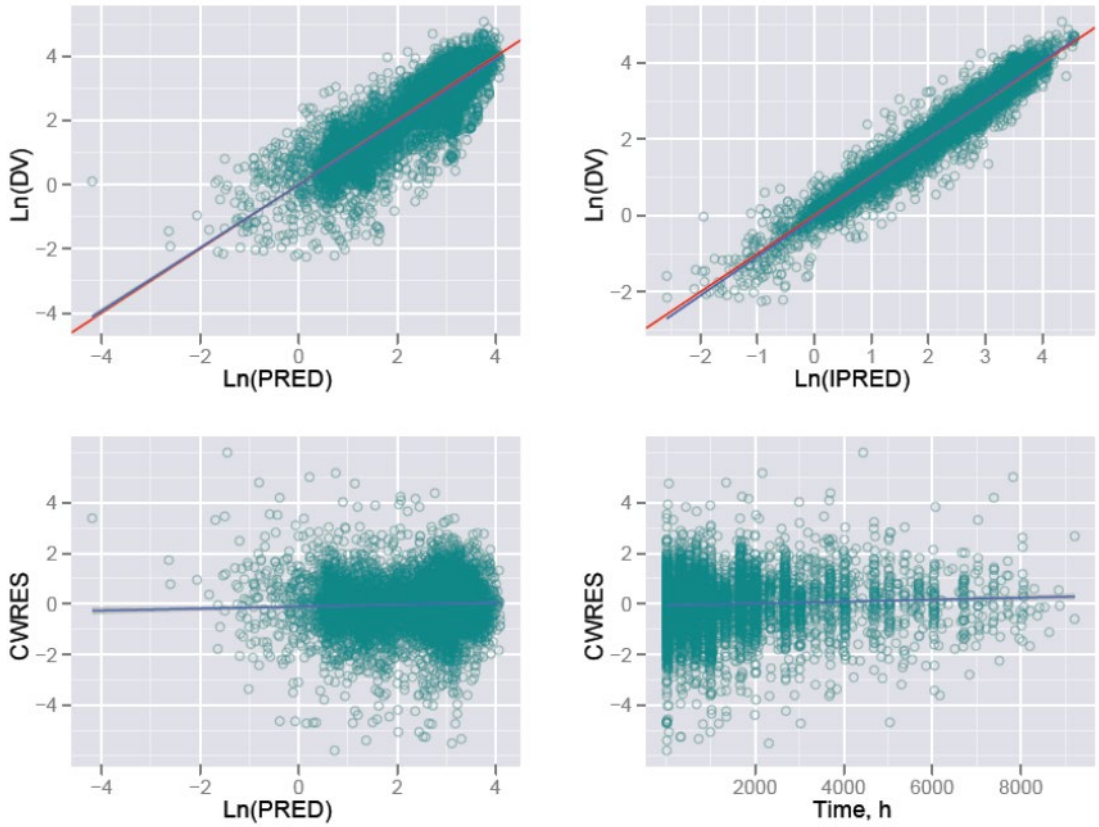
The effect of different covariates on the CL/F and Vc/F, and ka were examined using forward selection and backward elimination procedure until the final model was identified. The key PK parameters in the final model with significant (α=0.001) covariate effect are shown below:

$$CL/F = 22.1*(BBSA/1.81)^{1.12}*(1-0.225*SEX_F)*(1-0.279*TUM_{Solid})$$

$$V_c/F = 3170*(BBSA/1.81)^{2.01}*(1-0.278*TUM_{Solid})$$

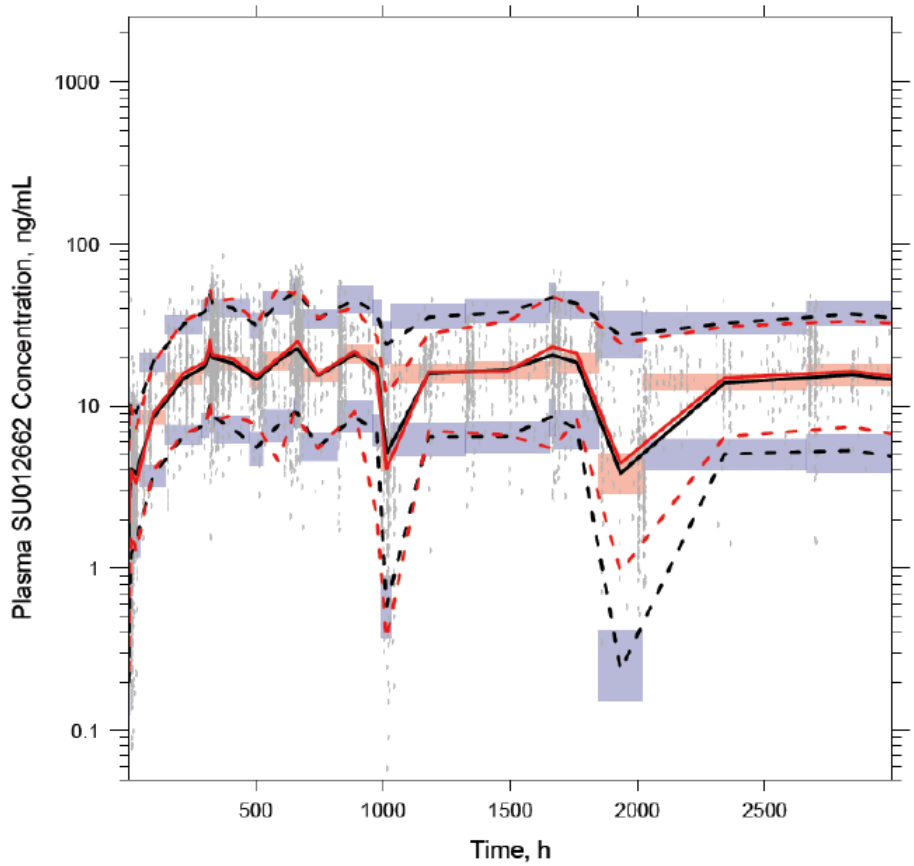
A 2-compartmental model with first order absorption and elimination rates were used as initial models for sunitinib active metabolite SU012662. Following exclusion of observations with apparent dosing errors, the effect of inclusion of lag time was tested and appeared to result in a significant change in OFV, hence, lag time for absorption was included in the base model for both sunitinib and its metabolite Also, the diagnostic plots appear to be satisfactory and the model appeared to be very stable. Subsequently, the effect of extreme outliers (|CWRES|>6) on the population parameter estimates and on the diagnostic plots were tested and based on each extreme outlier assessment, 10 observations with |CWRES|>6 were excluded from the dataset. Some of the key diagnostic plots for the base model are shown below:

Figure 9. Goodness-of-Fit Diagnostic Plots For Plasma SU012662 Concentrations (Final Model)



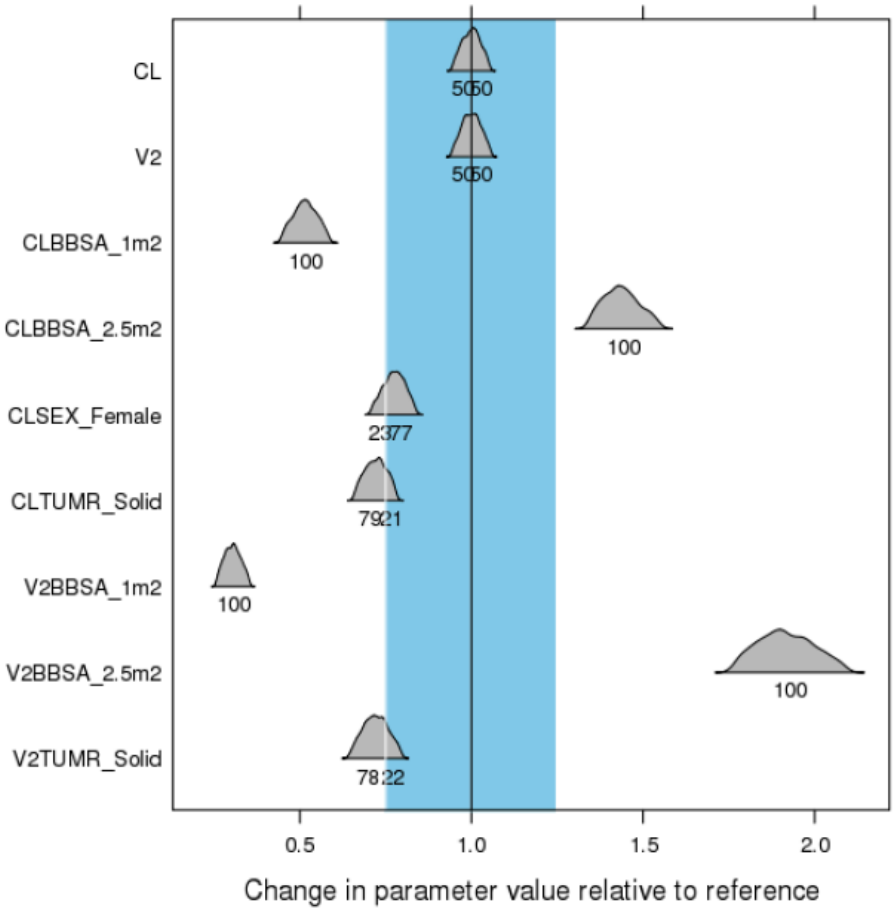
Solid red lines in observations (DV) versus population predictions (PRED) and individual predictions (IPRED) plots are lines of unity. Solid blue lines are the predictions regression lines (ePharm Folder ID 669170: Run # 119 and 184).

Figure 10. Prediction and Variance Corrected (PVC) Visual Predictive Check (VPC) Plot for Plasma SU012662 Concentrations (Final Model)



Red and black solid lines represent observed and predicted median lines and the dotted lines the upper and lower bounds of the 95% confidence intervals (CI). The red shaded areas represent 90% CI for the median predictions and the blue shaded area for the upper and lower bounds of the 95% CI (ePharm Folder ID 669170: Run #180).

Figure 11. Effect of Significant (α=0.001) Covariates on CL/F (CL) and V_c/F (V2) Values Relative to the Reference Based on SU012662 Final PK Model



Reference: a male GIST patient with BBSA=1.81 m^2; ePharm Folder ID 669170: Run # 185; CLBBSA_1m2: effect of BBSA (1 m^2 vs. 1.81 m^2) on CL/F; CLBBSA_2.5m2: effect of BBSA (2.5 m^2 vs. 1.81 m^2) on CL/F; CLSEX_Female: effect of SEX (female vs.male) on CL/F; CLTUMR_Solid: effect of TUM (solid tumors vs. GIST) on CL/F; V2BBSA_1m2: effect of BBSA (1 m^2 vs. 1.81 m^2) on V_c/F; V2BBSA_2.5m2: effect of BBSA (2.5 m^2 vs. 1.81 m^2) on V_c/F; V2TUMR_Solid: effect of TUM (solid tumors vs. GIST) on V_c/F.

Table 10. SU012662 Mean and 95% Confidence Interval Results for Base and Final Model

Parameter	Base Model		Final Model	
	Model Results[a]	Bootstrap Results[b]	Model Results[a]	Bootstrap Results[c]
Population Mean Estimates (95% CI)				
CL/F (θ_1), L/hr	17.9 (16.9–18.9)	17.8 (16.6–18.8)	22.1 (20.7–23.5)	22 (19.6–23.6)
V_c/F (θ_2), L	2760 (2581–2940)	2780 (2590–2980)	3170 (2968–3372)	3180 (2980–3390)
K_a (θ_3), hr^{-1}	0.35 (0.29–0.41)	0.372 (0.29–0.59)	0.348 (0.293–0.403)	0.37 (0.294–0.584)
t_{lag} (θ_4), hr	0.52 (0.5–0.54)	0.52 (0.5–0.54)	0.519 (0.502–0.536)	0.519 (0.489–0.825)
V_p/F (θ_5), L	477 (107–847)	498 (301–12400)	490 (78.4–902)	513 (298–46000)
Q/F (θ_6), L/hr	0.59 (0.38–0.8)	0.62 (0.42–1.36)	0.559 (0.365–0.753)	0.598 (0.405–2.32)
$\theta_{BBSA(CL/F)}$			1.12(0.84 – 1.4)	1.12 (0.82 – 1.46)
$\theta_{SEX(CL/F)}$			-0.225(-0.3– -0.15)	-0.229(-0.308– -0.149)
$\theta_{TUM(CL/F)}$			-0.279 (-0.354– -0.204)	-0.281 (-0.357– -0.2)
$\theta_{BBSA(Vc/F)}$			2.01(1.7– 2.32)	2.01(1.68– 2.34)
$\theta_{TUM(Vc/F)}$			-0.278(-0.363– -0.193)	-0.273(-0.352– -0.183)
Residual Variability CV (95% CI)				
$\sigma(\theta_7)$, %	30.9 (29.3–32.5)	31 (29.2–32.5)	31 (29.4–32.6)	31 (29.2–32.5)
Inter-Subject Variability CV (95% CI)				
$\omega_{\eta(CL/F)}$	57.9 (52.3–62.9)	57.9 (52.7–64.7)	47.5 (42.4–52.1)	47.6 (42.8–55)
$\omega_{\eta(Vc/F)}$	62.4 (56.1–68.1)	61.8 (56–68.2)	48.5 (42.6–53.7)	47.9 (42.7–53.7)
$\omega_{\eta(ka)}$	129 (110–144)	134 (113–162)	128 (109–144)	134 (114–162)

[a] 95% confidence interval was estimated as (mean-1.96*SE–mean+1.96*SE)
[b] 5% Run Failure (rounding error) with a single attempt; all runs were included. The numbers represent median (2.5%ile, 97.5%ile).
[c] 6% Run Failure (rounding error) with a single attempt; all runs were included. The numbers represent median (2.5%ile, 97.5%ile).
ePharm Folder ID 669170: Runs 18, 119, 136, and 189

For categorical safety endpoints hand foot syndrome, fatigue, nausea and vomiting, the PK-PD modeling was not used; however, the relationships between the average sunitinib plasma exposures up to time of the earliest worst grade and the incidence rate were explored by using ordered categorical logistic regression models. The individual average sunitinib exposure (concentration) up to time of earliest worst grade was calculated as the total dose up to the time of earliest worst grade divided by individual post hoc CL/F estimate for sunitinib divided by the time post first dose up to the time of earliest worst grade for the categorical safety endpoint. Based on sunitinib final PK and PK-PD models, trial simulations were performed to make predictions with respect to PK and key safety and efficacy endpoints in pediatric and adult patients with GIST.

ALT

The PK-PD response model with KPD 1st ordered rate Contant (ie, slope) on Kout appeared to be the only model with successful minimization which met the diagnostic criteria and therefore was selected as the base model. The correlation between the eta values for BASE and Kout, BASE and KPD, and Kout and KPD were -0.073, 0.06, and -0.29; hence, a full block or partial block model was not included in the base model for ALT. Based on each extreme outlier observation assessments, 6 observations with |CWRES|>6 were excluded from the dataset. The key PK-PD parameter in the final model (with significant (α=0.001) covariate effect is: BASE = $20.5*(AGE/55)^{-0.188}$.

ANC

A sequential transit compartments in series with feedback loop (TCSFL) PK-PD model with an Emax model effect on Kprol constant in stem cell compartment was used as the initial model for ANC. It appeared to be the most parsimonious model and was selected as the base model. The correlations between the eta values for BASE and MTT, BASE and Emax, BASE and EC50, MTT and Emax, MTT and EC50, Emax and EC50 were -0.0001, -0.098, 0.24, 0.089, -0.15, and -0.53, respectively; hence, a full block or partial omega block was not included in the base model for ANC. Based on extreme outlier observation assessments, 8 observations with |CWRES|>6 were excluded from the dataset. The PK-PD parameter in the final model with significant covariate (α=0.001) effect is: BASE = 4.715*(1-0.195*RAC_{Asian})

AST

The PK-PD indirect response model with KPD 1st ordered rate constant (ie, slope) on Kout appeared to be the only model with successful minimization and the lower OFV which met the diagnostic criteria and therefore was selected as the base model. The correlation between the eta values for BASE and Kout, BASE and KPD, and Kout and KPD were -0.06, -0.02, and -0.46; hence, a full block or partial block model was not included in the base model for AST. Based on extreme outlier observation assessments, 15 observations with |CWRES|>6 were excluded from the dataset. No significant covariates could be identified based on the initial screening using GAM.

Diastolic Blood Pressure

The PK-PD response model with KPD 1st ordered rate constant (ie, slope) on Kin appeared to be the most parsimonious model with successful minimization, lower OFV, and lower eta shrinkage which met the diagnostic criteria and therefore was selected as the base model. The correlation between the eta values for BASE and Kout, BASE and KPD, and Kout and KPD were 0.083, -0.10, -0.22, respectively; hence, a full block or partial block model was not included in the base model for diastolic blood pressure. Based on each extreme outlier observation assessments, 4 observations with |CWRES|>6 were excluded from the dataset. The key PK-PD parameters in the final model with significant (α=0.001) covariate effect are shown below:

$BASE = 72.8*(BWT/71)^{0.0768}$

$K_{PD} = 0.00223*(1-0.0151*(BBP-72))*(1-0.357*SCH_{CDD})$

Hemoglobin

Reduced model such as TCSFL with KPD type effect or simpler models such as IDR model was also examined and the reduced model with KPD type effect appeared to be the most parsimonious model and was selected as the base model. The correlations between the eta values for BASE and MTT, BASE and KPD, MTT and KPD were 0.15, -0.11, and -0.06, respectively; hence, a full block or partial omega block was not included in the base model for hemoglobin. Based on extreme outlier observation assessments, 3 observations with |CWRES|>6 were excluded from the dataset. The PK-PD parameter in the final model with significant (α=0.001) covariate effect is: $K_{PD} = 0.000277*(1+1.4*RAC_{Asian})$

Left Ventricular Ejection Fraction (LVEF)

The PK-PD response model with KPD 1st ordered rate constant (ie, slope) on Kin appeared to be the most parsimonious model with successful minimization, lower OFV, and lower eta shrinkage which met the diagnostic criteria and therefore was selected as the base model. The correlation between the eta values for BASE and Kout, BASE and KPD, and Kout and KPD were considered weak (- 0.27, -0.27, and 0.32, respectively); hence, a full block or partial block model was not included in the base model for

LVEF. Based on each extreme outlier observation assessments, 2 observations with |CWRES|>6 were excluded from the dataset. The key PK-PD parameter in the final model with significant (α=0.001) covariate effect is: BASE = $61.2*(1+0.0904*BEC_0)*(1+0.0413*SEX_F)$

Lymphocyte Count

Reduced model with KPD type effect appeared to be the most parsimonious model and was selected as the base model. The correlations between the eta values for BASE and MTT, BASE and KPD, MTT and KPD were considered weak (ie, 0.15, -0.11, and - 0.06, respectively); Based on extreme outlier observation assessments, 12 observations with |CWRES|>6 were excluded from the dataset. The PKPD parameters in the final model with significant (α=0.001) covariate effect is shown below:

BASE = $1.39*(1-0.174*TUM_{Solid})$

MTT = $246*(1-0.143*TUM_{Solid})$

Platelet Count

A sequential transit compartments in series with feedback loop (TCSFL) PK-PD model with an Emax model effect on Kprol constant in stem cell compartment was used as the initial model for platelet count and appeared to be the most parsimonious model and was selected as the base model. The correlations between the eta values for BASE and MTT, BASE and Emax, BASE and EC50, MTT and Emax, MTT and EC50, Emax and EC50 were considered weak (ie, -0.37, 0.41, -0.49, -0.17, 0.21, -0.37, respectively); hence, a full block or partial omega block was not included in the base model for ANC. Based on extreme outlier observation assessments, 8 observations with |CWRES|>6 were excluded from the dataset. The PK-PD parameters in the final model (Table 25: Step #7) with significant (α=0.001) covariate effect are shown below:

MTT = $106*(1-0.152*RAC_{Asian})$

Emax = $0.093*(AGE/55)^{0.672}*(1-0.00943*(BWT-70))$

EC50 = $32.7*(1-0.217*BEC_0)*(1+0.399*TUM_{Solid})*(AGE/55)^{0.571}$

Target Tumors Sum of Longest Diameters

A sequential indirect response (IDR) PK-PD model, with a tolerance function on Kout and an Emax effect function on Kin, was used as the initial model and was selected as the base model. The correlation between the eta values for BASE and Kout, BASE and EC50, BASE and Ktol, Kout and EC50, Kout and Ktol, EC50 and Ktol were considered to be weak (0.083, -0.10, -0.22, respectively); hence, a full block or partial block model was not included in the base model for SLD. Based on each extreme outlier observation assessments, 1 observation with |CWRES|>6 was excluded from the dataset.

The key PK-PD parameters with significant covariates in the final model are shown below:

BASE = $17.4*(1+0.306*BEC_0)*(1-0.403*SCH_{CDD})*(BWT/71.2)^{0.513}$

Kout = $0.00024*(BSLD/20.4)^{-0.509}$

Hand-Foot Syndrome (HFS)

The ordered categorical regression model with KPD 1st ordered rate constant (ie, slope) on BASE appeared to be the only model with successful minimization with acceptable relative standard errors for the parameter estimates and therefore was selected as the base model. The observed and predicted probability of worst grades ≥1 (ie, all grades), ≥2, and ≥3 have indicated concordance

between the observed and predicted probabilities across different grades. The key PK-PD parameter KPD (ie, slope) in the final model is: K_{PD} = 0.0254*(1+2.11*RAC)

Vomiting

The ordered categorical regression model with KPD 1st ordered rate constant (ie, slope) on BASE appeared to be the only model with successful minimization with acceptable relative standard errors for the parameter estimates and therefore was selected as the base model. The observed and predicted probability of worst grades ≥1 (ie, all grades), ≥2, and ≥3 have indicated concordance between the observed and predicted probabilities across different grades. No covariate was found to be significant, hence the final model was the same as the base model.

Nausea

The ordered categorical regression model with KPD 1st ordered rate constant (ie, slope) on BASE appeared to be the only model with successful minimization with acceptable relative standard errors for the parameter estimates and therefore was selected as the base model. The observed and predicted probability of worst grades ≥1 (ie, all grades), ≥2, and ≥3 indicated concordance between the observed and predicted probabilities across different grades. The key PK-PD parameter KPD (ie, slope) in the final model (Table 33: Step 4) is: K_{PD} = 0.023*(1+0.91*ECOG)

Fatigue

The ordered categorical regression model with KPD 1st ordered rate constant (ie, slope) on BASE appeared to be the only model with successful minimization with acceptable relative standard errors for the parameter estimates and therefore was selected as the base model. The observed and predicted probability of worst grades ≥1 (ie, all grades), ≥2, and ≥3 indicated concordance between the observed and predicted probabilities across different grades. The key PK-PD parameter KPD (ie, slope) in the final model (Table 35: Step 4) is: K_{PD} = 0.008*1.83*Age

PK-PD Trial Simulations in Pediatric and Adult Patients with GIST

Predicted PK, Safety, and Efficacy Profiles at 15 mg/m2 in Children 6-11 Years, 12-17 years, and in Adult Patients with GIST Based on Final PK-PD Models

Based on the final population PK and PK-PD models established, trial simulations were carried out to provide predictions with respect to PK, safety, and efficacy of sunitinib in pediatric patients with GIST (age groups 6-11 [n(number of patients)=210] and 12-17 years [n=210]) in comparison to adult patients with GIST [n=210]. In the pediatric age groups, children received doses ranging from 6.25 mg up to 50 mg on Schedule 4/2 whereas adults only received 50 mg doses on Schedule 4/2. A total of 20 trial simulations were run in which the pediatric arms consisted of pediatric patients, assigned demographics comparable to those for children growth statistics and for pediatric GIST; whereas, the comparator arm consisted of adult patients, assigned demographics consistent with those from dataset for adult patients with GIST. Subsequently, based on the simulated body size demographics, children within each age group who had received doses of 15 mg/m2 (ie, ≥12.5 mg/m2 and <17.5 mg/m2) were subsetted and the predicted PK and PD profiles were compared to those from adults. The simulated median profiles for safety (ALT, ANC, AST, BP, HGB, LVEF, lymphocyte count, and platelet count) and efficacy (SLD) endpoints based on the pooled data from all trials have been displayed below:

Figure 64. The Predicted Median Profiles for PK/Safety/Efficacy On Day 28 of Each Cycle Based on the Pooled Data from All Trial Simulations Following Multiple Dosing with Sunitinib 15 mg/m^2 in Pediatric Patients and 50 mg in Adults with GIST on 4/2 Schedule (28 Days On 14 Days Off)

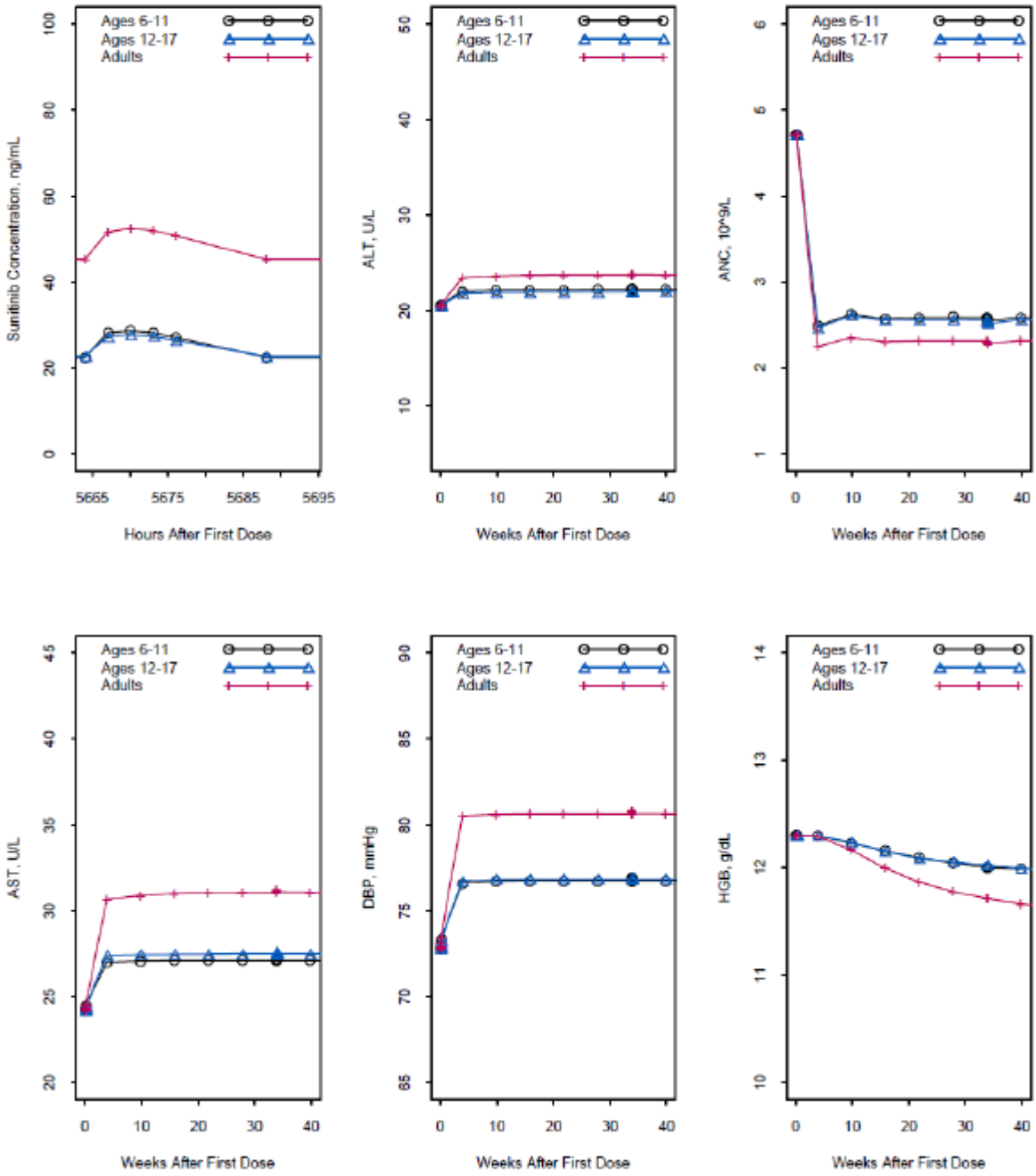
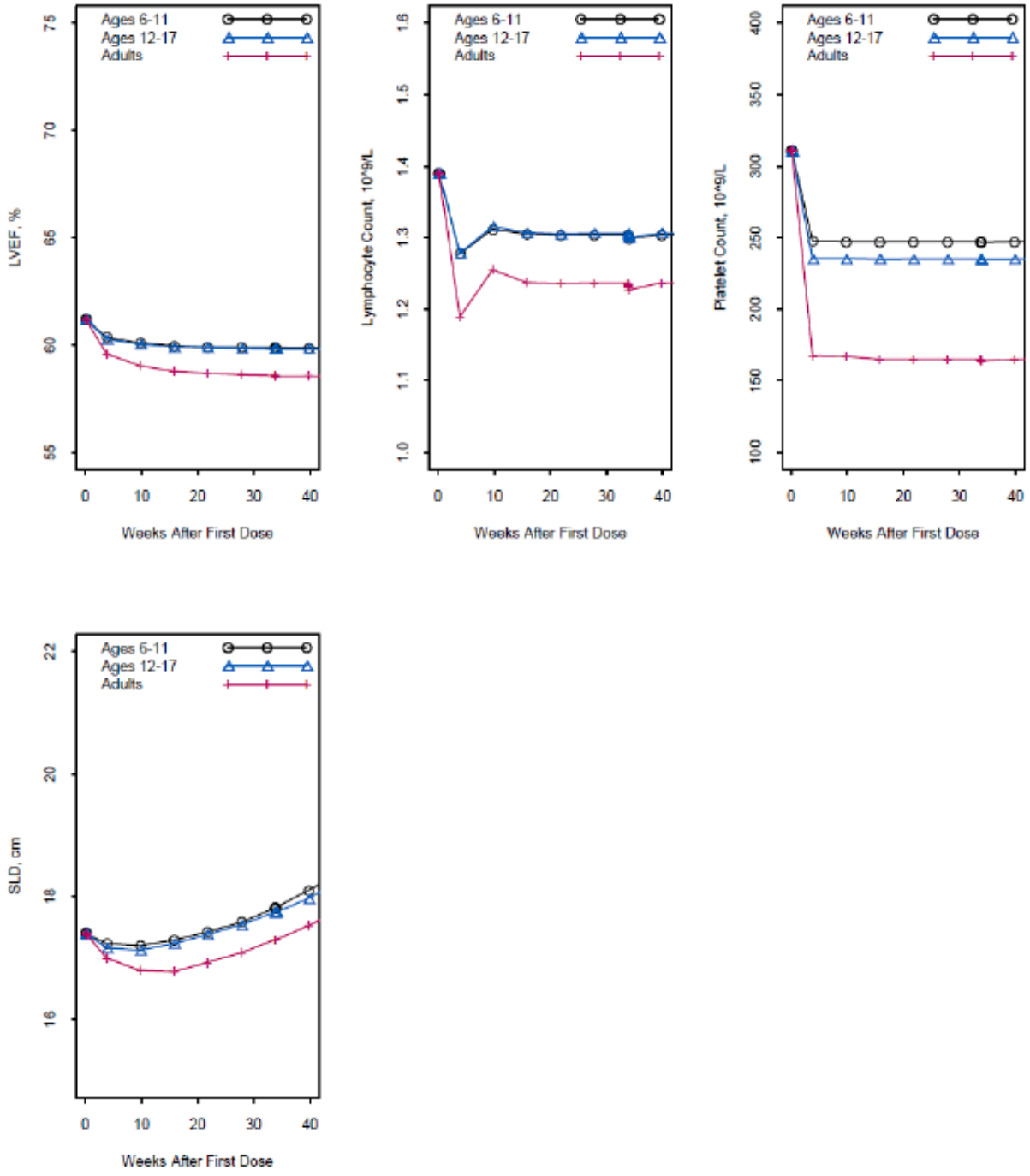


Figure 65. Predicted Median Profiles for PK/Safety/Efficacy On Day 28 of Each Cycle Based on the Pooled Data from All Trial Simulations Following Multiple Dosing with Sunitinib 15 mg/m2 in Pediatric Patients and 50 mg in Adults on 4/2 Schedule (28 Days On 14 Days Off)



The simulated median (95% CI) values for different endpoints are listed in the table below:

Table 37. The Predicted Median (95% CI) for PK/Safety/Efficacy On Day 27/28 of Cycle 6 Based on the Pooled Data from All Trial Simulations Following Multiple Dosing with Sunitinib 15 mg/m^2 in Pediatric Patients and 50 mg in Adults on 4/2 Schedule (28 Days On 14 Days Off)

PK-PD Endpoint	Baseline	Median (95% CI) For Each PK-PD Endpoint at Cycle 6 Day 27/28 for Each Age Group		
	All Ages	Ages 6-11	Ages 12-17	Adults
ALT, U/L	20.5	22 (20.7 – 40.3)	22.1 (20.7 – 38.4)	23.7 (21 – 118)
ANC, 10^9/L	4.71	2.58 (1.6 – 4.07)	2.61 (1.65 – 4.17)	2.31 (1.53 – 3.57)
AST, U/L	24.2	26.9 (24.8 – 42.4)	27.3 (25.0 – 44.7)	30.9 (25.5 – 143)
BP, mmHg	72.8	76.8 (74.1 – 83.6)	76.7 (74.2 – 83.2)	80.6 (75.4 – 95.1)
Hemoglobin, g/dL	12.3	12.0 (9.29 – 12.3)	12 (9.06 – 12.3)	11.7 (6.46 – 12.3)
LVEF, %	61.2	59.8 (51.7 – 61)	59.7 (52.9 – 61.0)	58.6 (42.7 – 60.8)
Lymphocyte Count, 10^9/L	1.39	1.29 (0.995 – 1.37)	1.31 (1.06 – 1.37)	1.24 (0.796 – 1.36)
Platelet Count, 10^9/L	311	246 (168 – 294)	235 (150 – 305)	165 (47.3 – 302)
SLD, % Change from Baseline	0.00	2.79 (-52.6 – 100)	2.56 (-57.2 – 99)	-0.685 (-65.7 – 93.9)
Sunitinib Trough Concentration, ng/mL	0.00	20.8 (6.38 – 46)	22.2 (8.11 – 54.3)	44.5 (17.9 – 102)
Sunitinib Average Concentration, ng/mL	0.00	24.7 (10.3 – 51.1)	25.9 (11.7 – 56.8)	48.8 (22.2 – 106)
SU012662 Trough Concentration, ng/mL	0.00	12.0 (4.07 – 31.7)	11.2 (4.19 – 27.0)	23.3 (7.62 – 62.2)
SU012662 Average Concentration, ng/mL	0.00	13.0 (5.17 – 32.8)	12.0 (5.05 – 27.6)	24.9 (8.85 – 64.2)

Baseline was set to the final model population BASE mean value for comparison of predicated relative changes of each endpoint across different age groups; median (95% CI) represents median (2.5%ile, 97.5%ile); sunitinib average concentration median (95% CI) represents mean of median (2.5%ile, 97.5%ile) values at 0, 3, 6, 9, 12, and 24 hrs post dose on Day 27 of Cycle 6.
ePharm Folder ID 694966: Run 7.

Subsequently, additional trial simulations were run using the predicted average sunitinib concentrations in each age group and assuming 40% intersubject variability to predict the probability of incidence of adverse events HFS, nausea, vomiting, and fatigue in pediatric patient age groups and in adults with GIST based on the final PK-PD models for each endpoint. The simulation results clearly indicate 47-48% lower sunitinib plasma exposures in both pediatric groups in comparison to adults

Predicted PK, Safety, and Efficacy Profiles Janeway/Agaram Patient Population and in Adult Patients with GIST Based on Final PK-PD Models

Based on the final population PK and PK-PD models established, for each endpoint, additional trial simulations were carried out to provide predictions with respect to PK, safety, and efficacy of sunitinib in a typical age and gender group pediatric patient population as those from studies conducted by Janeway et al and Agaram et al studies administered either the starting dose (ie, 25-50 mg; ~ 25 mg/m2) or the maximum dose (ie, 25-50 mg; ~ 30 mg/m2) within those studies. A total of 200 trial simulations were run in which the pediatric arm consisted of pediatric patients (n=11) with the same demographics as those in Janeway et al and Agaram et al studies receiving the initial starting doses and the comparator arm included adult patients (n=11) with GIST all receiving 50 mg on Schedule 4/2. Subsequently, another set of 200 trial simulations were run in which the pediatric arm received the maximum doses instead of the starting doses from the Janeway et al and Agaram et al studies. The simulated median profiles for safety (ALT, ANC, AST, BP, HG, LVEF, lymphocyte count, and platelet count) and efficacy (SLD) based on the pooled data from all trials with pediatric patients receiving starting doses have been displayed below:

Figure 67. The Predicted Median Profiles for PK/Safety/Efficacy On Day 28 of Each Cycle Based on the Pooled Data from All Trial Simulations Following Multiple Dosing with Sunitinib (Starting Doses) in Janeway et al and Agaram et al in Pediatric Patients and 50 mg in Adults on 4/2 Schedule (28 Days On 14 Days Off)

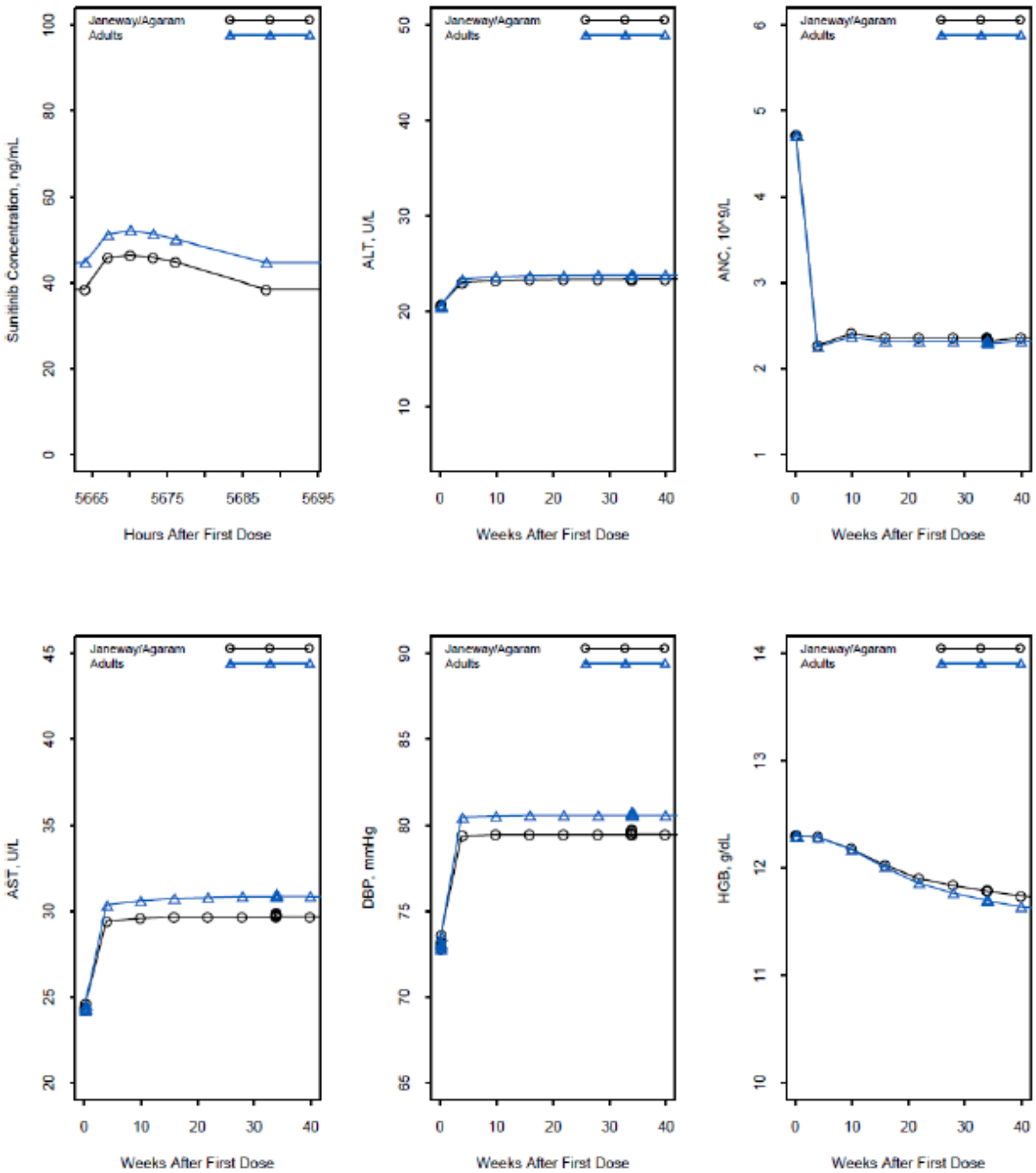
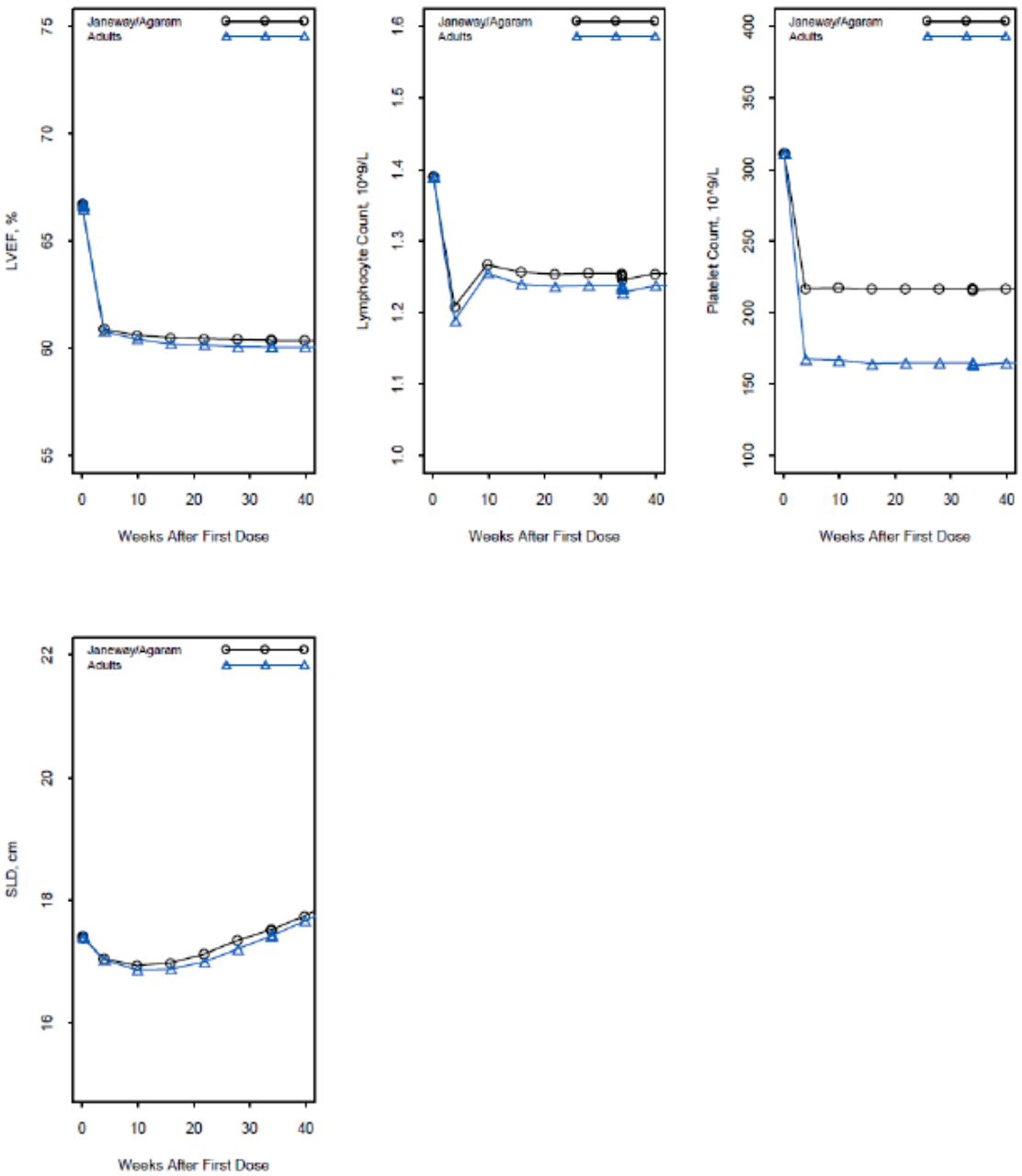


Figure 68. The Predicted Median Profiles for PK/Safety/Efficacy On Day 28 of Each Cycle Based on the Pooled Data from All Trial Simulations Following Multiple Dosing with Sunitinib (Starting Doses) in Janeway et al and Agaram et al in Pediatric Patients and 50 mg in Adults on 4/2 Schedule (28 Days On 14 Days Off)



The simulated median (95% CI) values for different endpoints have been listed below:

Table 39. The Predicted Median (95% CI) for PK/Safety/Efficacy On Day 28 of Cycle 6 Based on the Pooled Data from All Trial Simulations Following Multiple Dosing with Sunitinib (Starting Doses) in Janeway et al and Agaram et al in Pediatric Patients and 50 mg in Adults on 4/2 Schedule (28 Days On 14 Days Off)

PK-PD Endpoint	Median at Baseline	Median (95% CI) For Each PK-PD Endpoint at Cycle 6 Day 27/28 for Each Age Group	
	All Ages	Janeway/Agaram	Adults
ALT, U/L	20.5	23.3 (20.9 – 74.3)	23.8 (20.9 –109)
ANC, 10^9/L	4.71	2.36 (1.49 – 3.69)	2.32 (1.55 – 3.53)
AST, U/L	24.2	29.7 (25.3 – 119)	30.8 (25.5 – 127)
BP, mmHg	72.8	79.5 (74.9 – 92.1)	80.6 (75.3 – 95.0)
Hemoglobin, g/dL	12.3	11.8 (7.14 – 12.3)	11.7 (6.62 – 12.3)
LVEF, %	61.2	58.9 (42.9 – 60.9)–	58,5 (42.7 – 60.8)–
Lymphocyte Count, 10^9/L	1.39	1.25 (0.832– 1.36)	1.24 (0.817 – 1.35)
Platelet Count, 10^9/L	311	216 (112 – 283)	165 (51 – 302)
SLD, % Change from Baseline	0.00	0.69 (-64.8 – 91.0)	0.083 (-62.4 – 96.3)
Sunitinib Trough Concentration, ng/mL	0.00	38.5 (13.5 – 93.7)	44.7 (17.9 – 106)
Sunitinib Average Concentration, ng/mL	0.00	43.3 (18.3 – 99.8)	49.0 (22.7 – 110)
SU012662 Trough Concentration, ng/mL	0.00	18.7 (6.04 – 52.0)	19.7 (6.78 – 52.6)
SU012662 Average Concentration, ng/mL	0.00	19.8 (7.13 – 54.1)	20.9 (7.72 – 54.2)

Baseline was set to the final model population BASE mean value for comparison of predicated relative changes of each endpoint across different age groups; median (95% CI) represents median (2.5%ile, 97.5%ile); sunitinib average concentration median (95% CI) represents mean of median (2.5%ile, 97.5%ile) values at 0, 3, 6, 9, 12, and 24 hrs post dose on Day 27 of Cycle 6.
ePharm Folder ID 694966: Run 8.

Subsequently, additional trial simulations were run using the predicted average sunitinib concentrations in each age group and assuming 40% intersubject variability to predict the probability of incidence of adverse events HFS, nausea, vomiting, and fatigue in pediatric patient age groups and in adults with GIST based on the final PK-PD models for each endpoint. The results clearly indicate that sunitinib plasma exposures were higher in Janeway and Agaram patients dosed at their starting doses as compared to pediatric patients with GIST dosed at 15 mg/m2 in both pediatric groups, and that the levels in Janeway and Agaram studies although still lower (ie, by 12%) were much closer to those in adult patients with GIST receiving 50 mg. Based on the trial simulations described previously, the predicted median (95% CI) for TTP and ORR were 24.8(10.5-42.6) weeks and 9.0(0.0-36.0) % in Janeway and Agaram pediatric patient population, and were 24.7(12.7-42.6) weeks and 9.0(0.0-27.0) % in adult patients with GIST.

Population Modeling Analysis Report (PMAR-EQDD-A618b-DP4-846)

The effects of important covariates on PK parameters were evaluated using a stepwise covariate selection procedure in which BSA was the only statistically significant covariate ($p \leq 0.001$) for CL/F and Vc/F in the final PK models of both sunitinib and SU012662. Other covariates such as age, tumour type (GIST vs other solid tumours), race (Asian vs non- Asian), baseline Eastern Cooperative Oncology

Group (ECOG) performance status (>0 vs 0), Sex (male vs female) were not found to have statistically significant (p>0.001) effects on CL/F or Vc/F.

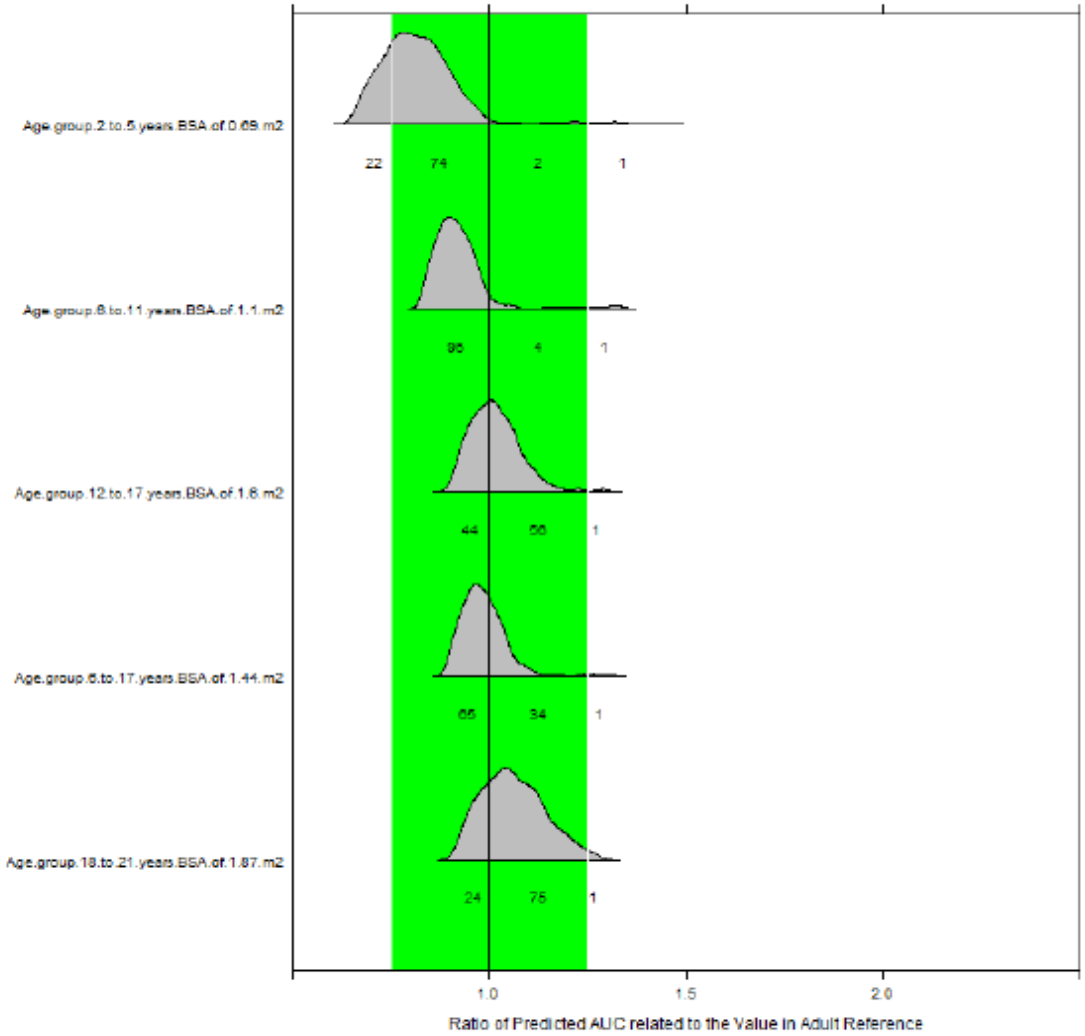
Based on the final PK models, in a typical paediatric patient with GIST or other solid tumours within the age groups of 2 years to 5 years (median BSA of 0.69 m2), 6 years to 11 years (median BSA of 1.1 m2), and 12 years to 17 years (median BSA of 1.6 m2), the sunitinib doses that will lead to predicted steady- state total plasma exposure over the dosing interval (ie, steady-state AUC24) similar to what have been observed in adults with GIST (1233 ng.hr/mL for sunitinib and 551 ng.hr/mL for SU012662) at 50 mg are 25 mg/m2, 22 mg/m2, and 20 mg/m2 for sunitinib and 22 mg/m2, 21 mg/m2, and 20 mg/m2 for SU012662, respectively. Therefore, in paediatric patients with GIST within the age range from 6 years to 17 years, a dose of approximately 20 mg/m2 is expected to provide overall similar extent of total plasma exposures to sunitinib and its active metabolite as compared to adults with GIST administered sunitinib 50 mg on Schedule 4/2. BSA-tiered dosing in children to achieve steady-state sunitinib and SU012662 AUC observed in adult patients with GIST at the sunitinib dose of 50 mg were predicted to be 12.5 mg, 25 mg, 37.5 mg, 50 mg QD on Schedule 4/2 for paediatric patients with BSAs of ≤0.7 m2, 0.8-1.5 m2, 1.6-2.4 m2, and ≥2.5 m2, respectively.

SIMULATIONS

Predicted Sunitinib AUC and BSA-Tiered Dosing Based on Final Sunitinib PK Model

Bootstrapping techniques were used to estimate the expected effect of the significant covariate BSA on sunitinib AUC relative to the reference, an adult patient with GIST at sunitinib dose of 50 mg (sunitinib AUC of 1233 ng.hr/mL). This analysis showed that the relative AUC values for a typical pediatric patient 6-17 years of age at sunitinib dose of 20 mg/m2 is predicted to be between 75% and 125% of the AUC of the reference.

Figure 25. Effect of Statistically Significant Covariate BSA on Sunitinib AUC Following Multiple Dosing of Sunitinib 20 mg/m^2 for Different Age Groups Based on the Final Population Pharmacokinetic Model



ePharmacology artifact ID RA14369525.

Reference: the geometric mean steady state 24-hour sunitinib AUC of 1233 ng.hr/mL in an adult patient with GIST at the sunitinib dose of 50 mg.[16] Effects of BSA on AUC are presented as probability density plots on a relative scale to indicate proportional size and precision relative to the adult reference patient. The plots represent distributions of 1,000 nonparametric bootstrap estimates, with the heights of the plots representing probability.

Furthermore, using the final sunitinib PK model, the doses (in mg) to achieve the steady state 24-hour sunitinib AUC of 1233 ng.hr/mL, observed in adult patients with GIST at the sunitinib dose of 50 mg, were calculated (Table below). Subsequently, based on the calculated dose and the commercially available sunitinib dose levels (i.e., 12.5, 25, 37.5, and 50 mg), sunitinib BSA-tiered dosing in children was determined.

Table 11. The BSA-Tiered Dosing of Sunitinib in Children to Achieve Sunitinib AUC Similar to That Observed in Adult Patients with GIST at 50 mg/day

BSA (m^2)	Calculated Dose (mg/day)	BSA-Tiered Dose (mg/day)
0.50	13.63	12.50
0.60	15.58	12.50
0.70	17.44	12.50
0.80	19.23	25.00
0.90	20.97	25.00
1.00	22.65	25.00
1.10	24.29	25.00
1.20	25.89	25.00
1.30	27.45	25.00
1.40	28.99	25.00
1.50	30.49	25.00
1.60	31.97	37.50
1.70	33.42	37.50
1.80	34.85	37.50
1.90	36.26	37.50
2.00	37.65	37.50
2.10	39.02	37.50
2.20	40.37	37.50
2.30	41.71	37.50
2.40	43.03	37.50
2.50	44.34	50.00
2.60	45.63	50.00
2.70	46.91	50.00
2.80	48.18	50.00
2.90	49.43	50.00
3.00	50.68	50.00

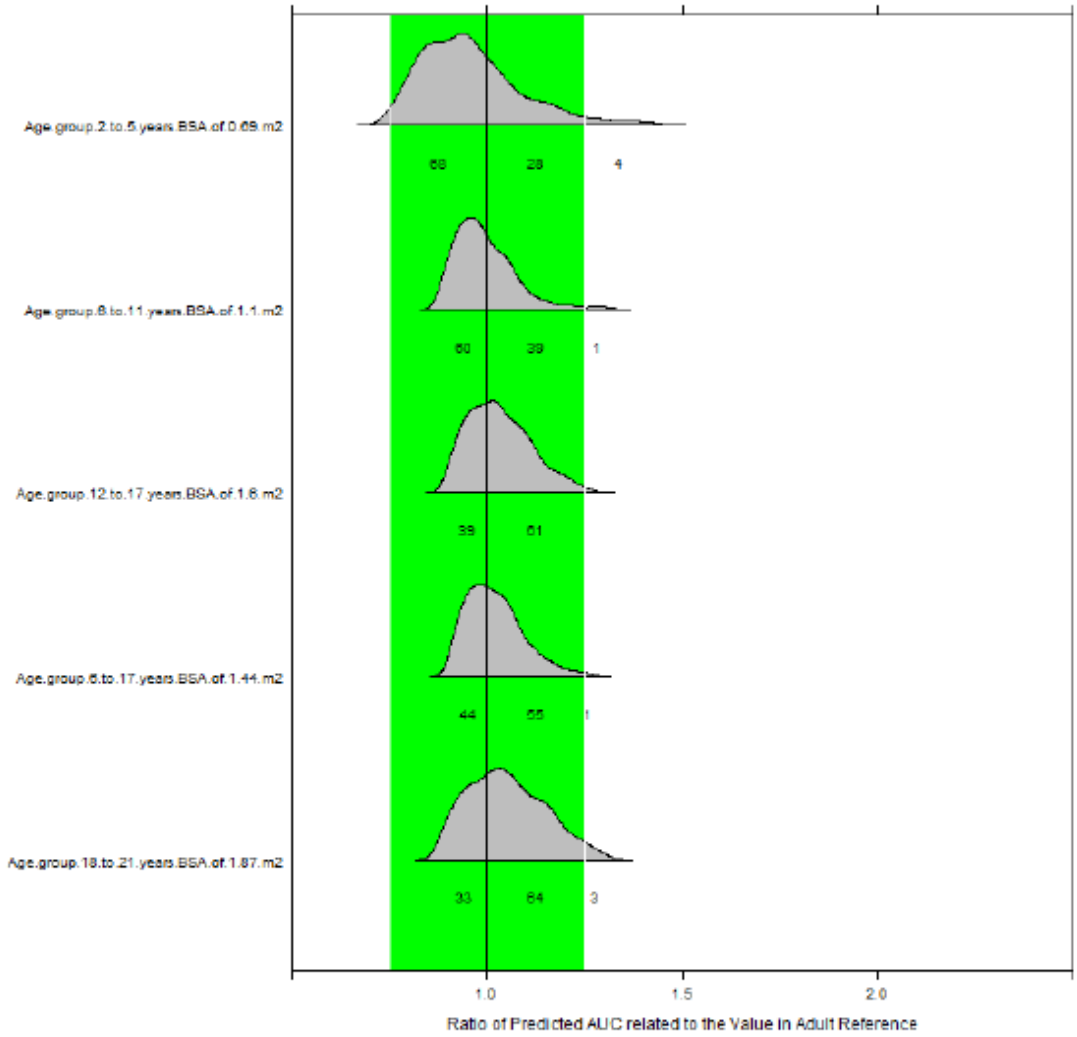
ePharmacology artifact ID RA14530887. Line 1 substituted.

The dose calculated in children to achieve the steady state 24-hour sunitinib AUC of 1233 ng.hr/mL observed in adult patients with GIST at the sunitinib dose of 50 mg.[16] Calculated Dose based on manual calculation: Dose (mg)=Clearance L/hr*1233 ng.hr/mL/1000

Predicted SU012662 AUC Based on Final SU012662 PK Model

Bootstrapping techniques were used to estimate the expected effect of the significant covariate BSA on SU01662 AUC relative to the reference, an adult patient with GIST at sunitinib dose of 50 mg (SU012662 AUC of 551 ng.hr/mL). This analysis showed that the relative AUC values for pediatric patients 6-17 years of age at sunitinib dose of 20 mg/m2 is predicted to be between 75% and 125% of the AUC of the reference.

Figure 26. Effect of Statistically Significant Covariate BSA on SU012662 AUC Following Multiple Dosing of Sunitinib 20 mg/m^2 for Different Age Groups Based on the Final Population Pharmacokinetic Model



ePharmacology artifact ID RA14621205.

Reference: the geometric mean steady state 24-hour SU012662 AUC of 551 ng.hr/mL in an adult patient with GIST at the sunitinib dose of 50 mg.[16] Effects of BSA on AUC are presented as probability density plots on a relative scale to indicate proportional size and precision relative to the adult reference patient. The plots represent distributions of 1,000 nonparametric bootstrap estimates, with the heights of the plots representing probability.

Furthermore, using the final SU012662 PK model, the doses (in mg) to achieve the steady state 24-hour SU012662 AUC of 551 ng.hr/mL, observed in adult patients with GIST at the sunitinib dose of 50 mg, were calculated (Table below). Subsequently, based on the calculated dose and the commercially available sunitinib dose levels (i.e.,12.5, 25, 37.5, and 50 mg), sunitinib BSA-tiered dosing in children was determined.

Table 12. The BSA-Tiered Dosing of Sunitinib in Children to Achieve SU012662 AUC Similar to That Observed in Adult Patients with GIST at 50 mg/day

BSA (m^2)	Calculated Dose (mg/day)	BSA-Tiered Dose (mg/day)
0.5	11.57	12.5
0.6	13.56	12.5
0.7	15.52	12.5
0.8	17.43	12.5
0.9	19.32	25
1	21.18	25
1.1	23.02	25
1.2	24.84	25
1.3	26.64	25
1.4	28.42	25
1.5	30.18	25
1.6	31.93	25
1.7	33.67	37.5
1.8	35.39	37.5
1.9	37.1	37.5
2	38.8	37.5
2.1	40.49	37.5
2.2	42.16	37.5
2.3	43.83	37.5
2.4	45.49	50
2.5	47.14	50
2.6	48.78	50
2.7	50.42	50
2.8	52.04	50
2.9	53.66	50
3	55.28	50

ePharmacology artifact ID RA14530886. Line 1 substituted.
The dose calculated in children to achieve the steady state 24-hour SU012662 AUC of 551 ng.hr/mL observed in adult patients with GIST at the sunitinib dose of 50 mg.[16] Calculated Dose based on manual calculation: Dose (mg)=Clearance L/hr*551 ng.hr/mL/1000/0.21.

There was a great overlap in the BSA-tiered dosing brackets based on the metabolite exposure as compared to the sunitinib exposure; however, in cases where there were differences in the determined tiered dose, the preference was given to the tiered dose determination based on sunitinib considering that the plasma exposure to sunitinib was much larger than that of the metabolite.

PBPK SimCYP

SimCYP Simulation Design

Simulations in SimCYP were performed with a virtual population of healthy volunteers in 10 trials of 10 subjects each in a fasted condition. The Standard model virtual population was used, and the Paediatric module was selected for performing PK prediction in paediatrics.

Simulation No. 1 (multiple oral dose sunitinib PK study in adults; age 20 to 50 years, proportion of females of 0.5): A multiple 50-mg oral daily dose of sunitinib was administered and the concentration-time profiles of sunitinib and SU012662 were simulated up to Day 29.

Simulation No. 2 (multiple oral dose sunitinib PK study in paediatrics; age 3 to 21 years old, proportion of females of 0.5): A multiple 15-mg/m2 oral daily dose (maximum tolerated dose in paediatrics) of sunitinib was administered and the concentration-time profiles of sunitinib and SU012662 were simulated up to Day 29 to mimic the observed concentration-time profile in Cycle 1 in Study ADVL0612.

Simulation No. 3 (multiple oral dose sunitinib PK study in paediatrics; age 3 to 19 years old, proportion of females of 0.4): A multiple 15-mg/m2 oral daily dose of sunitinib was administered and the concentration-time profiles of sunitinib and SU012662 were simulated up to Day 29 to mimic the observed concentration-time profile in Cycle 1 in Study ACNS1021.

Simulation No. 4 (multiple oral dose sunitinib PK study in paediatrics; age 13 to 16 years old, proportion of females of 0.8): A multiple 15-mg/m2 oral daily dose of sunitinib was administered and the concentration-time profiles of sunitinib and SU012662 were simulated up to Day 29 to mimic the observed concentration-time profile in Cycle 1 in Study A6181196.

Simulation No. 5 (multiple oral dose sunitinib PK study in paediatrics; age 2 to 5 years old, proportion of females of 0.5): A multiple 15-mg/m2 oral daily dose of sunitinib was administered and the concentration-time profiles of sunitinib and SU011246 were simulated up to Day 29.

Simulation No. 6 (multiple oral dose sunitinib PK study in paediatrics; age 6 to 11 years old, proportion of females of 0.5): A multiple 15-mg/m2 oral daily dose of sunitinib was administered and the concentration-time profiles of sunitinib and SU011246 were simulated up to Day 29.

Simulation No. 7 (multiple oral dose sunitinib PK study in paediatrics; age 12 to 17 years old, proportion of females of 0.5): A multiple 15-mg/m2 oral daily dose of sunitinib was administered and the concentration-time profiles of sunitinib and SU011246 were simulated up to Day 29.

RESULTS

Predicted and Observed Sunitinib and SU012662 PK Following 50-mg Oral Dose of Sunitinib in Adults

A comparison of the clinically observed and simulated systemic exposure of sunitinib and SU012662 following oral administration of a multiple 50-mg daily dose of sunitinib is summarised in the table below:

Table 4. Clinically Observed and SimCYP-Predicted Sunitinib and SU012662 Pharmacokinetic Parameter Estimates in Adults After a Multiple 50-mg Oral Daily Dose of Sunitinib

		Day 1		Day 28		
		C_{max} (ng/mL)	AUC_{0-24} (ng•h/mL)	C_{max} (ng/mL)	AUC_{0-24} (ng•h/mL)	C_{trough} (ng/mL)
Sunitinib	Predicted	29.8	465	74.1	1441	47.5
	Observed[a]	27.7	420	72.2	1296	44.0
	Predicted/Observed Ratio	1.08	1.11	1.03	1.11	1.08
SU012662	Predicted	4.09	75.6	25.7	586	22.8
	Observed[a]	4.12	63.6	33.7	592	18.8
	Predicted/Observed Ratio	0.99	1.19	0.76	0.99	1.21

AUC_{0-24}=area under the concentration-time curve from time 0 to 24 hours; C_{max}=maximum observed plasma concentration; C_{trough}=pre-dose plasma concentration during multiple dosing; SimCYP=physiologically-based pharmacokinetic modelling software.

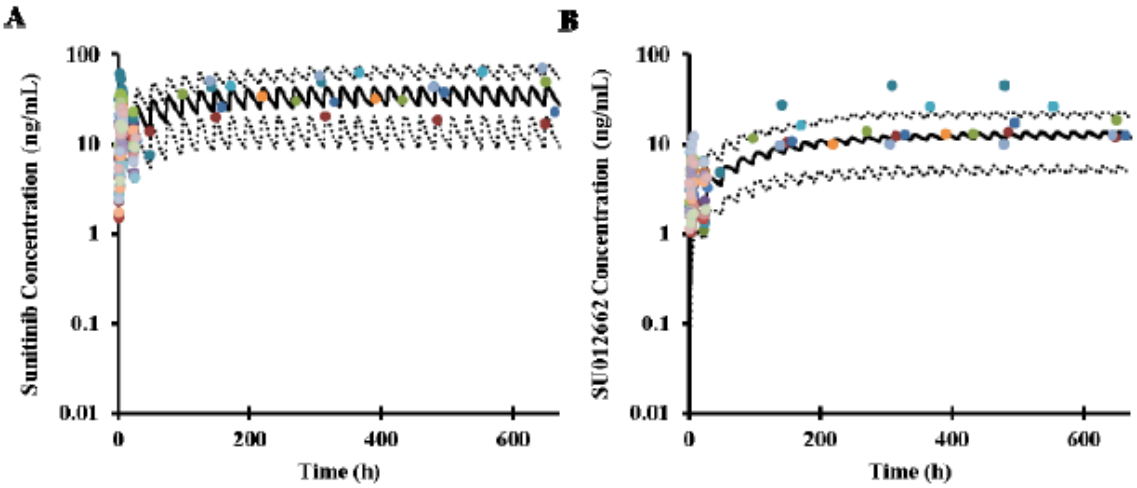
a. Observed data are from Reference 5.

The ratios of the predicted versus observed Cmax, AUC, and Ctrough values for sunitinib and SU012662 were within 80%-125%, except that the ratio of the predicted versus observed Cmax value for SU012662 on Day 28 was 0.76.

Predicted and Observed Sunitinib and SU012662 PK Following 15-mg/m2 Oral Dose of Sunitinib in Paediatrics

A graphical comparison of the clinically observed and simulated systemic exposure of sunitinib and SU012662 following oral administration of 15-mg/m2 multiple daily dose of sunitinib for age groups 3-21 years old with observed data from patients with solid tumour in Study ADVL0612, for age groups 3-19 years old with observed data from patients with solid tumour in Study ACNS1021, and for age groups 13-16 years old with observed data from patients with GIST in Study A6181196 were presented. Below the comparison for age groups 3 to 21 is reported:

Figure 1. Observed (Study ADVL0612) and SimCYP-Predicted Sunitinib and SU012662 Plasma Concentration-Time Profiles in Paediatrics at 3-21 Years Old After a Multiple 15-mg/m^2 Daily Oral Dose of Sunitinib



Solid black line is the predicted mean concentration-time profile; dashed black lines represent predicted 5th and 95th percentile concentration-time profile; coloured circles show the observed concentration-time profile in Study ADVL0612 at dose level of 15 mg/m^2.
(A) Sunitinib. (B) SU012662.
SimCYP=physiologically-based pharmacokinetic modelling software.

There is a relatively good prediction of the exposures of sunitinib for Study ADVL0612, instead the exposure of SU012662 for Study ADVL0612 was underestimated.

Table 5. Clinically Observed and SimCYP-Predicted Sunitinib and SU012662 Pharmacokinetic Parameter Estimates in Paediatrics in Study ADVL0612 (3-21 Years Old) After a Multiple 15-mg/m^2 Daily Oral Dose of Sunitinib

		C_{max} (ng/mL)	AUC_{0-24} (ng•h/mL)	$C_{trough,ss}$[a] (ng/mL)
Sunitinib	Predicted	19.0	306	27.1
	Observed[b]	21.2	337	31.5
	Predicted/Observed Ratio	0.90	0.91	0.86
SU012662	Predicted	2.46	46.6	11.9
	Observed[b]	4.16	73.2	14.7
	Predicted/Observed Ratio	0.59	0.64	0.81
Sunitinib+SU012662	Predicted	21.5	353	39.0
	Observed[b]	25.0	411	46.2
	Predicted/Observed Ratio	0.86	0.86	0.84

AUC_{0-24}=area under the concentration-time curve from time 0 to 24 hours; C_{max}=maximum concentration; C_{trough}=pre-dose plasma concentration during multiple dosing; $C_{trough,ss}$=trough plasma concentration at steady state; SimCYP=physiologically-based pharmacokinetic modelling software.

a. Observed is C_{trough} on Day 28.[9]
b. Based on the mean of the Sprinkled Capsule and Intact Capsule.[9]

There is a relatively good prediction of the exposures of sunitinib, SU012662, and the total active moieties for Study ACNS1021, instead the Ctrough was slightly underestimated for sunitinib, SU012662, and the total active moieties.

Table 6. Clinically Observed and SimCYP-Predicted Sunitinib and SU012662 Pharmacokinetic Parameter Estimates in Paediatrics in Study ACNS1021 (3-19 Years Old) After a Multiple 15-mg/m^2 Daily Oral Dose of Sunitinib

		C_{max} (ng/mL)	AUC_{0-24} (ng•h/mL)	$C_{trough,ss}$[a] (ng/mL)
Sunitinib	Predicted	19.4	314	28.3
	Observed	20.9	374	36.7
	Predicted/Observed Ratio	0.93	0.84	0.77
SU012662	Predicted	2.40	45.6	12.0
	Observed	2.75	54.5	17.7
	Predicted/Observed Ratio	0.87	0.84	0.68
Sunitinib+SU012662	Predicted	21.8	360	40.3
	Observed	23.7	429	54.4
	Predicted/Observed Ratio	0.92	0.84	0.74

AUC_{0-24}=area under the concentration-time curve from time 0 to 24 hours; C_{max}=maximum observed plasma concentration; C_{trough}=pre-dose plasma concentration during multiple dosing; $C_{trough,ss}$=trough plasma concentration at steady state; SimCYP=physiologically-based pharmacokinetic modelling software.
a. Observed is C_{trough} on Day 28.[10]

There is a relatively good prediction of the exposures of sunitinib and SU012662 for Study A6181196, as a result, there is also a good prediction of the exposures of the total active moieties.

Table 7. Clinically Observed and SimCYP-Predicted Sunitinib and SU012662 Pharmacokinetic Parameter Estimates in Paediatrics in Study A6181196 (13-16 Years Old) After a Multiple 15-mg/m^2 Daily Oral Dose of Sunitinib

		C_{max} (ng/mL)	AUC_{0-8} (ng•h/mL)	$C_{trough,ss}$[a] (ng/mL)
Sunitinib	Predicted	17.8	110	25.0
	Observed	18.4	82.7	29.1
	Predicted/Observed Ratio	0.97	1.33	0.86
SU012662	Predicted	2.29	10.8	11.5
	Observed	2.37	10.7	13.0
	Predicted/Observed Ratio	0.97	1.01	0.88
Sunitinib+SU012662	Predicted	20.1	121	36.5
	Observed	20.8	93.4	42.1
	Predicted/Observed Ratio	0.97	1.30	0.87

AUC_{0-8}=area under the concentration-time curve from time 0 to 8 hours; C_{max}=maximum observed plasma concentration; C_{trough}=pre-dose plasma concentration during multiple dosing; $C_{trough,ss}$=trough plasma concentration at steady state; SimCYP=physiologically-based pharmacokinetic modelling software.
a. Observed is C_{trough} on Day 28.[11]

Modelling underestimation of sunitinib, SU012662, and total active moieties exposures

Assuming an approximate 15% underestimation of SimCYP exposures (average total drug AUC24 underestimation, SimCYP Report Section 4), the revised projected doses based on SimCYP (ie, 19 mg/m2 for 6-11 years and 21 mg/m2 for 12-17 years instead of 22 mg/m2 for 6-11 years and 25 mg/m2 for 12-17 years) would be even closer to the dose of 20 mg/m2 (ie, within approximately 5% instead of 25%) and remain consistent with and confirming the dose determined by the integrated population PK analysis (20 mg/m2). Therefore, in both scenarios, the dose projections by SimCYP approach support the 20 mg/m2 dose determined by the integrated population PK analysis.

Comparison of Predicted and Observed Sunitinib and SU012662 Exposure at Steady State Following 15-mg/m2 Oral Dose of Sunitinib in Adults and Paediatrics

A comparison of the clinically observed and simulated steady state systemic exposure of sunitinib and SU012662 following 15-mg/m2 daily oral administration of sunitinib is summarised in the table below:

Table 8. SimCYP-Predicted Sunitinib and SU012662 Exposure at Steady State

Population	Dose	Sunitinib			SU012662			Sunitinib+SU012662		
		$AUC_{\tau,ss}$ (ng•h/mL)	$C_{max,ss}$ (ng/mL)	$C_{trough,ss}$ (ng/mL)	$AUC_{\tau,ss}$ (ng•h/mL)	$C_{max,ss}$ (ng/mL)	$C_{trough,ss}$ (ng/mL)	$AUC_{\tau,ss}$ (ng•h/mL)	$C_{max,ss}$ (ng/mL)	$C_{trough,ss}$ (ng/mL)
Adults (observed)[a]	Normalised to 15 mg/m^{2b}	648	36.1	22.0	296	16.9	9.4	944	53.0	31.4
Adults (predicted)	Normalised to 15 mg/m^{2b}	721	37.1	23.8	293	12.9	11.4	1014	49.9	35.2
Paediatrics (2-5 years old)	15 mg/m^2 QD	1081	56.4	33.9	296	13.1	11.3	1377	69.5	45.2
Paediatrics (6-11 years old)		919	47.7	29.3	301	13.3	11.6	1220	61.0	40.9
Paediatrics (12-17 years old)		783	40.6	25.3	313	13.7	12.1	1096	54.3	37.4

$AUC_{\tau,ss}$=area under the plasma concentration-time curve from time 0 to τ (24 h) in steady state; $C_{max,ss}$=maximum observed plasma concentration in steady state; $C_{trough,ss}$=trough plasma concentration at steady state; SimCYP=physiologically-based pharmacokinetic modelling software; QD=once daily.
a. Observed data are from Reference 5 as mean.
b. 50-mg dose equivalent to 30 mg/m^2.

The exposure of sunitinib decreases with the increase of age for the 3 paediatric age groups, and the exposure of SU012662 increases with the increase of age for the 3 paediatric age groups.

The MAH conducted additional simulations with 20 mg/m2 daily dosage and compared to the observed pediatric data. As the observed pediatric data were at 15 mg/m2 daily dosage, the observed exposure parameters were dose corrected to 20 mg/m2 for comparison purpose. The tables below show clinically observed dose-corrected and SimCYP-predicted sunitinib and SU012662 pharmacokinetic parameter estimates in pediatrics in Study ADVL0612 (3-21 years old), Study ACNS1021 (3-19 years old), and Study A6181196 (13-16 years old) after a multiple 20-mg/m2 daily oral dose of sunitinib, respectively. Overall, the ratios of the predicted versus observed dose-corrected exposure values following trial simulations with the dose of 20 mg/m2 were essentially the same as the ones obtained with the dose of 15 mg/m2 (SimCYP Report Section 4), which is not unexpected considering the dose-linearity in the PK model.

Table 1. Clinically Observed Dose-Corrected and SimCYP-Predicted Sunitinib and SU012662 Pharmacokinetic Parameter Estimates in Pediatrics in Study ADVL0612 (3-21 Years Old) After a Multiple 20-mg/m^2 Daily Oral Dose of Sunitinib

		C_{max} (ng/mL)	AUC_{0-24} (ng•h/mL)	$C_{trough,ss}$[c] (ng/mL)
Sunitinib	Predicted	25.3	408	36.2
	Observed[d]	28.3	449	42
	Predicted/Observed Ratio	0.89	0.91	0.86
SU012662	Predicted	3.28	62.1	15.9
	Observed[d]	5.55	98	19.6
	Predicted/Observed Ratio	0.59	0.63	0.81
Sunitinib+SU012662	Predicted	28.58	470	52.1
	Observed[d]	33.33	548	61.6
	Predicted/Observed Ratio	0.86	0.86	0.85

AUC0-24=area under the concentration-time curve from time 0 to 24 hours; Cmax=maximum concentration; Ctrough=pre-dose plasma concentration during multiple dosing; Ctrough,ss=trough plasma concentration at steady state; SimCYP=physiologically-based pharmacokinetic modelling software.
a. Observed is Ctrough on Day 28.
b. Based on the mean of the Sprinkled Capsule and Intact Capsule.

Table 2. Clinically Observed Dose-Corrected and SimCYP-Predicted Sunitinib and SU012662 Pharmacokinetic Parameter Estimates in Pediatrics in Study ACNS1021 (3-19 Years Old) After a Multiple 20-mg/m^2 Daily Oral Dose of Sunitinib

		C_{max} (ng/mL)	AUC_{0-24} (ng•h/mL)	$C_{trough,ss}$[b] (ng/mL)
Sunitinib	Predicted	25.8	419	37.7
	Observed	27.9	499	48.9
	Predicted/Observed Ratio	0.92	0.84	0.77
SU012662	Predicted	3.2	60.8	16
	Observed	3.67	73	23.6
	Predicted/Observed Ratio	0.87	0.83	0.68
Sunitinib+SU012662	Predicted	29	480	53.7
	Observed	31.6	572	72.5
	Predicted/Observed Ratio	0.92	0.84	0.74

AUC0-24=area under the concentration-time curve from time 0 to 24 hours; Cmax=maximum observed plasma concentration; Ctrough=pre-dose plasma concentration during multiple dosing; Ctrough,ss=trough plasma concentration at steady state; SimCYP=physiologically-based pharmacokinetic modelling software.
a. Observed is Ctrough on Day 28.

Table 3. Clinically Observed Dose-Corrected and SimCYP-Predicted Sunitinib, SU012662 Pharmacokinetic Parameter Estimates in Pediatrics in Study A6181196 (13-16 Years Old) After a Multiple 20-mg/m^2 Daily Oral Dose of Sunitinib

		C_{max} (ng/mL)	AUC_{0-8} (ng•h/mL)	$C_{trough,ss}$[b] (ng/mL)
Sunitinib	Predicted	23.7	147	33.4
	Observed	24.5	110	38.8
	Predicted/Observed Ratio	0.97	1.34	0.86
SU012662	Predicted	3.17	14.3	15.4
	Observed	3.16	14	17.33
	Predicted/Observed Ratio	1	1.02	0.89
Sunitinib+SU012662	Predicted	26.87	161	48.8
	Observed	27.73	125	56.1
	Predicted/Observed Ratio	0.97	1.29	0.87

AUC0-8=area under the concentration-time curve from time 0 to 8 hours; Cmax=maximum observed plasma concentration; Ctrough=pre-dose plasma concentration during multiple dosing; Ctrough,ss=trough plasma concentration at steady state; SimCYP=physiologically-based pharmacokinetic modelling software.
a. Observed is Ctrough on Day 28.

6.3. Discussion

In the PK-PD analysis of Sunitinib in Patients with GIST (PMAREQDD-A618w-Other-366) paediatric data from only 1 clinical study have been included in the dataset (study ADVL0612). In this study patients with solid tumours have been enrolled, but the MAH stated that for efficacy PK-PD analyses only studies of patients with GIST were used. ADVL0612 study data for the PK/PD model were included only for safety endpoints. The descriptive statistics for the subjects baseline characteristics from study ADVL0612 have not been provided, however it has been found in the study report body submitted for a previous variation application.

Considering that tumour type is a covariate for lymphocyte count and platelet count, and the impact of the different tumour type on PK-PD relationship has not been evaluated, the reliability of efficacy and safety predictions through trials simulation is questioned, but this issue will not be pursued being efficacy and safety analysis out of the scope of the present variation.

The popPK (PMAR-EQDD-A618b-DP4-846) analysis has confirmed the importance of the BSA as covariate on CL/F and Vc/F for both sunitinib and its active metabolite, as observed also in previous studies, i.e. ACNS1021 and ADVL0612. MAH's conclusions include the following: *respective BSA-tiered doses of 12.5, 25, 37.5, and 50 mg QD on Schedule 4/2 for pediatric patients with BSA of ≤0.7, 0.8 to 1.2, 1.6 to 2.4, and ≥2.5 m2 are predicted to provide plasma exposures to sunitinib comparable with those observed in adult patients with GIST treated with a dose of 50 mg/day on Schedule 4/2.* However the figure reporting the ratio of predicted AUC values related to the values in adult reference following multiple dosing of sunitinib 20 mg/m2 showed that, for paediatric patients with BSA values < 1.1 m^2 , the ratio is lower that 75%; therefore for this patient population the MAH's conclusion cannot be supported. Considering the above, a reference also to BSA values in the proposed text on SmPC has been added.

Regarding the PBPK model, except for the AUC0-8 values for study A6181196, the results of the external validation show that the predicted/observed ratios for all the other parameters for both sunitinib and its active metabolite are <1, indicating that all the predicted values are minor compared to the observed values. This lead to conclude that the model predicts with an (slightly) underestimation the exposure of sunitinib, SU012662, and total active moieties. Based on SimCYP, the revised projected dose, assuming an approximate 15% of SimCYP exposure, remains consistent with dose determined by the integrated population PK analysis (20 mg/m2). Moreover all the simulated exposure measures of sunitinib and SU012662 were done following 15mg/m2 daily oral administration of sunitinib, however the proposed dosage to be included in the SmPC is 20mg/m2 daily. As the observed pediatric data were at 15 mg/m2 daily dosage, the observed exposure parameters were dose corrected to 20 mg/m2 for comparison purpose and an additional simulation with 20 mg/m2 daily dosage and compared to the observed pediatric data. The ratios of the predicted versus observed dose-corrected exposure values following trial simulations with the dose of 20 mg/m2 were very closed to the ones obtained with the dose of 15 mg/m2.

Based on the information provided at the RSI, the difference between the initial population PK analysis (pooled data from adult and paediatric patients) and the integrated population PK analysis (only paediatric data) is the inclusion of Tumor type as covariate on CL/F. In the first analysis it resulted to be significant, in the second one not. The integrated population PK analysis was selected as final analysis to be used to calculate the dose in pediatric patients expected to provide exposures similar to that obtained in adult patients with GIST at 50 mg on Schedule 4/2.

However, data from the phase I study ADVL0612 identified the 15 mg/m2/day as the sunitinib MTD in paediatric subjects without previous exposure to anthracyclines or cardiac irradiation. As stated by the MAH in the RSI, the MTD projection in ADVL0612 study was done in heavily pretreated pediatric patients mainly with CNS tumors. In addition, the starting dose in both clinical trial A6181196 and ACNS1021 was 15 mg/m^2 (based on the MTD) with the option to escalate the dose based on toxicity. Further, the MAH noted that in the majority of the patients on the published case studies, the dose was higher than 20 mg/m^2. The information that children treated in clinical trials/in case series received starting or average daily doses of 20 mg/m^2 is not emerging from the SmPC, therefore it appears somewhat misleading to report that the MTD is 15 mg/m^2, and that 20 mg/m^2 is the dose in pediatric patients expected to provide exposures similar to that obtained in adult patients with GIST. As per CHMP request, the MAH modified the SmPC section 5.2 to describe the dosages of Sutent received by pediatric patients in the clinical experience, in order to clarify the apparent contradiction between MTD

and wording on 20 mg/m^2.

7. Clinical Efficacy aspects

7.1. Study A6181196

Study A6181196 was evaluated within EMA/H/C/000687/P46-053 procedure. A summary of key study results is presented below.

Methods – analysis of data submitted

Study A6181196 was a single-arm, open-label, multicenter, multinational, Phase 1/2 clinical trial evaluating the PK, safety, and preliminary anti-tumour efficacy of sunitinib in children diagnosed with advanced unresectable GIST.

Patient eligibility: Eligible patients were ≥6 and <21 years of age, with histological diagnosis of GIST with non-mutant KIT and demonstrated disease progression or intolerance to imatinib mesylate or could not obtain imatinib in their country.

Treatment: The starting dose of sunitinib was 15 mg/m^2 per day administrated orally on Schedule 4/2 (4 weeks on treatment followed by 2 weeks off treatment) for a maximum of 18 cycles, which was lower than the approved 50 mg/day on Schedule 4/2 dosing regimen in adults. The starting dose was based on the Phase 1 study ADVL0612 conducted in patients with solid tumor aged 2-21 years. Intrapatient dose escalation of sunitinib was allowed after completion of Cycle 1.

Objectives/endpoints: primary objective was to characterize PK profile of sunitinib and its active metabolite SU012662 in children and young adults with advanced unresectable GIST, primary endpoints were The primary study endpoints were the PK parameters [including AUC24 (total plasma exposure [AUC from 0 to 24 hrs]) and oral clearance (CL/F)]. Secondary objectives were whether doses greater than the established paediatric maximum tolerated dose (MTD) were tolerated, safety and antitumor activity, PK-PD relationships, in paediatric patients with GIST. Among the secondary endpoints, ORR, DOR, PFS and OS were collected.

No interim analysis was planned in this study.

Sample size: The sample size was reduced from the originally planned 15 patients to 6 patients because of the rarity of the disease and the difficulties in identifying pediatric patients suitable for participation in the study. The revised sample size was expected to still allow characterization of the PK profile, ie, analysis of the primary endpoint.

Results

Study A6181196 started on 12 June 2012 and was completed on 21 August 2017.

Patient disposition: A total of 6 patients aged 13 to 16 years were enrolled in the study and were included in the analysis of PK, safety, and efficacy (see table below).

Table: Patient Disposition - Study A6181196

Patients	Sunitinib (N=6)
Screening and Randomization	
Screened (n)	8 (-)
Assigned to Treatment (Enrolled), n (%)	6 (100)
Study Completion, n (%)	
Completed Study	5 (83.3)
Discontinued from Study	1 (16.7)
Treatment Phase Completion, n (%)	
Treated	6 (100)
Completed Treatment	1 (16.7)
Discontinued Treatment	5 (83.3)
due to an AE	1 (16.7)
due to Objective Disease Progression or Relapse	4 (66.7)
Analysis Sets, n (%)	
Intent-to-Treat [a]	6 (100)
As-treated [b]	6 (100)
PK set [c]	6 (100)

Sources: Study A6181196 CSR Tables 14.1.1.1, 14.1.1.3, 14.1.1.4.
Abbreviations: AE=adverse event; N=number of patients analyzed; n=number of patients with an assessment result; PK=pharmacokinetics.
[a] All enrolled patients; analysis set for efficacy assessment.
[b] All enrolled patients who received at least 1 dose of study treatment; analysis set for safety assessment.
[c] All treated patients with at least 1 PK observation; analysis set for PK assessment.

Baseline characteristics: see tables below

Table: Summary of Demographic Characteristics in the ITT Population - Study A6181196

Characteristic	Sunitinib (N=6)
Gender[a]	**n (%)**
Male	1 (16.7)
Female	5 (83.3)
Age, years	
Median	14.0
Mean (SD)	14.3 (1.4)
Range, minimum-maximum	13-16
Race	**n (%)**
White	5 (83.3)
Asian	1 (16.7)
Weight, kg	
Median	45.3
Mean (SD)	47.3 (9.9)
Range, minimum-maximum	39.2-66.8
Height, cm	
Median	155.4
Mean (SD)	155.6 (6.3)
Range, minimum-maximum	147.2-163.0

ECOG Performance Status	n (%)
0	6 (100)

Sources: Study A6181196 CSR Tables 14.1.2.1, 14.1.1.7.
Abbreviations: cm=centimeter; ECOG= Eastern Cooperative Oncology Group; kg=kilogram; N=number of patients enrolled; n=number of patients with an assessment result; SD=standard deviation.
[a] Percentages were calculated based on the number of patients enrolled.

Table: Other Baseline Characteristics in the ITT Population - Study A6181196

Characteristic	Sunitinib (N=6) n (%)
Measurable Disease Present [a]	
Yes	6 (100)
Adequate Baseline Assessment [b]	
Yes	6 (100)
Number of Involved Disease Sites [c]	
1	2 (33.3)
2	1 (16.7)
3	3 (50.0)
Involved Disease Sites [d]	
Liver	4 (66.7)
Lung	1 (16.7)
Peritoneum	3 (50.0)
Stomach	3 (50.0)
Other	2 (33.3)

Source: Study A6181196 CSR Table 14.1.1.8.
Abbreviations: N=number of patients analyzed; n=number of patients with an assessment result.
[a] At least 1 target lesion as assessed according to RECIST version 1.1.
[b] Patients with target lesions=patients with all target lesions that have measurement(s) within the baseline window and are measurable.
[c] Each disease site is counted as a separate disease site.
[d] Involved sites include both target and non-target sites. Sites with multiple lesions are counted once.

In all 6 patients, there were no detectable alterations in *KIT* and *PDGFRA*. In the 2 patients for whom data were available, there were no detectable alterations in *BRAF.* The expression of *SDH* by immunohistochemistry was normal in 4 patients, not detectable in 1 patient, and not tested in 1 patient.

Efficacy results: see table below

Table: Best Overall Response and Progression-Free Survival in the Intent-to-Treat Population - Study A6181196

Response	Sunitinib (N=6)
Best Overall Response	**n (%)**
Complete response	0
Partial response	0
Stable/No response	3 (50.0)
Objective progression	3 (50.0)
Symptomatic deterioration	0
Early death	0
Indeterminate	0
Progression-Free Survival Event Status	**n (%)**
Objective progression	4 (66.7)
Censored	2 (33.3)

Off treatment prior to progression	1 (16.7)
In follow-up for progression	1 (16.7)
Time to Progression, Months	
Kaplan-Meier estimates of time to event (median)	5.8 (95% CI: 2.3, NR)

Sources: Study A6181196 CSR Tables 14.2.1, 14.2.2.
Abbreviations: CI=confidence interval; CT=computerized tomography; N=number of patients analyzed; n=number of patients with an event; NR=not reached; PET=positron emission tomography.
For patient #10521002 best response was determined based on the CT PET scans at baseline.
ORR: CR or PR according to RECIST 1.1
PFS: time from the date of the first dose of study drug to the date of the first documentation of objective tumour progression or death due to any cause, whichever occurred firs

Since none of the study patients experienced CR or PR, an analysis of the DOR was not performed. There were no deaths in the study population. Consequently, all patients were censored, and OS was not summarized using the Kaplan-Meier method. The time from the first study dose to the last available survival follow-up time ranged from 0.9 years to 2.4 years for the 6 patients.

7.2. Case series Reports

Retrospective analyses of medical records from paediatric and young adult patients with GIST treated with sunitinib from 3 case-series publications have been identified and presented by the MAH (Agaram et al. 2008[1], Janeway et al. 2009[2], Rutkowski et al. 2017[3]), for a total of 20 paediatric patients.

Methods – analysis of data submitted, and Results

Agram et al (2008)

This publication concerns a clinic-biological study of 17 patients with a diagnosis of GIST who were 18 years of age or younger that were identified from the Memorial Sloan-Kettering Cancer Center database.

Among them, **4 patients received sunitinib treatment**, after failure of or intolerance to imatinib. Patient's age was 10-18 years.

Patients were assessed by CT/PET according to local standard practice, and the overall tumour assessment evaluations were reported.

The major purpose of the study was to compare the tumour samples with adult patients' samples regarding KIT or PDGFRα mutations and pathway activation, as well as in vitro sensitivity to TKIs.

Neither precise data on tumour assessment at baseline, nor precise scheme of dosing were available for all patients (Schedule 4/2 or continuous daily dosing schedule).

PR, SD and PD was achieved by one patient each. No data on tumor response is available for one patient who developed sunitinib intolerance after one month and could not resume therapy (see table below).

[1] Agaram NP, Laquaglia MP, Ustun B, et al. Molecular characterization of pediatric gastrointestinal stromal tumors. Clin Cancer Res 2008;14(10):3208–15.

[2] Janeway KA, Albritton KH, Van Den Abbeele AD, et al. Sunitinib treatment in pediatric patients with advanced GIST following failure of imatinib. Pediatr Blood Cancer 2009;52:767–71.

[3] Rutkowski, et al. Treatment of gastrointestinal stromal tumours in paediatric and young adult patients with sunitinib: a multicentre case series. BMC Cancer 2017;17:717.

Table: Agaram et al: Key Data

Age	Gender	Genotype KIT/ PDGFRα	Response to Sunitinib	SU TX Duration (mo)	Sunitinib Dose (mg/day) min/max	Survival Follow-up (mo)a	Subsequent Therapies
10	F	WT/WT	SD	8	25	69/AWD	NA
16	F	WT/WT	Intolerant^	1	37.5	60/AWD	NA
14	F	WT/WT	PD	5	25	36/AWD	NA
18	F	WT/WT	PRb	8	37.5/50	48/AWD	Nilotinib (9 mo)

^ The patient intolerant to sunitinib was also intolerant to imatinib.
AWD=alive with disease; F=female; KIT=stem cell factor receptor; mo = months; NA=not available; PD=progressive disease; PDGFRα=platelet-derived growth factor receptor alpha; PR=partial response; SD=stable disease; SU=sunitinib; WT=wild type.
a. Follow-up is calculated from the time of the diagnosis.
b. The PR reflected complete resolution of liver metastases and decreased size (1 cm or more) of all abdominal masses, dose was 50 mg/d. SD after the initial dose of 37.5 mg. Therapy was continued for 5 cycles (8 months) after which the patient developed PD.

Janeway et al (2009)

This publication describes **7 paediatric patients**, 6 of which with confirmed metastatic or relapsed GIST that were treated with sunitinib within the Expanded Access Program (Pfizer A6181036 protocol) after previous failure to imatinib. Patient's age was 10-17 years.

Six out of seven patients had available disease measure by CT at the time of enrolment. Response to prior imatinib therapy was SD in 3 patients and PD in 3 patients. All patients had been off prior therapy for over 2 weeks when sunitinib was started.

For the 6 patients with evaluable data on dose, the mean starting dose was 24.6 mg/m^2 (range 17.7-34.2). In 3 out of 6 patients the dose was increased (range 29.9-40.4 mg/m^2). In 2 patients where dose was increased to 40.4 and 30.9 mg/m^2 respectively, the dose had to be decreased ultimately because of AE. The mean cumulative daily dose (the mean daily dose over all cycles) on this 4/2 schedule was 26.8 mg/m^2/d (range 17-6-34.1 mg/m^2).

One patient had a PR (resolution of lung metastasis), 5 patients SD, and 1 patient showed PD on sunitinib therapy (see table below). The duration of PR or SD was 7 - >21 months, with an average of 15 months. In 5 out of 6 patients with SD/PR, sunitinib resulted in a longer TTP than was achieved during imatinib treatment, difference in TTP ranging from 2 to 17 months. Two patients with SD showed a significant reduction in tumour metabolic activity on FDG-PET imaging.

Table: Janeway et al: Key Data

Age	Gender	Genotype KIT/ PDGFRα	Response to Sunitinib	SU TX Duration (mo)	Sunitinib Dose (mg/day) min/max	Mean Daily Sunitinib Dose mg/m^2	Survival Follow-up (mo)a	Subsequent Therapies
17	F	WT/WT	SD	7	37.5/50*	27.8*	31*	imatinib (5 days) nilotinib (18 mo)
10	F	WT/WT	PRb	>21	25/37.5*	22.2*	33*	sunitinib (13 mo)
16	F	WT/WT	SD	8	25/25*	17.6*	19*	nilotinib (8 mo)

Age	Gender	Genotype KIT/ PDGFRα	Response to Sunitinib	SU TX Duration (mo)	Sunitinib Dose (mg/day) min/max	Mean Daily Sunitinib Dose mg/m^2	Survival Follow-up (mo)a	Subsequent Therapies
16	M	WT/WT	SD	18	50/50*	34.1*	34*	nilotinib (14 mo)
16	F	WT/WT	SD	>18	50/50*	31.8*	NA*	NA
16	M	NA	PD	<1^	37.5/37.5*		NA*	NA
14	F	NA	SD	18	25/50*	27.4*	31*	nilotinib (17 mo)

* Not reported in Janeway publication (data extracted from A6181036 database).
^ The patient intolerant to sunitinib was also intolerant to imatinib.
F=female; KIT=stem cell factor receptor; M=male; mo=months; NA=not available; PD=progressive disease; PDGFRα=platelet-derived growth factor receptor alpha; PR=partial response; SD=stable disease; SU=sunitinib; WT=wild type.
a. Follow-up is calculated from the time of the diagnosis.
b. The PR reflected complete resolution of metastatic disease in the lung.

Rutkowski et al (2017)

This publication describes **9 paediatric/young adult patients**, aged 11-21 years, with GIST and treated with sunitinib. Those patients were identified from clinical records from 2 centers in Europe and 1 center in the US.

There were no mutations in neither KIT nor PDGFRα for any patient.

Before being treated with sunitinib, 8 patients were treated with surgery and 8 patients did receive imatinib. On imatinib, all but one patient had SD as the best response, and 8 out of 9 patients had documented PD.

Sunitinib dosing regimens varied with 5 patients treated with Schedule 4/2 using a standard approved dosage of 50 mg/day while other patients received 37.5 mg/day in an alternative continuous regimen. Four patients started with Schedule 4/2 and moved to continuous dosing, mostly because of AEs. The mean treatment duration was 23 months (range 1->73). Two patients were still on therapy as per data cut-off of 20 February 2016 (>42 and > 73 months).

The objective response of GIST to sunitinib therapy was evaluated with serial CT scans (performed every 2-3 months) according to RECIST. In accordance with the PDCO request, the raw data on tumour measurements for 4 of the patients included in this publication have been retrospectively collected.

A best response of SD was observed in 7 of the 9 patients on sunitinib treatment (see table below). All but 1 patient eventually had PD. Among the 8 patients who progressed, PFS and TTP duration ranged from 1 to 28 months, while 1 patient remained progression free after 73 months (as per date of data cut-off). Overall, median PFS was 15 months.

FU in this publication ranged from 25 months to 260 months. At the time of data cut off, 8 patients remained alive with disease (AWD), with 2 being still treated with sunitinib, 4 are being treated with other targeted agents, and 2 patients have stopped treatment. One patient died of disease during the course of therapy.

Table: Rutkowski: Key Data

Age at Diagnosis	Gender	Best Response to Sunitinib a	SU TTP and (Tx Duration) (months)	Sunitinib Dose (mg/day) min/max	Sunitinib Dose min/max mg/m^2	Sunitinib Starting Dose mg/m^2	Survival Follow-up (mo)b	Subsequent Therapies
15	F	SD*	(>73)	37.5/50	24.7/ 32.9	32.9	163/AWD	On sunitinib since 2008
13	F	SD	6 (6)	37.5/50	27.0/36.0	27.0	159/AWD	On regorafenib
11	F	SD**	6 (23)	25/37.5	19.5/29.3	19.5	88/AWD	On imatinib/doxorubicin
17	F	SD	23 (24)	37.5/50	27.0/36.0	36	260/AWD	nilotinib, then imatinib + doxorubicin , then imatinib
14	F	PD	5 (5)	25	16.6	16.6	139/AWD	nilotinib (PD)- no treatment since 2011
17	M	PD	1 (1)	50	33.3	33.3	25/DOD	trametinib, regorafenib,phase I CT , pazopanib
18	M	SD	17 (17)	12.5/37.5	7.6/22.7	22.7	76/AWD	No treatment SD under observation from 2012
15	F	SD	5 (17)	12.5/50	7.8/31.3	31.3	173/AWD	On imatinib
21	M	SD	28 (>42)***	37.5/50	22.3/29.8	29.8	86/AWD	On sunitinib

*Duration of treatment until data cut-off; patient still on sunitinib.
** After PD at 6 months of 25 mg, dose was increased to 37.5 mg leading to SD with a treatment duration of 23 months.
*** This patient showed PD on a liver lesion that was treated with radiofrequency ablation (RFA). Sunitinib was continued for > 42 months as of data cut-off.
AWD=alive with disease; F=female; KIT=stem cell factor receptor; M=male; mo=months; NA=not available; PD=progressive disease; PDGFRα=platelet-derived growth factor receptor alpha; PR=partial response; SD=stable disease; SU=sunitinib; TTP=time to tumour progression; WT=wild type.
a. Eight out of 9 patients ultimately had PD while 2 patients continued on sunitinib for > 73 and > 42 months.
b. Follow-up is calculated from the time of the diagnosis.

7.3. Discussion – Clinical Efficacy

Gastrointestinal stromal tumours (GIST) are rare mesenchymal tumours that arise in the gastrointestinal tract (stomach in 60% of the cases), more often occurring in the adult ageing population. Paediatric patients with GIST represent an even rarer sub population (1%-2% of all GIST cases), presenting a different clinical behavior and biology than typical adult GIST. Paediatric GIST patients tend to be predominantly female, with a median age at diagnosis in most series of 14 years. Mutations in KIT or PDGFRá are uncommon, negative immunohistochemistry for any of the SDH-proteins are common (SDH-B mostly). Despite multiple recurrences and lack of dramatic responses to TKI therapy, most paediatric patients survive with active disease for many years, suggesting a more indolent clinical course than observed with adult GIST. Pediatric patients with metastatic WT GIST can survive as long as 15 years from the development of metastatic disease (Mullassery et al 2016[4],

[4] Mullassery D, Weldon CB. Pediatric/"Wildtype" gastrointestinal stromal tumors. Semin Pediatr Surg. 2016 Oct;25(5):305-310.

Janeway et al 2012[5]).

There is currently no consensus in the paediatric oncology expert community on which compound to use in metastatic disease or recurrent tumours: systemic treatment with TKI is recommended. The choice of which compound to use is under debate and depends on the presence of mutations and clinical factors.

In adult patients with GIST, Sutent is currently indicated for the treatment of unresectable and/or metastatic malignant disease after failure of imatinib treatment due to resistance or intolerance.

The MAH has presented the results of the clinical study A6181196 of sunitinib in pediatric GIST patients. In addition, data coming from three case series have been provided.

Study A6181196

Study A6181196 was a single-arm, multi-center, multi-national, Phase 1/2 clinical trial evaluating the PK, safety, and preliminary anti-tumour efficacy of sunitinib in children and young adults diagnosed with advanced unresectable GIST. The primary objective of the study was characterization of PK profile.

A total of 8 patients were screened, of which **6 patients aged 6-16 years** (median 14.0 years) were enrolled in the study and were included in the analysis of PK, safety, and efficacy. Patients demonstrated disease progression or intolerance to imatinib mesylate or could not obtain imatinib in their country. All patients had no detectable alterations in *KIT* and *PDGFRa*.

The starting dose of sunitinib was 15 mg/m2 per day administered orally per Schedule 4/2, based on previously identified MTD in children (in phase I study ADVL0612), for up to 18 cycles (24 months). Intra-patient dose escalation was allowed after completion of Cycle 1, not to exceed 50 mg/day. The dose was increased to 22.5 mg/m2 per day in 5 of the 6 patients, and a further increase to 30 mg/m2 per day in 2 patients. Dose reduction due to an AE is reported in one patient (see safety).
Patients were to be followed for OS until either 2 years from the first dose of the study drug or completion of 18 cycles of study treatment.
In study A6181196, there were no confirmed objective responses. SD was reported in 3 (50%) patients, and objective disease progression was observed in 3 patients (50%). Since none of the patients experienced a CR or PR, an analysis of DOR was not performed.

PFS events were reported in 4 (66.7%) patients, for an estimated median PFS of 5.8 months (95% CI: 2.3, NR).

No deaths were reported after a follow-up survival period ranging from 0.9 to 2.4 years, therefore all patients were censored, and OS was not summarized using the Kaplan-Meier method.

Case series reports

The efficacy results from the 6 paediatric patients with GIST treated with sunitinib in Study A6181196 were supported by published efficacy results from **20 sunitinib-treated paediatric or young adult patients** with GIST retrieved in literature. Nearly all of whom were previously treated with imatinib.

In the publication by *Agram et al (2008)*, 4 patients aged 10-18 years with wild type KIT and PDGFRá GIST received sunitinib treatment after failure of or intolerance to imatinib. Overall tumour assessment evaluations according to local standard practice were reported, although neither precise data on tumour assessment at baseline, nor precise scheme of dosing were available for all patients. PR, SD and PD was achieved by one patient each. No data on tumor response is available for one patient who developed sunitinib intolerance after one month and could not resume therapy.

[5] Janeway KA, Weldon CB. Pediatric gastrointestinal stromal tumor. Semin Pediatr Surg. 2012 Feb;21(1):31-43.

In the publication by *Janeway et al (2009)*, 7 paediatric patients aged 10-17 years (6 of which with confirmed metastatic or relapsed GIST that were treated with sunitinib within the Expanded Access Program after previous failure to imatinib), are described. Five of them had wild type KIT and PDGFRα GIST, while data is not available for the other two patients. For the 6 patients with evaluable data on dose, the mean starting dose was 24.6 mg/m^2 (range 17.7-34.2). In 3 out of 6 patients the dose was increased (range 29.9-40.4 mg/m^2), and in 2 of them the dose had to be decreased ultimately because of AE. One patient had a PR (resolution of lung metastasis) and 5 patients SD, and 1 patient showed PD for a duration of PR/SD of 7 - >21 months (average 15 months). In 5 out of 6 patients with SD/PR, sunitinib resulted in a longer TTP than was achieved during imatinib treatment. One patient experienced PD as best overall response.

In the publication by *Rutkowski et al (2017)*, 9 paediatric/young adult patients, aged 11-21 years, with wild type KIT and PDGFRá GIST, are described. Eight patients did receive imatinib before sunitinib. Five patients were treated with sunitinib 50 mg/day on schedule 4/2, while other patients received 37.5 mg/day in an alternative continuous regimen. Four patients started with Schedule 4/2 and moved to continuous dosing, mostly because of AEs. Seven patients experienced SD and 2 patients had PD as best response. One patient died of disease during the course of therapy. All but one patients having SD, eventually experienced PD. PFS and TTP duration ranged from 1 to 28 months, while 1 patient remained progression free after 73 months (as per date of data cut-off). Overall, median PFS is 15 months. At the time of the data cut-off, two patients were still receiving sunitinib.

The starting dose of sunitinib in the two case series that include data on dosage (i.e. Janeway and Rutkowski) appered higher compared to the RP2D of 15 mg/m^2 identified in the ADVL0612 Phase 1 study.

Of note, the 2 partial responses reported in literature (one in *Agram et al,* described as resolution of liver metastases, and one in *Janeway et al,* reported as resolution of lung metastases) were considered by the MAH as SDs, in the absence of raw data and/or confirmation by RECIST. Therefore, taking together, evidence from Study A6181196 and the 3 case-series indicated that sunitinib treatment resulted in disease stabilization in 18 of 26 (69.2%) paediatric or young adult patients with GIST, either after imatinib failure or intolerance (16 out of 21, 76%), or de novo/after surgery (2 out of 5, 40%).

Due to the lack of objective confirmed radiological responses, the limited number of patients in the clinical trial, the intrinsic limitation of retrospective case series, along with the very indolent nature of GIST in paediatric patients, it is considered that the available evidence are not conclusively supporting the clinical activity of sunitinib in children with GIST.

8. Clinical Safety aspects

The MAH presented safety data for sunitinib in children with refractory solid tumours, supported by the 3 clinical studies performed in paediatric patients (see table below). No combined or integrated analyses of safety across studies were planned or performed due to different disease type, different treated populations and the different dosing regimens studied. Overall, safety data from 70 paediatric patients have been reported in the submitted dossier.

Table: Summary of Clinical Studies of Sunitinib in Paediatric Patients

Study Number (Status)	Study Title/Population	Study Drug Doses	Number of Patients Enrolled [N]/ Safety Population (n)
A6181196 (Completed)	A Phase I/II Study Of Sunitinib In Young Patients With Advanced Gastrointestinal Stromal Tumour Paediatric patients: ages 6 years to <18 years of age Young adults: ages 18 years to <21 years of age	Starting dose of sunitinib 15 mg/m^2/QD for 4 weeks followed by 2 weeks with no study drug. Patients could receive up to 18 cycles of sunitinib therapy for up to 24 months.	Total patients: 6 Safety population: 6
ADVL0612 (W828159327) (Completed)	A Phase I Study of Sunitinib (SU11248), an Oral Multi-Targeted Tyrosine Kinase Inhibitor, in Children With Refractory Solid Tumours Paediatric patients: ≥2 years and ≤21 years of age	The aim of the study was to determine the maximum tolerated dose (MTD) of sunitinib when given on the recommended adult schedule of QD for 28 days followed by 14 days with no study drug. The study included 3 parts: Part A (inter-patient dose escalation): The starting dose was 20 mg/m^2/QD with dose levels for subsequent groups of patients as follows: 20, 30, or 40 mg/m^2/QD. If the MTD had been exceeded at the first dose level, then the subsequent cohort of patients were treated at a dose of 15 mg/m^2/QD. Part B (inter-patient dose escalation): The starting dose was 15 mg/m^2/QD with dose levels for subsequent groups of patients as follows: 15, 20, or 30 mg/m^2/QD. Subjects in Part B of the study had not received prior anthracycline treatment or cardiac radiation exposure (after observing cardiac related dose limiting toxicity (DLTs) in Part A of the study). Part C: All patients treated in Part C received the recommended dose determined in Part B. Patients in Part C took each sunitinib dose using the powder contained within sunitinib capsules sprinkled onto 5 mL of applesauce or yogurt per capsule.	Total patients: 35 Safety Population: 35
ACNS1021 (WS281593-48) (Completed)[a]	A Phase II Study of Sunitinib (NSC# 736511, IND# 74019) in Recurrent, Refractory or Progressive High Grade Glioma and Ependymoma Tumours in Paediatric and Young Adult Patients Paediatric patients: 18 months to 17 years of age Young adults: 18 to	Sunitinib 15 mg/m^2 /QD for 28 days followed by a 14 day rest period as capsules in 6-week cycles. Sunitinib was to be taken at approximately the same time each day for a maximum of 18 cycles (approximately 2 years) in the absence of disease progression or unacceptable toxicity.	Total patients: 30 Safety Population: 29

Study Number (Status)	Study Title/Population	Study Drug Doses	Number of Patients Enrolled [N]/ Safety Population (n)
	22 years of age.		

Source: CSRs – Study A6181196, Study ADVL0612, and Study ACNS1021
Abbreviations: DLT=dose limiting toxicity; MTD=maximum tolerated dose; N=total number of patients enrolled in the study; n=numbers of patients included in the safety analysis; PK=pharmacokinetic; IV=intravenous/intravenously; QD=once daily.

8.1. Methods – analysis of data submitted

Patients who received at least 1 dose of study treatment in **Study A6181196**, **Study ADVL0612**, and **Study ACNS1021** were included in the evaluation of safety. In all the 3 studies, safety endpoints included adverse events (AEs), serious adverse events (SAEs), deaths, laboratory evaluations, vital signs, concomitant medication use, and electrocardiogram (ECG) and echocardiogram results.

In Study ACNS1021, Grade 3 or higher AEs, SAEs, and deaths were actively collected during the study. Although not required by the protocol, Grade <3 AEs may also have been reported. All reported AEs (any grade) were included in the AE summaries.

All AEs (serious and non-serious) that occurred on or after the first day of study treatment and up to 28 days after the last sunitinib dose for Studies A6181196 and ADVL0612 and up to 30 days for Study ACNS1021 were considered as treatment-emergent AEs (TEAEs).

All AEs were coded by system organ class (SOC) and preferred term (PT) using Medical Dictionary for Regulatory Activities (MedDRA) Version 20.0 in Studies A6181196 and ACNS1021, and Version 15.1 in Study ADVL0612. Intensity (severity) of the AEs was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 in all 3 studies. Haematology and blood chemistry data were graded according to NCI CTCAE version 4.0 severity grade, if applicable.

In Study ADVL0612, in addition to the AEs, dose-limiting toxicity (DLT), and the maximum tolerated dose (MTD) were also evaluated as described below:

1) Dose-Limiting Toxicity (DLT)

DLT is defined as any of the following events that are possibly, probably or definitely attributed to sunitinib:

- Non-Hematological Dose-Limiting Toxicity:

1. Any Grade 4 non-hematological toxicity.
2. Any Grade 3 non-hematological toxicity with the specific exception of:
   - Grade 3 nausea and vomiting of <3 days duration despite appropriate anti-emetic administration.
   - Grade 3 ALT or AST that resolved to ≤Grade 2 within 7 days of study drug interruption and that did not recur upon re-challenge with study drug. Note: For the purposes of this study the ULN for ALT was defined as 45 U/L.
   - Grade 3 bilirubin that resolved to Grade ≤2 within 7 days of study drug interruption and that did not recur upon re-challenge with study drug.
   - Grade 3 fever or infection of <5 days duration.

- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia, or hypomagnesemia responsive to oral supplementation.
- Asymptomatic Grade 3 elevations in amylase or lipase that resolved to Grade <1 within 7 days of study drug interruption and that did not recur upon re challenge with study drug.

3. Left ventricular ejection fraction <50-40%, shortening fraction <24-15%, or an absolute decrease in shortening fraction of 8% points from baseline.
4. Grade 2 allergic reactions that necessitated discontinuation of study drug was not considered a DLT.
5. A BP >25 mmHg above the 95% for age, height, and gender confirmed by repeated measurement was dose-limiting.
6. In patients on antihypertensive therapy, a persistently elevated BP, but ≤25 mmHg above the 95% for age, height, and gender for >14 days was dose-limiting.
7. Any Grade 2 non-hematological toxicity that persisted for ≥7 days and was considered sufficiently medically significant or sufficiently intolerable by patients that it required treatment interruption.
8. Any AE that required interruption of study drug for >7 days or which recurred upon drug re-challenge.

- Hematological Dose Limiting Toxicity:

Grade 4 thrombocytopenia (platelet count <25,000/mm3) or Grade 4 neutropenia.

2) Maximum Tolerated Dose (MTD)

The MTD was the maximum dose at which fewer than 1/3 of patients experienced a DLT during Cycle 1 of therapy. In the event that 2 DLTs were observed out of 6 evaluable patients, but were of different classes of adverse effects (e.g., hepatotoxicity and myelosuppression), expansion of the cohort to 12 patients was considered if all of the following conditions were met:

- One of the DLTs did not appear to be related to dose (i.e., for at least 1 DLT, the same adverse effect, attributed to study drug, was not previously experienced at a lower dose level 1 increment below [in CTCAE grade or duration] the DLT definition).
- The adverse effect was readily reversible.
- The study chair, statistician, committee chair or vice chair, Cancer Therapy Evaluation Program (CTEP), and Investigational New Drug sponsor all agreed that expansion of the cohort was acceptable.

If less than 1/3 of patients in the expanded cohort experienced dose-limiting toxicities, the dose escalation proceeded.

For Study ADVL0612, additional reporting requirement included Secondary Acute Myeloid Leukemia (AML)/ Myelodysplastic Syndrome (MDS).

8.2. Results

Exposure: A total of 70 paediatric and young adult patients received at least 1 dose of study medication in Studies A6181196 (6 patients), ADVL0612 (35 patients), and ACNS1021 (29 patients). Summary tables for each study are presented below:

Table: Dose Administration of Sunitinib - Study ADVL0612, Safety Population

	Sunitinib							
	Part A			Part B			Total	Part C
	15 mg/m^2	20 mg/m^2	Total	15 mg/m^2	20 mg/m^2	Total	Part A+Part B	15 mg/m^2
	N=6	N=6	N=12	N=8	N=3	N=11	N=23	N=12
Total number of cycles started	9	8	17	25	4	29	46	45
Median number of cycles started	1	1	1	1	1	1	1	1
Range	1-4	1-3	1-4	1-9	1-2	1-9	1-9	1-18
Number (%) of patients starting								
1 Cycle	5 (83.3)	5 (83.3)	10 (83.3)	5 (62.5)	2 (66.7)	7 (63.6)	17 (73.9)	8 (66.7)
2 Cycles	0	0	0	1 (12.5)	1 (33.3)	2 (18.2)	2 (8.7)	0
3 Cycles	0	1 (16.7)	1 (8.3)	0	0	0	1 (4.3)	2 (16.7)
4 Cycles	1 (16.7)	0	1 (8.3)	0	0	0	1 (4.3)	0
≥5 Cycles	0	0	0	2 (25.0)	0	2 (18.2)	2 (8.7)	2 (16.7)

Source: Study ADVL0612 Report Body Table 18.
N=Total number of patients in respective cohort.

Table: Extent of Exposure to Study Treatment – Study A6181196, Safety Population

Parameter	Sunitinib (N=6)
Duration of Treatment, days	
Median	219.0
Mean (SD)	292.2 (229.42)
Range	110 – 742
Treatment cycles administered	
Median cycles administered	5.5
Range of cycles administered	3.0 – 18.0
Patients per cycle, n (%)	
Cycles 1 to 3	6 (100.0%)
Cycle 4	5 (83.3%)
Cycle 5	4 (66.7%)
Cycle 6	3 (50.0)
Cycle 7	2 (33.3%)
Cycles 8 to 18	1 (16.7%)
Actual Cumulative Dose (mg)[a]	
Median	5046.88
Mean (SD)	4866.67 (2350.338)
Range	2237.5 - 8468.8
Relative dose intensity (%)[b]	
Median	98.85
Mean (SD)	97.62 (3.992)
Range	89.6 - 100.0
Average daily dose (mg)[c]	
Median	29.25
Mean (SD)	27.12 (7.192)
Range	16.8 - 35.4
Average daily dose (mg/m^2)[c]	
Median	18.75
Mean (SD)	19.07 (5.053)
Range	12.1 - 25.1

Sources: Study A6181196 Report Body Table 14.
Abbreviations: N=number of patients analyzed; n=number of patients with events; SD=standard deviation.

a. Actual Cumulative Dose is actual total dose taken in the cycle.
b. Relative Dose Intensity (%) is defined as Actual Dose Intensity (per week)/Intended Dose Intensity (per week)*100%, where Actual Dose Intensity (per week) is defined as Actual Total Dose in cycle/Actual number of weeks in cycle, and Intended Dose Intensity is based on the prescribed dose at the cycles.
c. Average daily dose calculated as administered, excluding the 2-week off period.

In study A6181196, the starting dose of sunitinib was 15 mg/m2 per day administered orally per Schedule 4/2 (MTD previously defined); intra-patient dose escalation of sunitinib was allowed after completion of Cycle 1. The dose was increased to 22.5 mg/m2 per day in 5 of the 6 patients, and a further increase to 30 mg/m2 per day in 2 patients. Dose reduction due to an AE is reported in one patient (see below).

Table Extent of Exposure to Study Treatment – Study ACNS1021, Safety Population

Parameter	Recurrent/Progressive/Refractory High-Grade Glioma	Recurrent/Progressive/ Refractory Ependymoma	Total
	Sunitinib		
	(N=16)	(N=13)	(N=29)
Duration of Treatment, days			
Mean (SD)	40.8 (22.85)	75.1 (43.61)	56.1 (37.37)
Range	(12.0-71.0)	(28.0-196)	(12.0-196)
Patients per cycle, n (%)			
Cycle 1	16 (100.0)	13 (100.0)	29 (100.0)
Cycle 2	7 (43.8)	10 (76.9)	17 (58.6)
Cycle 3	-	2 (15.4)	2 (6.9)
Cycle 4	-	1 (7.7)	1 (3.4)
Cycle 5	-	1 (7.7)	1 (3.4)
Actual Cumulative Dose (mg)			
Median	678.1	1050.0	700.0
Mean (SD)	763.7 (446.2)	1170.2 (783.9)	945.9 (642.2)
Range	(143.8-1750.0)	(175.0-2937.5)	(143.8-2937.5)
Relative dose intensity (%)			
Median	106.8	100.0	100.0
Mean (SD)	114.0 (28.6)	98.0 (4.0)	106.8 (22.6)
Range	(41.1-150.0)	(86.6-100.0)	(41.1-150.0)
Average daily dose (mg)			
Median	18.8	13.6	18.2
Mean (SD)	20.0 (7.8)	15.4 (6.0)	17.9 (7.3)
Range	(5.1-31.3)	(6.3-25.0)	(5.1-31.3)

Source: Study ACNS1021 Report Table 14.4.1.2.1; Table 14.4.1.3; Table 14.3.4.2.1.
Actual Cumulative Dose is actual total dose taken in the cycle.
Actual Dose Intensity is actual total dose taken in cycle divided by actual number of days in the cycle including delays.
Relative Dose Intensity is % of Actual to Intended Dose Intensities.
Average Daily Dose (excluding 2 week off) is actual total dose taken in cycle divided by actual number of days in the cycle excluding 2 week off.
Abbreviations: N=number of patients in each group; n=number of patient(s) with observation; SD=standard deviation;

Adverse events: summary of all causality TEAE in all the studies analysed are presented in tables below:

Table Treatment-Emergent Adverse Events (All Causalities) – Study A6181196, Safety Population

Treatment-emergent adverse events	Sunitinib, (N=6)
Number of TEAEs	**82**
Patients with:	**n (%)**
TEAE	6 (100)
SAE	0
TEAE of severity Grade 3 or 4	5 (83.3)
TEAE of severity Grade 5	0
Dose reduction due to an AE	1 (16.7)
Temporary discontinuation due to an AE	4 (66.7)
Permanent discontinuation due to an AE	1 (16.7)

Source: Study A6181196 Report Body Table 16.
All AEs were considered as treatment-emergent AEs, unless present at baseline with the same severity grade.
Includes data up to 28 days after last dose of study drug.
Patients are counted only once per treatment in each row.
SAEs - according to the Investigator's assessment.
Severity counts are based on the maximum severity or grade of events.
Abbreviations: AE=adverse event, N=number of patients analyzed; n=number of patients with an event; SAE=serious adverse event, TEAE=treatment-emergent adverse event.

Table Treatment-Emergent Adverse Events (All Causalities) – Study ADVL0612, Safety Population,

Number (%) of Subjects	Sunitinib		
	Part A[a]	Part B[a]	Part C[b]
Subjects evaluable for AEs	12	11	12
Number of AEs	197	129	244
Subjects with AEs	12 (100.0)	11 (100.0)	12 (100.0)
Subjects with Grade 3 or 4 AEs	10 (83.3)	7 (63.6)	11 (91.7)
Subjects with SAEs	6 (50.0)	6 (54.4)	6 (50.0)
Subjects with Grade 5 AEs	0	1 (9.1)	4 (33.3)
Discontinuations			
Insufficient clinical response[d]	7 (58.3)	6 (54.5)	8 (66.7)
Withdrew consent[d]	0	2 (18.2)	2 (16.7)
Due to AE[e]	5 (41.7)	1 (9.1)	1 (8.3)

Source: Study ADVL0612 Report Body Table 5, Table 19 and Table 24.
Includes data up to 9999 days after last dose of study drug.
Except for the number of AEs patients were counted only once per treatment in each row.
MedDRA (v15.1) coding dictionary applied.
AEs=Adverse events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in respective group; n=number of patient(s) with observation.
a. 15 mg/m^2: 6 patients; 20 mg/m^2: 6 patients
b. 15 mg/m^2: 8 patients; 20 mg/m^2: 3 patients
c. 15 mg/m^2: 12 patients
d. Relation to Study Drug not Defined
e. Treatment-related AE

Table 21. Treatment-Emergent Adverse Events (All-Causality and Treatment-Related) - Safety Population

	Recurrent/Progressive/ Refractory High-Grade Glioma (N=16)		Recurrent/Progressive/ Refractory Ependymoma (N=13)		Total (N=29)	
	All-Causality	Treatment-Related	All-Causality	Treatment-Related	All-Causality	Treatment-Related
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Patients evaluable for AEs	16	16	13	13	29	29
Number of AEs	31	16	20	13	51	29
Patients with AEs	13 (81.3)	7 (43.8)	9 (69.2)	7 (53.8)	22 (75.9)	14 (48.3)
Patients with SAEs	10 (62.5)	3 (18.8)	3 (23.1)	1 (7.7)	13 (44.8)	4 (13.8)
Patients with Grade 3 or Grade 4 AEs	11 (68.8)	5 (31.3)	7 (53.8)	5 (38.5)	18 (62.1)	10 (34.5)
Patients with Grade 5 AEs	5 (31.3)	0	0	0	5 (17.2)	0

Source: Table 14.3.1.2.1 and Table 14.3.1.3.1
Includes data up to 30 days after last dose of study drug.
Except for the number of AEs patients were counted only once per treatment in each row.
SAEs - according to the investigator's assessment.
Severity counts were based on the maximum severity or grade of events.
MedDRA (Version 20.0) coding dictionary applied.
Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in respective group; n=number of patient(s) with observation; SAE=serious adverse event.

Summary tables of **TEAE** for each study are presented below:

Table Decreasing Frequency of TEAEs in ≥2 Patients by MedDRA Preferred Term and Maximum CTCAE Grade (All Causalities) – Study A6181196, Safety Population

Adverse Events by Preferred Term	Sunitinib, (N=6)				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
			n (%)		
Any AEs	0 (0.0)	1 (16.7)	3 (50.0)	2 (33.3)	6 (100.0)
Headache	3 (50.0)	1 (16.7)	0 (0.0)	0 (0.0)	4 (66.7)
Diarrhoea	2 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)	3 (50.0)
Nausea	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)
Neutropenia	0 (0.0)	1 (16.7)	1 (16.7)	1 (16.7)	3 (50.0)
White blood cell count decreased	0 (0.0)	3 (50.0)	0 (0.0)	0 (0.0)	3 (50.0)
Anaemia	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	2 (33.3)
Back pain	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)
Decreased appetite	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	2 (33.3)
Dyspepsia	2 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (33.3)
Thrombocytopenia	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	2 (33.3)

Source: Study A6181196 Report Table 14.3.1.2.11.1.
Includes data up to 28 days after last dose of study drug.
All AEs were considered as treatment-emergent AEs, unless present at baseline with the same severity grade.
CTCAE version 4.0 was used. Maximum CTCAE grade is defined as the maximum CTCAE grade value for the specific Preferred Term. MedDRA (version 20.0) coding dictionary applied.
Abbreviations: AE=adverse event, CTCAE=Common Terminology Criteria for Adverse Events, MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients analyzed; n=number of patients with an event; SAE=serious adverse event.

In study A6181196, the majority of the reported AEs were Grade 1 or 2 in severity. Three patients had 1 Grade 3 AE each, and 2 patients had 1 Grade 4 AE each. There were no reports of Grade 5 TEAEs. Overall, Headache (Grades 1 or 2) was reported in 4 (66.7%) patients and Diarrhoea (Grades 1 or 2), Nausea (Grade 1), Neutropenia (Grades 2 to 4), or white blood cell (WBC) count decreased (Grade 2) were reported in 3 patients each, respectively. Hepatic hematoma and Intra-abdominal hemorrhage TEAEs (Grade 4) were reported in 1 patient. Both of these events were determined by the Investigator to be related to disease progression. This conclusion was supported by laparotomy showing multiple lesions localized at stomach wall, liver, lymph node at falx hepatis, and massive peritoneal dissemination, with hemorrhagic ascites. The other Grade 4 TEAE was Neutropenia that was reported in 1 patient and led to dose reduction. Grade 3 TEAEs reported were Hypoglycaemia, Hypophosphataemia, Neutropenia, and Thrombocytopenia.

Table Treatment-Emergent Adverse Events (Treatment-Related) – Study ADVL0612, Safety Population,

Number (%) of Subjects	Sunitinib		
	Part A[a]	Part B[a]	Part C[b]
Patients evaluable for AEs	12	11	12
Number of AEs	115	76	125
Patients with AEs	12 (100.0)	11 (100.0)	12 (100.0)
Patients with Grade 3 or 4 AEs	10 (83.3)	5 (45.5)	6 (50.0)
Patients with Grade 5 AEs	0	1 (9.1)	0

Source: Study ADVL0612 Report 14.3.1.3.1a, 14.3.1.3.1b and 14.3.1.3.1c.
Except for the number of AEs patients were counted only once per treatment in each row.
MedDRA (v15.1) coding dictionary applied.
AEs=Adverse events; MedDRA=Medical Dictionary for Regulatory Activities.
a. 15 mg/m^2: 6 patients; 20 mg/m^2: 6 patients
b. 15 mg/m^2: 8 patients; 20 mg/m^2: 3 patients
c. 15 mg/m^2: 12 patients

Table Treatment-Emergent Adverse Events Reported by >2 Patients by MedDRA Preferred Term and Maximum CTCAE Grade (All Causalities, All Cycles) by Dose Groups and Total – Study ADVL0612, Safety Population (extract)

MedDRA Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Total
	n (%)				
Part A - Sunitinib 15 mg/m^2, N=6					
Any AEs	0 (0.0)	1 (16.7)	4 (66.7)	1 (16.7)	6 (100.0)
Platelet count decreased	4 (66.7)	1 (16.7)	0 (0.0)	0 (0.0)	5 (83.3)
Hypercalcaemia	3 (50.0)	1 (16.7)	0 (0.0)	0 (0.0)	4 (66.7)
Lymphocyte count decreased	1 (16.7)	0 (0.0)	2 (33.3)	1 (16.7)	4 (66.7)
White blood cell count decreased	2 (33.3)	2 (33.3)	0 (0.0)	0 (0.0)	4 (66.7)
Alanine aminotransferase increased	2 (33.3)	0 (0.0)	1 (16.7)	0 (0.0)	3 (50.0)
Anaemia	2 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)	3 (50.0)
Aspartate aminotransferase increased	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)
Constipation	2 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)	3 (50.0)
Diarrhoea	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)
Fatigue	1 (16.7)	2 (33.3)	0 (0.0)	0 (0.0)	3 (50.0)
Hypoalbuminaemia	1 (16.7)	2 (33.3)	0 (0.0)	0 (0.0)	3 (50.0)
Nausea	2 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)	3 (50.0)
Neutrophil count decreased	0 (0.0)	1 (16.7)	2 (33.3)	0 (0.0)	3 (50.0)
Part A - Sunitinib 20 mg/m^2, N=6					
Any AEs	0 (0.0)	1 (16.7)	4 (66.7)	1 (16.7)	6 (100.0)
Aspartate aminotransferase increased	4 (66.7)	1 (16.7)	0 (0.0)	0 (0.0)	5 (83.3)
Neutrophil count decreased	1 (16.7)	0 (0.0)	3 (50.0)	1 (16.7)	5 (83.3)
White blood cell count decreased	2 (33.3)	0 (0.0)	3 (50.0)	0 (0.0)	5 (83.3)
Platelet count decreased	2 (33.3)	2 (33.3)	0 (0.0)	0 (0.0)	4 (66.7)
Alanine aminotransferase increased	2 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)	3 (50.0)
Vomiting	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)
Part B - Sunitinib 15 mg/m^2, N=8					
Any AEs	2 (25.0)	2 (25.0)	3 (37.5)	1 (12.5)	8 (100.0)
Hypophosphataemia	2 (25.0)	1 (12.5)	1 (12.5)	0 (0.0)	4 (50.0)
Neutrophil count decreased	2 (25.0)	0 (0.0)	1 (12.5)	1 (12.5)	4 (50.0)
Vomiting	1 (12.5)	2 (25.0)	1 (12.5)	0 (0.0)	4 (50.0)
Aspartate aminotransferase increased	3 (37.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (37.5)
Diarrhoea	2 (25.0)	1 (12.5)	0 (0.0)	0 (0.0)	3 (37.5)
Hypertension	0 (0.0)	3 (37.5)	0 (0.0)	0 (0.0)	3 (37.5)
White blood cell count decreased	2 (25.0)	1 (12.5)	0 (0.0)	0 (0.0)	3 (37.5)
Part B - Sunitinib 20 mg/m^2, N=3					
Any AEs	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	2 (66.7)

Table Treatment-Emergent Adverse Events (Treatment-Related) – Study ADVL0612, Safety Population,

Number (%) of Subjects	Sunitinib				
	Part A[a]		Part B[a]	Part C[b]	
No AE was reported by >2 patients in this cohort.					
Part C - Sunitinib 15 mg/m^2, N=12					
Any AEs	0 (0.0)	1 (8.3)	7 (58.3)	0 (0.0)	8 (66.7)
Fatigue	4 (33.3)	2 (16.7)	2 (16.7)	0 (0.0)	8 (66.7)
Alanine aminotransferase increased	6 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (50.0)
Anaemia	4 (33.3)	1 (8.3)	1 (8.3)	0 (0.0)	6 (50.0)
Hypermagnesaemia	6 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (50.0)
Lymphocyte count decreased	2 (16.7)	2 (16.7)	2 (16.7)	0 (0.0)	6 (50.0)
Neutrophil count decreased	1 (8.3)	3 (25.0)	2 (16.7)	0 (0.0)	6 (50.0)
White blood cell count decreased	3 (25.0)	3 (25.0)	0 (0.0)	0 (0.0)	6 (50.0)
Hypercalcaemia	4 (33.3)	1 (8.3)	0 (0.0)	0 (0.0)	5 (41.7)
Hypertension	4 (33.3)	1 (8.3)	0 (0.0)	0 (0.0)	5 (41.7)
Abdominal pain	3 (25.0)	0 (0.0)	1 (8.3)	0 (0.0)	4 (33.3)
Ataxia	0 (0.0)	1 (8.3)	3 (25.0)	0 (0.0)	4 (33.3)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	4 (33.3)
Dizziness	2 (16.7)	1 (8.3)	1 (8.3)	0 (0.0)	4 (33.3)
Headache	2 (16.7)	2 (16.7)	0 (0.0)	0 (0.0)	4 (33.3)
Hyperglycaemia	3 (25.0)	0 (0.0)	1 (8.3)	0 (0.0)	4 (33.3)
Hypocalcaemia	4 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (33.3)
Hypokalaemia	4 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (33.3)
Nausea	2 (16.7)	1 (8.3)	1 (8.3)	0 (0.0)	4 (33.3)
Platelet count decreased	3 (25.0)	1 (8.3)	0 (0.0)	0 (0.0)	4 (33.3)
Vomiting	1 (8.3)	3 (25.0)	0 (0.0)	0 (0.0)	4 (33.3)
Aspartate aminotransferase increased	2 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)	3 (25.0)
Blood alkaline phosphatase increased	2 (16.7)	0 (0.0)	1 (8.3)	0 (0.0)	3 (25.0)
Constipation	2 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)	3 (25.0)
Diarrhoea	1 (8.3)	2 (16.7)	0 (0.0)	0 (0.0)	3 (25.0)
Dysgeusia	3 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (25.0)
Glossopharyngeal nerve disorder	0 (0.0)	2 (16.7)	0 (0.0)	1 (8.3)	3 (25.0)
Hyperkalaemia	1 (8.3)	1 (8.3)	1 (8.3)	0 (0.0)	3 (25.0)
Hypoglycaemia	3 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (25.0)
Hyponatraemia	2 (16.7)	0 (0.0)	1 (8.3)	0 (0.0)	3 (25.0)
Insomnia	3 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (25.0)
Lipase increased	2 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)	3 (25.0)
Pyrexia	3 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (25.0)
Sinus tachycardia	2 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)	3 (25.0)
Vision blurred	3 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (25.0)

Source: Study ADVL0612 Report Body Table 21.
MedDRA (v15.1) coding dictionary applied.
AEs=Adverse events; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; n=Number of patients with observation; N=Total number of patients in respective group.

Table **Descending Order of Frequency of Treatment-Emergent Adverse Events in ≥ 2 Patients by MedDRA Preferred Term and Maximum CTCAE Grade (All-causality, All Cycles) - Study ACNS1021, Safety Population**

MedDRA Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Total
	n (%)				
Recurrent/Progressive/Refractory High-Grade Glioma (N=16)					
Any AEs	**1 (6.3)**	**0 (0.0)**	**7 (43.8)**	**0 (0.0)**	**8 (50.0)**
Seizure	0 (0.0)	0 (0.0)	1 (6.3)	2 (12.5)	3 (18.8)
Fatigue	1 (6.3)	0 (0.0)	1 (6.3)	0 (0.0)	2 (12.5)
Haemorrhage intracranial	1 (6.3)	0 (0.0)	0 (0.0)	1 (6.3)	2 (12.5)
Headache	1 (6.3)	0 (0.0)	1 (6.3)	0 (0.0)	2 (12.5)
Hydrocephalus	0 (0.0)	0 (0.0)	1 (6.3)	1 (6.3)	2 (12.5)
Recurrent/Progressive/Refractory Ependymoma (N=13)					
Any AEs	**2 (15.4)**	**0 (0.0)**	**4 (30.8)**	**3 (23.1)**	**9 (69.2)**
Neutrophil count decreased	0 (0.0)	0 (0.0)	4 (30.8)	1 (7.7)	5 (38.5)
Paraesthesia	1 (7.7)	0 (0.0)	1 (7.7)	0 (0.0)	2 (15.4)
Total (N=29)					
Any AEs	**3 (10.3)**	**0 (0.0)**	**11 (37.9)**	**3 (10.3)**	**17 (58.6)**
Neutrophil count decreased	0 (0.0)	0 (0.0)	5 (17.2)	1 (3.4)	6 (20.7)
Haemorrhage intracranial	1 (3.4)	0 (0.0)	1 (3.4)	1 (3.4)	3 (10.3)
Hydrocephalus	0 (0.0)	0 (0.0)	1 (3.4)	2 (6.9)	3 (10.3)
Seizure	0 (0.0)	0 (0.0)	1 (3.4)	2 (6.9)	3 (10.3)
Amylase increased	1 (3.4)	0 (0.0)	1 (3.4)	0 (0.0)	2 (6.9)
Fatigue	1 (3.4)	0 (0.0)	1 (3.4)	0 (0.0)	2 (6.9)
Headache	1 (3.4)	0 (0.0)	1 (3.4)	0 (0.0)	2 (6.9)
Paraesthesia	1 (3.4)	0 (0.0)	1 (3.4)	0 (0.0)	2 (6.9)

Source: Study ACNS1021 Report Body Table 22.
Includes data up to 28 days after last dose of study drug.
MedDRA (Version 20.0) coding dictionary applied.
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in respective group; n=number of patients with observation.

Summary tables of **treatment-related TEAEs** for each study are presented below:

Table **Treatment-Emergent Adverse Events (Treatment-Related) – Study A6181196, Safety Population**

Treatment-related adverse events	Sunitinib (N=6), n (%)
Number of Treatment-related AEs	**59**
At least 1 treatment-related AEs	6 (100)
At least 1 treatment-related SAE	0
Treatment-related AEs of severity Grade 3 or 4	4 (66.7)
Treatment-related AEs of severity Grade 5	0
Temporary discontinuation due to treatment-related AEs	4 (66.7)
Permanent discontinuation due to a treatment-related AEs	1 (16.7)

Source: Study A6181196 Report Body Table 18.
Includes data up to 28 days after last dose of study drug.
Patients are counted only once per treatment in each row.
SAEs were according to the Investigator's assessment.
Severity counts are based on the maximum severity or grade of events.
Abbreviations: AE=adverse event, N=number of patients analyzed; n=number of patients with an event; SAE=serious adverse event, TEAE=treatment-emergent adverse event

Table **Decreasing Frequency of TEAEs in ≥2 Patients by MedDRA Preferred Term and Maximum CTCAE Grade (Treatment-Related) – Study A6181196, Safety Population**

Adverse Events by Preferred Term	Sunitinib, N = 6				
	Grade 1	Grade 2	Grade 3	Grade 4	Total
			n (%)		
Any AEs	**0 (0.0)**	**2 (33.3)**	**3 (50.0)**	**1 (16.7)**	**6 (100.0)**
Diarrhoea	2 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)	3 (50.0)
Headache	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)
Nausea	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)
Neutropenia	0 (0.0)	1 (16.7)	1 (16.7)	1 (16.7)	3 (50.0)
White blood cell count decreased	0 (0.0)	3 (50.0)	0 (0.0)	0 (0.0)	3 (50.0)
Anaemia	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	2 (33.3)
Decreased appetite	1 (16.7)	1 (16.7)	0 (0.0)	0 (0.0)	2 (33.3)
Dyspepsia	2 (33.3)	0 (0.0))	0 (0.0)	0 (0.0)	2 (33.3)
Thrombocytopenia	0 (0.0)	1 (16.7)	1 (16.7)	0 (0.0)	2 (33.3)

Source: Study A6181196 Report Table 14.3.1.3.11.1.
Includes data up to 28 days after last dose of study drug.
All AEs were considered as treatment-emergent AEs, unless present at baseline with the same severity grade.
CTCAE version 4.0 was used. Maximum CTCAE grade is defined as the maximum CTCAE grade value for the specific Preferred Term. MedDRA (version 20.0) coding dictionary applied.
Abbreviations: AE=adverse event, CTCAE=Common Terminology Criteria for Adverse Events, MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients analyzed; n=number of patients with an event; SAE=serious adverse event.

Table **Treatment-Emergent Adverse Events Reported in >2 Patients by MedDRA PT and Maximum CTCAE Grade (Treatment-Related, All Cycles) by Dose Groups and Total – Study ADVL0612, Safety Population (extract)**

MedDRA Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Part A - Sunitinib 15 mg/m^2, N=6					
Any AEs	1 (16.7)	0 (0.0)	4 (66.7)	1 (16.7)	6 (100.0)
Platelet count decreased	4 (66.7)	1 (16.7)	0 (0.0)	0 (0.0)	5 (83.3)
Lymphocyte count decreased	1 (16.7)	0 (0.0)	2 (33.3)	1 (16.7)	4 (66.7)
White blood cell count decreased	2 (33.3)	2 (33.3)	0 (0.0)	0 (0.0)	4 (66.7)
Diarrhoea	3 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (50.0)
Neutrophil count decreased	0 (0.0)	1 (16.7)	2 (33.3)	0 (0.0)	3 (50.0)
Part A - Sunitinib 20 mg/m^2, N=6					
Any AEs	0 (0.0)	1 (16.7)	4 (66.7)	1 (16.7)	6 (100.0)
Neutrophil count decreased	1 (16.7)	0 (0.0)	3 (50.0)	1 (16.7)	5 (83.3)
White blood cell count decreased	2 (33.3)	0 (0.0)	3 (50.0)	0 (0.0)	5 (83.3)
Aspartate aminotransferase increased	3 (50.0)	1 (16.7)	0 (0.0)	0 (0.0)	4 (66.7)
Platelet count decreased	2 (33.3)	2 (33.3)	0 (0.0)	0 (0.0)	4 (66.7)
Alanine aminotransferase increased	2 (33.3)	1 (16.7)	0 (0.0)	0 (0.0)	3 (50.0)
Part B - Sunitinib 15 mg/m^2, N=8					
Any AEs	3 (37.5)	2 (25.0)	2 (25.0)	1 (12.5)	8 (100.0)
Neutrophil count decreased	2 (25.0)	0 (0.0)	1 (12.5)	1 (12.5)	4 (50.0)
Aspartate aminotransferase increased	3 (37.5)	0 (0.0)	0 (0.0)	0 (0.0)	3 (37.5)
Hypophosphataemia	2 (25.0)	0 (0.0)	1 (12.5)	0 (0.0)	3 (37.5)
White blood cell count decreased	2 (25.0)	1 (12.5)	0 (0.0)	0 (0.0)	3 (37.5)

Table **Treatment-Emergent Adverse Events Reported in >2 Patients by MedDRA PT and Maximum CTCAE Grade (Treatment-Related, All Cycles) by Dose Groups and Total – Study ADVL0612, Safety Population (extract)**

MedDRA Preferred Term	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Part B - Sunitinib 20 mg/m^2, N=3					
Any AEs	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)	3 (100.0)
None of the AE was reported by >2 patients in this cohort.					
Part C - Sunitinib 15 mg/m^2, N=12					
Any AEs	1 (8.3)	5 (41.7)	5 (41.7)	1 (8.3)	12 (100.0)
Alanine aminotransferase increased	6 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (50.0)
Fatigue	3 (25.0)	3 (25.0)	0 (0.0)	0 (0.0)	6 (50.0)
Neutrophil count decreased	1 (8.3)	3 (25.0)	2 (16.7)	0 (0.0)	6 (50.0)
White blood cell count decreased	3 (25.0)	3 (25.0)	0 (0.0)	0 (0.0)	6 (50.0)
Lymphocyte count decreased	2 (16.7)	1 (8.3)	2 (16.7)	0 (0.0)	5 (41.7)
Anaemia	3 (25.0)	1 (8.3)	0 (0.0)	0 (0.0)	4 (33.3)
Hypermagnesaemia	4 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (33.3)
Hypertension	3 (25.0)	1 (8.3)	0 (0.0)	0 (0.0)	4 (33.3)
Platelet count decreased	3 (25.0)	1 (8.3)	0 (0.0)	0 (0.0)	4 (33.3)
Aspartate aminotransferase increased	2 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)	3 (25.0)
Blood alkaline phosphatase increased	2 (16.7)	0 (0.0)	1 (8.3)	0 (0.0)	3 (25.0)
Diarrhoea	1 (8.3)	2 (16.7)	0 (0.0)	0 (0.0)	3 (25.0)
Hypercalcaemia	2 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)	3 (25.0)
Hypokalaemia	3 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (25.0)
Lipase increased	2 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)	3 (25.0)
Nausea	2 (16.7)	1 (8.3)	0 (0.0)	0 (0.0)	3 (25.0)
Vomiting	1 (8.3)	2 (16.7)	0 (0.0)	0 (0.0)	3 (25.0)

Source: Table 14.3.1.3.3a, Table 14.3.1.3.3b, Table 14.3.1.3.3c.
MedDRA (v15.1) coding dictionary applied.
AEs=Adverse events; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; n=Number of patients with observation; N=Total number of patients in respective group; PT=Preferred term.

Table **Descending Order of Frequency of Treatment-Emergent Adverse Events in ≥2 Patients by MedDRA Preferred Term and Maximum CTCAE Grade (Treatment-Related, All Cycles) – Study ACNS1021, Safety Population**

MedDRA Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Total
	n (%)				
Recurrent/Progressive/Refractory High-Grade Glioma (N=16)					
Any AEs	**2 (12.5)**	**0 (0.0)**	**4 (25.0)**	**1 (6.3)**	**7 (43.8)**
Fatigue	1 (6.3)	0 (0.0)	1 (6.3)	0 (0.0)	2 (12.5)
Haemorrhage intracranial	1 (6.3)	0 (0.0)	0 (0.0)	1 (6.3)	2 (12.5)
Recurrent/Progressive/Refractory Ependymoma (N=13)					
Any AEs	**2 (15.4)**	**0 (0.0)**	**4 (30.8)**	**1 (7.7)**	**7 (53.8)**
Neutrophil count decreased	0 (0.0)	0 (0.0)	4 (30.8)	1 (7.7)	5 (38.5)
Total (N=29)					
Any AEs	**4 (13.8)**	**0 (0.0)**	**8 (27.6)**	**2 (6.9)**	**14 (48.3)**
Neutrophil count decreased	0 (0.0)	0 (0.0)	5 (17.2)	1 (3.4)	6 (20.7)
Haemorrhage intracranial	1 (3.4)	0 (0.0)	1 (3.4)	1 (3.4)	3 (10.3)

Table Descending Order of Frequency of Treatment-Emergent Adverse Events in ≥2 Patients by MedDRA Preferred Term and Maximum CTCAE Grade (Treatment-Related, All Cycles) – Study ACNS1021, Safety Population

MedDRA Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Total
	n (%)				
Amylase increased	1 (3.4)	0 (0.0)	1 (3.4)	0 (0.0)	2 (6.9)
Fatigue	1 (3.4)	0 (0.0)	1 (3.4)	0 (0.0)	2 (6.9)

Source: Study ACNS1021 Report Body Table 23.
Includes data up to 28 days after last dose of study drug.
MedDRA (Version 20.0) coding dictionary applied.
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in respective group; n=number of patients with observation.

Deaths:

Study A6181196: no deaths were reported.

Study ADVL0612: A total of 5 patients died during Part A of the study due to the disease under study (1 patient in the 15 mg/m2 and 4 in the 20 mg/m2 dose group) and none of the deaths were considered to be related to study treatment.

A total of 5 patients died during Part B of the study due to the disease under study (3 patients in the sunitinib 15 mg/m2 and 2 patients in the sunitinib 20 mg/m2 dose group). One patient (a 6-years old girl with diffuse-pontine glioma) in 20 mg/m2 group also experienced Grade 5 Aspiration. The investigator assessed the causality of aspiration as possibly related to sunitinib stating the AE played a minor contribution to death, and the causality of the death was reported as the disease under study (Malignant glioma). The other deaths were not considered related to study treatment.

A total of 5 patients died during the Part C of the study due to the disease under study and none of the deaths were considered to be related to study treatment.

Study ACNS1021: A total of 18 patients died during the study, with 12 (75%) patients in glioma group and 6 (46.2%) patients in ependymoma group. Five (27.8%) patients died during active treatment including up to 30 days after the last dose of the study drug. All 18 patients died due to the disease under study; none of the deaths were considered to be related to study treatment except for the death of 1 patient (4-years old boy with globlastoma multiforme) for which protocol therapy was considered to have had a "minor contribution to death". The investigator stated that there was reasonable possibility that the reported AE Heamorrhage intracranial grade 4 occurred 13 days before the death was related to product sunitinib based on a plausible temporal association and the known safety profile of the drug. In addition, the AEs Hydrocephalus and Disease progression were unrelated to the study drug sunitinib, but related to deterioration of the underlying glioblastoma multiforme. The progressive disease, which was confirmed by the MRI might have contributed to Haemorrhage intracranial.

Serious Adverse Events:

Study A6181196: no SAEs were reported.

Study ADVL0612: Overall, 18 patients (51%) experienced SAEs. A summary of SAEs is reported in table below:

Table Summary of Serious Adverse Events – Study ADVL0612, Safety Population

Subject Identifier	Suspected Drug(s)/Dose[a]	Action Taken (Drug Level)	MedDRA Preferred Term	Causality	Clinical Outcome/Seriousness
Part A - Sunitinib 15 mg/m^2, N=6					
717694	Sunitinib malate/15.00 mg/m^2	Unknown	Diastolic dysfunction	Related	Unknown/hospitalization
			Left ventricular dysfunction	Related	Unknown/hospitalization
			Myocardial ischaemia	Related	Unknown/hospitalization
744560	Sunitinib malate/15.00 mg/m^2	Permanently withdrawn	Alanine aminotransferase	Related	Recovered/resolved/imp med event
	Valaciclovir hydrochloride	Temporarily withdrawn	Alanine aminotransferase	No data	Recovered/resolved/imp med event
763699	Sunitinib malate/15.00 mg/m^2	Post-therapy	Hyponatraemia	Related	Recovering/resolving/imp med event
	Vinblastine/6.00 mg/m^2	Not applicable	Hyponatraemia	No data	Recovering/resolving/imp med event
Part A - Sunitinib 20 mg/m^2, N=6					
133300	Potassium iodide	Not applicable	Hypotension	No data	Unknown/imp med event
			Weight decreased	No data	Unknown/hospitalization
			Hypothyroidism	No data	Recovered/resolved/hospitalization
			Decreased appetite	No data	Unknown/hospitalization
			Dehydration	No data	Unknown/imp med event
			Alanine aminotransferase increased	No data	Recovered/resolved/imp med event
			Aspartate aminotransferase increased	No data	Recovered/resolved/imp med event
			Hypophosphataemia	No data	Recovered/resolved/hospitalization
			Hypokalaemia	No data	Recovered/resolved/hospitalization
			Oedema	No data	Recovered/resolved imp med event/
			Fatigue	No data	Recovered/resolved hospitalization/
	Sunitinib malate/20.00 mg/m^2	Dose not changed	Hypotension	Related	Unknown/imp med event
			Weight decreased	Related	Unknown/hospitalization
			Hypothyroidism	Unrelated	Recovered/resolved/hospitalization
			Decreased appetite	Related	Unknown/hospitalization
			Dehydration	Related	Unknown/imp med event
			Alanine aminotransferase increased	Related	Recovered/resolved/imp med event
			Aspartate aminotransferase increased	Related	Recovered/resolved/imp med event
			Hypophosphataemia	Related	Recovered/resolved hospitalization/
			Hypokalaemia	Related	Recovered/resolved/hospitalization
			Oedema	Unrelated	Recovered/resolved/imp med event
			Fatigue	Related	Recovered/resolved/hospitalization
763788	Sunitinib malate/20.00 mg/m^2	Permanently withdrawn	Left ventricular dysfunction	Related	Recovered/resolved/imp med event
767336	Sunitinib malate/20.00 mg/m^2	Dose not changed	Hypothyroidism	Related	Recovered/resolved/imp med event
Part B - Sunitinib 15 mg/m^2, N=8					

Table Summary of Serious Adverse Events – Study ADVL0612, Safety Population

Subject Identifier	Suspected Drug(s)/Dose[a]	Action Taken (Drug Level)	MedDRA Preferred Term	Causality	Clinical Outcome/Seriousness
780961	Sunitinib malate/15.00 mg/m^2	Permanently withdrawn	Dehydration	Unrelated	Recovering/resolving/hospitalization
			Shunt malfunction	Unrelated	Recovering/resolving/hospitalization
			Vomiting	Unrelated	Recovering/resolving/hospitalization
			Convulsion	Unrelated	Recovering/resolving/hospitalization
782618	Sunitinib malate/15.00 mg/m^2	Temporarily withdrawn	Nephrolithiasis	Related	Recovering/resolving/hospitalization imp med event
	Sunitinib malate/15.00 mg/m^2	Dose not changed	Hypertension	Related	Unknown/imp med event
			Renal pain	Related	Recovered/resolved/hospitalization
			Hyperkalaemia	Related	Unknown/imp med event
	Sunitinib malate	Temporarily withdrawn	Dysphagia	Unrelated	Not recovered/not resolved/hospitalization
784205	Sunitinib malate/15.00 mg/m^2	Permanently withdrawn	Neutrophil count decreased	Related	Recovered/resolved/imp med event
		Permanently withdrawn	Electrocardiogram QT prolonged	Related	Recovered/resolved/imp med event
Part B - Sunitinib 20 mg/m^2, N=3					
536584	Sunitinib malate/20.00 mg/m^2	Permanently withdrawn	Hyperuricaemia	Related	Recovered/resolved/imp med event
782720	Sunitinib malate/20.00 mg/m^2	Dose not changed	Aspiration	Unrelated	Recovering/resolving/hospitalization
783385	Sunitinib malate/20.00 mg/m^2	No data	Aspiration	Related	Fatal/hospitalization
			Cranial nerve disorder	Related	Unknown/hospitalization
			Cerebral haemorrhage	Related	Unknown/hospitalization
Part C - Sunitinib 15 mg/m^2, N=12					
744676	Sunitinib malate/15.00 mg/m^2	Permanently withdrawn	Flushing	Related	Recovered/resolved/imp med event
			Wound complication	Unrelated	Recovering/resolving/hospitalization
			Dizziness	Related	Recovering/resolving/imp med event
			Wound dehiscence	Unrelated	Recovering/resolving/hospitalization
780201	Sunitinib malate/15.00 mg/m^2	Dose reduced	Disease progression	Unrelated	Fatal
			Anaplastic astrocytoma	Unrelated	Fatal
795993	Sunitinib malate/15.00 mg/m^2	Unknown	Disease progression	Unrelated	Fatal
			Brain stem glioma	Unrelated	Fatal
			Ataxia	Unrelated	Not recovered/not resolved/hospitalization
			Peripheral motor neuropathy	Unrelated	Not recovered/not resolved/hospitalization
796334	Bevacizumab	Post-therapy	Proteinuria	Related	Recovering/resolving/imp med event
	Sunitinib malate/25.00 mg	Temporarily withdrawn	Proteinuria	Related	Recovering/resolving/imp med event
799609	Amlodipine	No data	Pneumatosis	No data	Recovering/resolving/hospitalization
			Intestinal dilatation	No data	Recovering/resolving/hospitalization

Table Summary of Serious Adverse Events – Study ADVL0612, Safety Population

Subject Identifier	Suspected Drug(s)/Dose[a]	Action Taken (Drug Level)	MedDRA Preferred Term	Causality	Clinical Outcome/Seriousness
	Sunitinib malate/15.00 mg/m^2	Temporarily withdrawn	Abdominal pain	No data	Recovering/resolving/hospitalization
			Pneumatosis	Unrelated	Recovering/resolving/hospitalization
			Intestinal dilatation	Unrelated	Recovering/resolving/hospitalization
			Abdominal pain	Unrelated	Recovering/resolving/hospitalization
800231	Dexamethasone	No data	Hypoxia	No data	Unknown/hospitalization; life-threatening
			Cerebral haemorrhage	No data	Unknown/hospitalization; life-threatening
			Disease progression	No data	Fatal/hospitalization
			Glioblastoma multiforme	No data	Fatal/hospitalization
			Hyperglycaemia	No data	Recovered/resolved/hospitalization
			Dysphagia	No data	Unknown/hospitalization
			Somnolence	No data	Unknown/hospitalization
			Cranial nerve disorder	No data	Unknown/hospitalization; life-threatening
	Sunitinib malate/15.00 mg/m^2	Post-therapy	Hypoxia	Related	Unknown/hospitalization; life-threatening
			Cerebral haemorrhage	Related	Unknown/hospitalization; life-threatening
			Disease progression	Unrelated	Fatal/hospitalization
			Glioblastoma multiforme	Unrelated	Fatal/hospitalization
			Hyperglycaemia	Unrelated	Recovered/resolved/hospitalization
			Dysphagia	Unrelated	Unknown/hospitalization
			Somnolence	Unrelated	Unknown/hospitalization
			Cranial nerve disorder	Unrelated	Unknown/hospitalization; life-threatening

Source: Study ADVL0612 Report Table 14.3.2.2.
MedDRA v.15.1 coding dictionary applied.
imp med event=Important medical event; MedDRA=Medical Dictionary for Regulatory Activities; N=Total number of patients in respective group.
a. Source of actual treatment group or sequence is OC (Oracle Clinical) or PIMS (Phase I Management System). Source of suspect drug was from SDW (Safety Data Warehouse). Dose for treatment(s) at the earliest onset date.

Study ACNS1021: Overall, 13 (44.8%) patients in the safety population had all-causality SAEs. The most common (≥10%) all-causality SAEs were Haemorrhage intracranial, Hydrocephalus, Neoplasm progression, and Seizure (each reported for 3 [10.3%] patients). The majority of the SAEs was associated with disease under study and considered unrelated to study treatment. The SAEs considered treatment-related were intracranial hemorrhage (3 patients, 1 grade 1 and 2 grade 3 events) and rash maculo-papular (1 patient, grade 2). Data on SAEs in presented in the table below:

Table **Descending Order of Frequency of Treatment-Emergent Serious Adverse Events by MedDRA Preferred Term and Maximum CTCAE Grade (All-Causalities, All Cycles) – Study ACNS1021, Safety Population**

MedDRA Preferred Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
	n (%)					
	Total (N=29)					
Any AEs	**1 (3.4)**	**1 (3.4)**	**4 (13.8)**	**2 (6.9)**	**5 (17.2)**	**13 (44.8)**
Neoplasm progression	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (10.3)	3 (10.3)
Haemorrhage intracranial	1 (3.4)	0 (0.0)	1 (3.4)	1 (3.4)	0 (0.0)	3 (10.3)
Hydrocephalus	0 (0.0)	0 (0.0)	1 (3.4)	2 (6.9)	0 (0.0)	3 (10.3)
Seizure	0 (0.0)	0 (0.0)	1 (3.4)	2 (6.9)	0 (0.0)	3 (10.3)
Dysarthria	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)
Facial nerve disorder	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)
Gait disturbance	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)
Glioblastoma multiforme	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	1 (3.4)
Headache	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	1 (3.4)
Neoplasm	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	1 (3.4)
Paraesthesia	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)
Peripheral motor neuropathy	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)	0 (0.0)	1 (3.4)
Rash maculo-papular	0 (0.0)	1 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3.4)

Source: Study ACNS1021 Report Body Table 24.
MedDRA (Version 20.0) coding dictionary applied.
Abbreviations: AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients in respective group; n=number of patients with observation.

Permanent discontinuations:

Study A6181196: one patient was permanently discontinued during cycle 6 due to a treatment-related adverse event of Grade 2 Anaemia that was reported as resolved.

Study ADVL0612: overall, 7 patients (20%) discontinued due to AEs related to study drug, and the event was reported as "AE unspecified".

Study ACNS1021: two patients (7%) discontinued due to intracranial hemorrhage, reported both as SAE and considered related to study drug.

Dose Limiting Toxicity (DLT) – Study ADVL0612:

Part A: A total of 6 out of 12 patients experienced DLTs, with 3 (50.0%) patients each in the sunitinib 15 mg/m^2 and 20 mg/m^2 dose groups. One of the first 3 patients in the sunitinib 20 mg/m^2 dose group had 1 cardiac event (Grade 2 Left ventricular dysfunction) during the first treatment cycle. This dose level was expanded to 6 patients, and 2 other patients reported DLTs in Cycle 1. A Grade 4 Neutrophil count decreased in 1 patient, and Grade 3 Fatigue, Weight decreased, Decreased appetite, Dehydration, Hypokalemia and Hypophosphatemia in 1 patient. The dose was then reduced to 15 mg/m^2. One of the first 3 patients in the sunitinib 15 mg/m^2 dose group experienced 3 cardiac events (Grade 3 Cardiac failure, Grade 2 Acute coronary syndrome, and Grade 2 Left ventricular dysfunction) during the first treatment cycle. The dose level was expanded to 6 patients and 2 other patients experienced DLTs in Cycle 1 (Grade 3 ALT increased in 1 patient and Grade 3 Hyponatraemia in 1 patient). The protocol was amended to exclude patients with previous anthracycline or cardiac radiation exposure. No maximum tolerated dose (MTD) was defined for the Part A population.

Part B: A total of 4 out of 11 patients experienced DLTs (2 out of 8 patients in the sunitinib 15 mg/m2 group and 2 out of 3 patients in the sunitinib 20 mg/m^2 dose groups; any cycle DLTs). None of the patients experienced cardiac events. None of the 8 patients in the sunitinib 15 mg/m2 dose group had DLTs in Cycle 1. Two patients in the sunitinib 15 mg/m^2 dose group experienced DLTs in subsequent cycles, a Grade 3 nephrolithiasis during Cycle 5 in 1 patient, and Grade 4 Neutrophil count decreased and Grade 2 QT prolongation during Cycle 2 in 1 patient. Two out of 3 patients in the sunitinib 20 mg/m^2 dose group experienced DLTs during the first treatment cycle, a Grade 4 Hyperuricemia in 1 patient, and Grade 4 Haemorrhage intracranial, Grade 4 Vagus nerve disorder, and Grade 5 Aspiration in 1 patient.

Based on Part B of the study, The MTD and the RP2D for sunitinib in children without previous cardiac radiation or anthracycline exposure was 15 mg/m2 QD for 28 days followed by 14 days off treatment.

Part C: A total of 6 out of 12 patients experienced DLTs (any cycle) in the sunitinib 15 mg/m^2 dose group. None of the patients experienced cardiac events. In the first treatment cycle, 3 patients experienced DLTs, a Grade 4 Haemorrhage intracranial and Hypoxia in 1 patient; Grade 3 Palmar plantar erythrodysesthesia syndrome in 1 patient; and Grade 3 Back pain and Dizziness in 1 patient. In Part C, there were 3 out of 12 patients with Cycle 1 DLT (25%) which was below the threshold of 33% for Cycle 1 DLT rate. DLTs in later cycles were captured, but not used in determination of recommended phase 2 dose (RP2D). One additional patient had Grade 3 Abdominal pain and Pneumatosis intestinalis during the first treatment cycle. Both these events were reported as DLT, though they were considered unlikely related to the study drug. Two patients experienced DLTs in subsequent cycles, a Grade 3 Blood alkaline phosphatase increased during Cycle 3 in 1 patient and Grade 3 Proteinuria during Cycle 2 in 1 patient.

Laboratory and other events:

Study A6181196: Haemathology: Grade 4 neutrophils (absolute) decreased was reported in 1 (16.7%) patient, and Grade 3 neutrophils (absolute) decreased, platelets decreased, and anemia were reported in 1 (16.7%) patient each, all of which were also reported as TEAEs. Grade 2 decrease in WBC, decrease in neutrophils (absolute), and anaemia were reported in 6 (100%), 4 (66.7%), and 1 (16.7%) patients, respectively.

Chemistry: The majority of the results were within normal range (shown as Grade 0) or Grade 1 in severity, and there were no Grade 4 chemistry laboratory abnormalities. Grade 3 hypoglycaemia and hypophosphataemia were reported in 1 (16.7%) patient each, both of which were also reported as TEAEs.

Blood pressure: A change from baseline in diastolic blood pressure (BP) of ≥10 mm Hg was reported in 5 (83.3%) patients and ≥20 mm Hg in 3 (50.0%) patients. A change from baseline in systolic BP of ≥20 mm Hg was reported in 1 (16.7%) patient. Overall, the mean changes from baseline in BP during and at the end of treatment were small and not clinically meaningful, as there were no TEAEs of Hypertension or BP increased reported in this study.

QTc interval: Overall, mean changes from baseline in QTcB and QTcF interval during and at the end of treatment were small, and none were reported as AEs. Shifts in QTcF interval from Grade 0 (within normal range) at baseline to Grade ≥3 (QTcF interval ≥30 msec) post-baseline was reported in 2 (33.3%) patients.

Study ADVL0612: Hematology: laboratory abnormalities were reported in the majority of patients in the safety population. The majority of the events were Grade 1 or Grade 2 in severity. Three (50.0%)

patients in the 20 mg/m2 group of Part A and 1 (8.3%) patient in Part C had Grade 3 WBC decreased and anaemia. These events were reported as TEAEs.

Chemistry: laboratory test abnormalities were reported in the majority of patients in the safety analysis population. In Part A-Total, hypophosphatemia and elevated lipase (Grade 3 and Grade 2, respectively) were reported in 1 (8.3%) patient each. In Part B-Total, hypophosphatemia (Grade 3) was reported in 1 (9.1%) patient, and elevated creatinine (Grade 2) was reported in 2 (18.2%) patients. In Part C, elevated lipase (Grade 2) was reported in 1 (8.3%) patient. Grade 3 hypophosphatemia was also reported as TEAEs as described in Study ADVL0612 CSR Table 21 in Part A-Total and in Part B-Total. Grade 2 lipase increased was reported as a TEAE in Part C.

QTc interval: In Part A of the study, 1 (16.7%) patient in the 15 mg/m2 group and 2 (33.3%) patients in the 20 mg/m2 group had maximum increases between 30 msec to 60 msec from baseline in QTc interval. In Part B of the study, 1 (12.5%) patient in the 15 mg/m2 group had maximum increase between 30 msec to 60 msec from baseline in QTc interval. In Part C of the study, 2 (16.7%) patients in the 15 mg/m2 group had maximum increase between 30 msec to 60 msec from baseline in QTc interval.

Study ACNS1021: Hematology: The majority of patients in both treatment groups had haematology baseline severities of Grade 0 or Grade 1. Seven (7) patients had haematology laboratory abnormalities reported as AEs. Five patients overall had Grade 3 Neutrophil count decreased; 1 patient had activated partial thromboplastin time prolonged, and 1 patient had Grade 4 Neutrophil count decreased, Lymphocyte count decreased, and Grade 3 WBC count decreased. Neutrophil count decreased (Grade 3 in 5 [17.2%] patients and Grade 4 in 1 [3.4%] patient); Lymphocyte count decreased (Grade 4 in 1 [3.4%] patient); and White blood cell count decreased (Grade 3 in 1 [3.4%] patient) were reported as TEAEs.

Chemistry: The majority of patients in both treatment groups had chemistry baseline severities of Grade 0 or Grade 1. Two patients had Grade 4 hypocalcemia; Grade 3 abnormalities were reported for ALT increased (3 patients), AST increased (2 patients), hypokalemia (1 patient), and elevated lipase (1 patient).

Safety data from the retrospective case series

Agaram et al (2008): the manuscript does not offer a detailed review of the safety of the 4 patients. One patient stopped sunitinib treatment after 1 month. This patient, however, was intolerant to imatinib. Another patient stopped treatment after 5 months due to drug intolerance and disease progression. The other 2 patients continued on sunitinib treatment until disease progression.

Janewy et al (2009): of the 7 patients described (age ranges 10 to 17 years), no Grade 4 or 5 treatment-related AEs were reported. Three Grade 3 events (fatigue, gastrointestinal AEs, haematological) occurred in 2 of 7 patients. These Grade 3 AEs led to dose reductions in 2 patients. Grade 1 or 2 events reported were: fatigue in 3 patients, haematological in 3 patients, gastrointestinal in 4 patients (including abdominal pain, vomiting, anorexia or diarrhoea); musculoskeletal events in 4 patients (including creatinine kinase elevation in 1 patient); leg pain in 2 patients, and joint pain in 1 patient. Hair hypopigmentation in 4 patients; headache in 2 patients; hypothyroidism in 2 patients; hepatic dysfunction in 1 patient.

Rutkowski et al (2017): of the 9 patients described (age ranges 11 to 21 years), the majority of AEs were Grade 1 or 2 in severity. No Grade 5 treatment-related AEs were reported. Grade 3 AEs (cholecystitis [n=1], hypothyroidism and anaemia [n=1], fatigue, mucositis and diarrhoea [n=1]) occurred in 3 patients. Two patients permanently discontinued treatment due to Grade 1/2 AEs (Grade

2 abdominal/bone pain and fatigue [n=1], Grade 2 oedema and Grade 1 fatigue, epistaxis, and headache [n=1]), and 2 patients required dose reduction. Most AEs experienced by patients treated with sunitinib were manageable and reversible after dose adjustments.

Post-marketing data

Use in paediatric patients is monitored and discussed in each PSUR. As of 30 April 2017, no new safety signals with regards to paediatric use have been identified. Estimated post-marketing exposure in children and adolescents under 18 years old is not available. During the 01 May 2016 through 30 April 2017 interval, there were 43 cases which reported the use of sunitinib in the paediatric population. The most common AEs (≥2) in paediatric patients included the following PTs: Disease progression (4), Fatigue, GIST, and Headache (2 each). These events are listed in the sunitinib SmPC or are consistent with progression of the underlying malignancy.

8.3. Discussion

A total of 70 paediatric and young adult patients received at least 1 dose of study medication in Studies A6181196 (6 patients), ADVL0612 (35 patients), and ACNS1021 (29 patients) were included in the evaluation of safety. Data have been presented separately for each study: the MAH did not present pooled analyses due to different disease type, different treated populations and the different dosing regimens studied.

The majority of patients in all 3 studies were white, with a prevalence of female in studies A6181196 and ADVL0612, while more male were enrolled in ACNS1021 study. Mean age was 14.3 years (SD 1.4, range 13-16) in A6181196 study, 12 years (range 3-21) in ADVL0612 study, and 11.5 years (SD 4.6, range 3-19) in ACNS1021 study.

Study ADVL0612: This is a phase I study to determine the MTD of sunitinib in children with refractory solid tumours when given on the recommended adult schedule 4/2.

During the initial portion of the study (Part A, 20 mg/m2), 1 of first 3 subjects experienced 1 cardiac event during the first treatment cycle. This dose level was expanded to 6 subjects and 2 other subjects reported DLTs in Cycle 1. The dose was then reduced to 15 mg/m2. One subjects in this dose group experienced 3 cardiac events during the first treatment cycle. Therefore, due to cardiac DLTs, the protocol was amended to exclude subjects with previous anthracycline or cardiac radiation exposure, which were not enrolled in the subsequent Part B of the study, and no further cardiac events occurred in part B. No MTD was defined for Part A population. None of the 8 subjects in the Part B sunitinib 15 mg/m2 dose group had DLTs in Cycle 1. The dose was escalated to 20 mg/m2 with 2 out of first 3 subjects experiencing DLTs during the first treatment cycle. These results established 15 mg/m2 per day on schedule 4/2 as the MTD for subjects without previous cardiac radiation or anthracycline exposure (which was lower as compared to adults, i.e. 15 mg/m^2 versus 30 mg/m^2). During Part C of the study (sunitinib 15 mg/m2, with sunitinib capsule contents sprinkled over applesauce or yogurt), 4 out of 12 enrolled subjects experienced DLTs in the first treatment cycle.

A total of 35 patients were enrolled in this study: across the three Parts of the trial, 26 subjects were treated with sunitinib 15 mg/m^2 and 9 patients were treated with 20 mg/m^2. The median number of cycles started was 1 for all 3 parts of the study. Four patients overall had started ≥5 cycles.

All the 35 patients evaluated experienced at least one TEAEs and at least one treatment-related TEAEs. Approximately half of the patients experienced a SAE. Grade 5 AEs were reported in 6 patients: of them, only one Grade 5 AE, occurred in a 6-years old girl with diffuse-pontine glioma in Part B (20

mg/m^2), was reported to be treatment-related. The investigator assessed the causality of aspiration as possibly related to sunitinib, stating the AE played a minor contribution to death, and the causality of the death was reported as the disease under study. According to the National Cancer Institute CTEP (Cancer Therapy Evaluation Program) assessment, the grade 5 aspiration was considered unrelated to sunitinib and related to the glioma and to disease progression. All the other deaths occurred in the study were not considered related to sunitinib.

Overall, in Part A of the study, the most frequent all causality TEAEs, mainly of Grade 1 or Grade 2 in severity were decreased platelet count and WBC, decreased neutrophil count and increased ALT (decreased neutrophil count mainly of severity Grade 3 or 4). In Part B of the study, the most frequent all causality TEAEs, mainly of Grade 1 or Grade 2 in severity were hypertension, hypophosphatemia, diarrhea, vomiting, decreased WBC count, decreased neutrophil, and increased AST. In Part C of the study, the most frequent all causality TEAEs, mainly of Grade 1 or Grade 2 in severity were fatigue, anemia, hypermagnesemia, decreased lymphocyte, decreased neutrophil, decreased WBC count, and increased ALT.

Study A6181196: This is a phase I/II study of sunitinib in young patients with advanced GIST. Starting dose of sunitinib was 15 mg/m^2 per day on schedule 4/2 for up to 18 cycles (24 months). A total of 6 patients received at least 3 cycles of the study treatment and 1 patient received all 18 of the planned cycles. Overall, the median duration of treatment was 219 days (i.e. 7.3 months) and the mean daily dose (SD) was 27.12 (7.192) mg. The dose was increased to 22.5 mg/m2 per day in 5 of the 6 patients, and a further increase to 30 mg/m2 per day in 2 patients. Dose reduction due to an AE is reported in one patient.

All 6 patients in the safety population experienced at least one TEAE and at least one treatment-related TEAEs. AEs of Grade 3 or 4 were reported in 5 patients, of them 4 patients (66.7%) had Grades 3 or 4 treatment–related TEAEs. No Grade 5 TEAEs were reported. In all 6 patients, at least 1 TEAE and treatment-related AE were reported in the SOC Blood and lymphatic system disorders. The most commonly reported treatment-related TEAEs were diarrhea, Headache, Nausea, Neutropenia and WBC count decreased in 3 (50.0%) patients each, the majority being Grade 1-2. Grade 3 Hypophosphatemia, Neutropenia, and Thrombocytopenia were reported in 1 (16.7%) patient each. Grade 4 Neutropenia was reported in 1 patient. Not deaths or SAE were reported in this study. One patient permanently discontinued due to Grade 2 anemia.

Study ACNS1021: This is a phase II study of sunitinib in recurrent, refractory or progressive High Grade Glioma and Ependymoma in paediatric and young adult patients. This study was prematurely closed due to the lack of disease control. The safety population included 29 subjects: of them, 13 (44.8%) had all-causality SAEs, the most common (≥10%) being Haemorrhage intracranial, Hydrocephalus, Neoplasm progression, and Seizure (each reported for 3 [10.3%] patients). Most common treatment-related TEAEs were neutrophil count decrease (20.7%, 6 events all Grade 3-4), intracranial haemorrage (10.3%, 3 patients having one grade 1, one grade 3 and one grade 4 events), amylase increase and fatigue (both 6.9%). A total of 18 patients died during the study: for one of which protocol therapy was considered to have had a "minor contribution to death", due to an intracranial haemorrage developed 13 days before death. Intracranial haemorrage was also the most common SAE (3 events, all considered treatment related). Cerebral haemorrage (including fatal events) is a known ADR for sutent, but with frequency "uncommon". The relative high rate of intracranial haemorrage in the pediatric CNS tumor setting has been highlighted in the SmPC.

Safety data from the retrospective case series in GIST: In Janeway et al (7 patients), the more commonly reported AEs were fatigue, haematoological and GI events. In the 9 patients described by Rutkowski, the grade 3 events reported were cholecystitis, hypothyroidism and anaemia, fatigue,

mucositis and diarrhoea in 3 patients overall. No grade 4 and 5 treatment related AEs were reported in both studies. No safety data have been collected in the Agaram manuscript (4 patients).

Post-marketing data: post-marketing data revealed that Sutent use has been reported in the paediatric population. The MAH stated that no new safety signals with regards to paediatric use have been identified.

Although the MAH considered sunitinib to be well tolerated in the paediatric population, it should be noted the high rate of grade 3-4 treatment related events reported across the studies (e.g. 66.7% in study A6181196; 88.3%, 45.5% and 50% in Part A, B and C of Study ADVL0612 respectively, 34.5% in Study ACNS1021), indicating that the toxicity of the agent is not negligible. Information regarding ADR reported from the available paediatric studies has been included in the SmPC.

Based on the data provided, several TEAEs of electrolyte disturbances, also with high severity grade, have been reported across clinical trials with sunitinib in children reported also as related to sunitinib. The MAH was requested to discuss this finding. The MAH reviewed the TEAEs of electrolyte disturbances occurred in paediatric studies, reporting that 9/70 (13%) patients reported 11 Grade 3 TEAEs [hypophosphatemia (4), hyperkalaemia (3), hyponatraemia (2), hypokalaemia (2)]; 6/11 were considered probably or possibly related to sunitinib, and 3/6 of them were serious and resolved. The three SAEs (hypophosphatemia, hypokalaemia, hyponatraemia) were considered confounded by advanced primary tumor and paraneoplastic syndrome (SIADH). In study ACNS1021, the 3 episodes of electrolyte disturbances reported (G4 hypocalcemia (2 episodes) and G3 hypokaliemia (1 event)) were reported on laboratory values and not as TEAE, and no further information regarding possible relationship with study drug as evaluated by investigator are available. Hypophosphatemia has been reported in 4.8 section as Grade 3 ADR recorded in A6181196 study. Based on the data provided, no further information is considered needed in the SmPC.

9. Changes to the Product Information

As a result of this variation, sections 4.2, 4.8, 5.1 and 5.2 of the SmPC are being updated.

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

9.1. User consultation

The MAH was previously requested by the CHMP (procedure EMEA/H/C/000687/II/0065) to perform and to submit a new user testing in the next relevant variation. The MAH submitted the results of the readability testing.

The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

10. Request for supplementary information

10.1. Other concerns

Clinical aspects

Pharmacokinetic

PMAREQDD-A618w-Other-366

1. It seems that paediatric data from study ADVL0612 have not been included in the PK-PD analysis, the MAH should clarify and provide the descriptive statistics for the subjects baseline characteristics and covariates considered in building the population PK-PD model, if different compared to the population PK model.

PMAR-EQDD-A618b-DP4-846

2. Considering the importance of the BSA values, the MAH is request to add a reference also to BSA values in the proposed text on SmPC.

SimCYP Simulation

3. Possible consequences of modelling underestimation of sunitinib, SU012662, and total active moieties exposures from a safety point of view should be discussed.

4. All the simulated exposure measures of sunitinib and SU012662 were done following 15mg/m2 daily oral administration of sunitinib, however the proposed dosage to be included in the SmPC is 20mg/m2 daily. Therefore the MAH is requested to perform the same simulation and the same comparison with the observed data also with 20mg/m2 daily dosage in order to directly compare the simulated exposure of the proposed dosage to be reported on the SmPC and the observed paediatric data.

5. An in depth discussion on the proposed dose reported in the SmPC is needed:

a) Population PK and PK-PD analysis (PMAR-EQDD-A618w-Other-366, *using pooled data from paediatric and adult patients*) conclusions: Based on the PK, safety, and efficacy trial simulation results, a starting dose of ~15 mg/m2/day appears to be inadequate; however, **a starting dose of ~25 mg/m2/day** is predicted to be more appropriate in pediatric patients with GIST and provides comparable plasma drug exposures, and subsequently safety, and efficacy to those in adult patients with GIST treated at 50 mg/day on Schedule 4/2. Although the starting dose of 15 mg/m2 was selected as the starting dose for the GIST pediatric study A6181196, based on the Phase 1 data from heavily pre-treated pediatric patients with CNS tumours (solid tumours), the option for intra-patient dose escalation to 22.5 mg/m2 and subsequently to 30 mg/m2 was allowed to ensure maximum plasma drug exposure for each individual patient;

b) Population PK analysis (PMAR-EQDD-A618b-DP4-846, *using data from paediatric patients*) conclusions: Based on the final PK model predictions, a sunitinib **dose of approximately 20 mg/m2/day** in paediatric patients with GIST aged 6-17 years would be expected to lead to similar total plasma exposures for sunitinib and SU012662 as compared to adult patients with GIST on 50 mg/day, on Schedule 4/2;

c) PBPK analysis conclusions: Based on the simulated exposures in different ages groups of paediatrics patients, the sunitinib dose that will lead to predicted steady-state total plasma

exposure over the dosing interval (i.e. steady-state AUC) similar to what has been observed in adults with GIST (1233 ng•hr/mL for sunitinib, 551 ng•hr/mL for SU012662, and 1822 ng•hr/mL for the total active moieties) at 50 mg once daily (QD) is 17 mg/m2, **20 mg/m2, and 24 mg/m2 for sunitinib**; 28 mg/m2, 27 mg/m2, and 26 mg/m2 for SU012662; 20 mg/m2, 22 mg/m2, and 25 mg/m2 for the total active moieties, respectively, for the age groups 2 to 5, **6 to 11, and 12 to 17 years old**.

d) In the Summary of Clinical Pharmacology Studies **25 mg/m2/day** and **20 mg/m2/day** are reported into two different sections as dose predicted to provide comparable sunitinib exposure to those in adult patients with GIST treated at 50 mg QD on schedule 4/2.

e) The MTD calculated in study ADVL0612 was lower compared to the doses reported above: MDT for pediatric patients without previous exposure to anthracyclines or cardiac irradiation was indeed established to be **15 mg/m2** schedule 4/2. Although the MAH noted that in some cases patients were able to escalate sunitinib dose (e.g. in study A6181196), there is a concern of safety with doses higher than the MTD. The MAH should take this data into account in its discussion.

Given all the above considerations, the indication of the dose appears confounding, therefore, further discussion and analyses are requested.

Clinical safety

6. Based on the data provided, several TEAEs of electrolyte disturbances (i.e., hypo/hypercalcemia, hypophosphatemia, hypo/hyperkaliemia, hyponatriemia, hypermagnesemia), also with high severity grade, have been reported across clinical trials with sunitinib in children (e.g. in Study A6181196: hypophosphatemia G3; in Study ADVL0612, G3 hyponatriemia, G3 hypophosphatemia, G3 hyperkaliemia; in study ACNS1021 hypocalcemia G4 and hyponatriemia G3). In various cases they are reported as related to sunitinib. It is noted that no electrolyte imbalances are reported as ADR of sunitinib in the SmPC section 4.8. The MAH should discuss this finding, and evaluate how to eventually reflect relevant information for paediatric patients in the SmPC.

User testing

7. The MAH has committed to provide the results of a new readability testing (requested by CHMP with EMA procedure EMEA/H/C/000687/II/0065) during the 1st RSI of this procedure.

11. Assessment of the responses to the 1st Request for Supplementary Information

11.1. Other concerns

Clinical aspects

Pharmacokinetic

Question 1

PMAREQDD-A618w-Other-366

It seems that paediatric data from study ADVL0612 have not been included in the PK-PD analysis, the MAH should clarify and provide the descriptive statistics for the subjects baseline characteristics and

covariates considered in building the population PK-PD model, if different compared to the population PK model.

Summary of the MAH's response

For the integrated population PK-PD analyses of safety endpoints in pediatric and adult patients with GIST and solid tumors, the data collected from Studies 248-ONC-0511-002, RTKC-0511-005, RTKC-0511-016, and RTKC-0511-018 in adult patients with solid tumors; Study ADVL0612 in pediatric patients with solid tumors; and Studies A6181004, A6181045, A6181047, and RTKC-0511-013 in adult patients with GIST were pooled. However, for the efficacy, only the studies in patients with GIST were included (PMAR-EQDD-A618w-Other-366 PKPD – Published Part A Section 3).

All the available safety data from Study ADVL0612 were included in the PK-PD analyses for safety endpoints. However, for efficacy, the PK-PD modeling for the Sum of the Longest Diameters (SLD) only included adult GIST data. This approach is consistent with the key binding elements included in Measure #3 of the approved Pediatric Investigational Plan (PIP) in which it was specified to only perform the PK-PD modeling using SLD data in adult patients with GIST. However, to further confirm the efficacy predictions in pediatric patients with GIST, the predictions were compared to the available literature efficacy data from Janeway et al and Agaram et al (PMAR-EQDD-A618w-Other-366 PKPD – Published Part A Section 6.4).

The descriptive statistics for the subject baseline characteristics and covariates considered in building the final PK-PD models for each PK-PD endpoint are provided in Table 1. Therefore, with the exception of Tumor Type effect for the efficacy endpoint SLD, all the covariates listed in Table 1 were examined in building the PK-PD models for safety and efficacy endpoints.

Table 1. The Summary Descriptive Statistics for Patients Baseline Characteristics and Covariates Considered in Building Safety and Efficacy PK-PD Model

PD Endpoint	No	AGE, Year Median (Range)	SEX (M/F)	RAC (Asian/Non-Asian)	TUM (GIST/Solid Tumors)	BEC (=0/>0)	BWT, Kg Median (Range)	BBSA, m^2 Median (Range)	Baseline PD Median (Range)	ADVL0612 Included (Y/N)
Safety Endpoints										
ALT (U/L)	502	55 (3-84)	306/196	57/438	368/134	223/267	70 (17.1-163.7)	1.81 (0.686-2.982)	20 (4-168)	Y
ANC (10^9/L)	466	56 (23-84)	290/176	54/408	367/99	213/252	71.15 (34.2-163.7)	1.817 (1.189-2.982)	4.543 (1.147-20.15)	N (NR)
AST (U/L)	469	56 (14-84)	290/179	54/411	368/101	216/252	71 (34.2-163.7)	1.817 (1.189-2.982)	23 (7-235)	Y
Diastolic BP (mmHg)	485	56 (4-84)	300/185	55/426	364/121	217/262	71 (21-163.7)	1.813 (0.791-2.982)	72 (20-102)	Y
Hgb (g/dL)	501	55 (3-84)	306/195	57/437	367/134	222/267	70 (17.1-163.7)	1.81 (0.686-2.982)	11.8 (7.8-18.5)	Y
LVEF (%)	339	56 (10-84)	214/125	52/285	276/63	149/187	72 (28.1-163.7)	1.835 (1.057-2.982)	63 (47-84)	Y
Lymph Count (10^9/L)	466	56 (23-84)	290/176	54/408	367/99	213/252	71.15 (34.2-163.7)	1.817 (1.189-2.982)	1.34 (0.13-12.7)	N (NR)
Platelet Count (10^9/L)	500	55 (3-84)	305/195	57/436	366/134	221/267	70.1 (17.1-163.7)	1.810 (0.686-2.982)	287 (87-939)	Y
Nausea	502	55 (3-84)	305/197	56/439	371/131	194/296	70.2 (17.1-163.7)	1.811 (0.686-2.982)	NA	Y
Vomiting	502	55 (3-84)	305/197	56/439	371/131	194/296	70.2 (17.1-163.7)	1.811 (0.686-2.982)	NA	Y
Hand-Foot Syndrome	502	55 (3-84)	305/197	56/439	371/131	194/296	70.2 (17.1-163.7)	1.811 (0.686-2.982)	NA	Y
Fatigue	502	55 (3-84)	305/197	56/439	371/131	194/296	70.2 (17.1-163.7)	1.811 (0.686-2.982)	NA	Y
Efficacy Endpoint										
Target Tumors SLD (cm)	364	56 (23-84)	232/132	48/312	0/364 (NT)	191/172	71.2 (38.5-140.2)	1.82 (1.281-2.570)	20.4 (3.1-82.20)	N

AGE=baseline age; Baseline PD=baseline value for the pharmacodynamic end point; BBSA=baseline body surface area; BEC=baseline performance status (0 for ECOG 0 or Karnofski Score >90, and 1 for ECOG ≥1 or Karnofski score ≤90); BWT=baseline total body weight; ECOG=Eastern Cooperative Oncology Group; GIST=gastrointestinal stromal tumor; N=No, NA= not applicable; NR=not available as part of Study ADVL0612, a Children Oncology Group (COG) investigator-initiated study, safety database, NT=not tested as a covariate since only data from GIST patients were included in building the PK-PD model for SLD; PD=pharmacodynamic; PK-PD=pharmacokinetic-pharmacodynamic; RAC=race (0 for Non-Asian and 1 for Asian); SEX=gender (0 for males and 1 for females); TUM=tumor type (0 for solid tumors and 1 for GIST), Y=yes.

Assessment of the MAH's response

The MAH has clarified the use of ADVL0612 study data for the PK/PD model: data from this study were included only for safety endpoints. The descriptive statistics for the subjects baseline characteristics from study ADVL0612 have not been provided, however it has been found in the study report body submitted for a previous variation application.

Conclusion

Issue resolved

Question 2

Considering the importance of the BSA values, the MAH is request to add a reference also to BSA values in the proposed text on SmPC.

Summary of the MAH's response

The reference to the BSA range of 1.1 to 1.87 m2 (PMAR-EQDD-A618b-DP4-846 Figures 25 and 26) has been now added to the SmPC Section 5.2 under Pediatric Population.

Following is reported the relative part of the SmPC, section 5.2, proposed as to be added:

Furthermore, based on an integrated population PK analysis of pooled data from the 3 paediatric studies (2 pediatric solid tumor studies and 1 pediatric GIST study; ages: 6 years to 11 years and 12 years to 17 years), baseline body surface area (BSA) was a significant covariate on apparent clearance of sunitinib and its active metabolite. Based on this analysis, a dose of approximately 20 mg/m2 daily ~~(BSA range: 1.10-1.87 m2)~~ in paediatric patients, with BSA values between 1.10 and 1.87 m^2, is expected to provide plasma exposures to sunitinib and its active metabolite comparable (between 75 and 125% of the AUC) to those in adults with GIST administered sunitinib 50 mg daily on Schedule 4/2 (AUC 1233 ng.hr/mL).

Assessment of the MAH's response

The MAH agrees with EMA recommendation, and the BSA value has been added to Section 5.2 of the SmPC, subsection "*Paediatric population*".

Conclusion

Issue solved, provided that the changes to the proposed text to be added in section 5.2 of the SmPC will be implemented.

Question 3

SimCYP Simulation

Possible consequences of modelling underestimation of sunitinib, SU012662, and total active moieties exposures from a safety point of view should be discussed.

Summary of the MAH's response

It is important to note that the determined pediatric dose of 20 mg/m2 was based on the integrated population PK analysis. This is a well-established methodology based on non-linear mixed-effects modeling (NONMEM) and it allowed the development of a parsimonious PK model that best fit/described the pediatric data in both solid tumors and GIST in order to derive the pediatric dose that achieves comparable systemic exposures to those in adults with GIST. Therefore, the observed potential underestimation of predicted concentrations of sunitinib, SU012662, and total drug by the SimCYP PBPK model would not be clinically relevant in relation to the determined dose of 20 mg/m2, which was based on the integrated population PK analysis.

Unlike the integrated population pharmacokinetic analysis approach which fit a PK model to the clinically observed data in pediatrics, the SimCYP PBPK model development strategy used a hybrid approach, the bottom up approach (ie, in vitro measured values) coupled with the top down approach (observed pharmacokinetics in adults), to extrapolate and predict the plasma exposures in pediatrics (SimCYP Report Section 3.1). As a result, a slight difference between the predicted exposures and the observed exposures in pediatrics would not be unexpected. Nevertheless, as requested by the CHMP, the MAH assessed whether this difference (ie, underestimation in this case) would alter the dose recommendation in the pediatrics, based on the SimCYP PBPK model.

Assuming an approximate 15% underestimation of SimCYP exposures (average total drug AUC24 underestimation, SimCYP Report Section 4), the revised projected doses based on SimCYP (ie, 19 mg/m2 for 6-11 years and 21 mg/m2 for 12-17 years instead of 22 mg/m2 for 6-11 years and 25 mg/m2 for 12-17 years) would be even closer to the dose of 20 mg/m2 (ie, within approximately 5% instead of 25%) and remain consistent with and confirming the dose determined by the integrated

population PK analysis (20 mg/m2). Therefore, in both scenarios, the dose projections by SimCYP approach support the 20 mg/m2 dose determined by the integrated population PK analysis.

Assessment of the MAH's response

Based on SimCYP, the revised projected dose, assuming an approximate 15% of SimCYP exposure, remains consistent with dose determined by the integrated population PK analysis (20 mg/m2).

Conclusion

Issue resolved

Question 4

SimCYP Simulation

All the simulated exposure measures of sunitinib and SU012662 were done following 15mg/m2 daily oral administration of sunitinib, however the proposed dosage to be included in the SmPC is 20mg/m2 daily. Therefore the MAH is requested to perform the same simulation and the same comparison with the observed data also with 20mg/m2 daily dosage in order to directly compare the simulated exposure of the proposed dosage to be reported on the SmPC and the observed paediatric data.

Summary of the MAH's response

Upon the request by the CHMP, the MAH conducted additional simulations with 20 mg/m2 daily dosage and compared to the observed pediatric data. As the observed pediatric data were at 15 mg/m2 daily dosage, the observed exposure parameters were dose corrected to 20 mg/m2 for comparison purpose. Table 4, Table 5, and Table 6 show clinically observed dose-corrected and SimCYP-predicted sunitinib and SU012662 pharmacokinetic parameter estimates in pediatrics in Study ADVL0612 (3-21 years old), Study ACNS1021 (3-19 years old), and Study A6181196 (13-16 years old) after a multiple 20-mg/m2 daily oral dose of sunitinib, respectively. Overall, the ratios of the predicted versus observed dose-corrected exposure values following trial simulations with the dose of 20 mg/m2 were essentially the same as the ones obtained with the dose of 15 mg/m2 (SimCYP Report Section 4), which is not unexpected considering the dose-linearity in the PK model.

Table 4. Clinically Observed Dose-Corrected and SimCYP-Predicted Sunitinib and SU012662 Pharmacokinetic Parameter Estimates in Pediatrics in Study ADVL0612 (3-21 Years Old) After a Multiple 20-mg/m^2 Daily Oral Dose of Sunitinib

		C_{max} (ng/mL)	AUC_{0-24} (ng•h/mL)	$C_{trough,ss}$c (ng/mL)
Sunitinib	Predicted	25.3	408	36.2
	Observedd	28.3	449	42
	Predicted/Observed Ratio	0.89	0.91	0.86
SU012662	Predicted	3.28	62.1	15.9
	Observedd	5.55	98	19.6
	Predicted/Observed Ratio	0.59	0.63	0.81
Sunitinib+SU012662	Predicted	28.58	470	52.1
	Observedd	33.33	548	61.6
	Predicted/Observed Ratio	0.86	0.86	0.85

AUC0-24=area under the concentration-time curve from time 0 to 24 hours; Cmax=maximum concentration; Ctrough=pre-dose plasma concentration during multiple dosing; Ctrough,ss=trough plasma concentration at steady state; SimCYP=physiologically-based pharmacokinetic modelling software.
c. Observed is Ctrough on Day 28.
d. Based on the mean of the Sprinkled Capsule and Intact Capsule.

Table 5. Clinically Observed Dose-Corrected and SimCYP-Predicted Sunitinib and SU012662 Pharmacokinetic Parameter Estimates in Pediatrics in Study ACNS1021 (3-19 Years Old) After a Multiple 20-mg/m^2 Daily Oral Dose of Sunitinib

		C_{max} (ng/mL)	AUC_{0-24} (ng•h/mL)	$C_{trough,ss}$b (ng/mL)
Sunitinib	Predicted	25.8	419	37.7
	Observed	27.9	499	48.9
	Predicted/Observed Ratio	0.92	0.84	0.77
SU012662	Predicted	3.2	60.8	16
	Observed	3.67	73	23.6
	Predicted/Observed Ratio	0.87	0.83	0.68
Sunitinib+SU012662	Predicted	29	480	53.7
	Observed	31.6	572	72.5
	Predicted/Observed Ratio	0.92	0.84	0.74

AUC0-24=area under the concentration-time curve from time 0 to 24 hours; Cmax=maximum observed plasma concentration; Ctrough=pre-dose plasma concentration during multiple dosing; Ctrough,ss=trough plasma concentration at steady state; SimCYP=physiologically-based pharmacokinetic modelling software.
b. Observed is Ctrough on Day 28.

Table 6. Clinically Observed Dose-Corrected and SimCYP-Predicted Sunitinib, SU012662 Pharmacokinetic Parameter Estimates in Pediatrics in Study A6181196 (13-16 Years Old) After a Multiple 20-mg/m^2 Daily Oral Dose of Sunitinib

		C_{max} (ng/mL)	AUC_{0-8} (ng•h/mL)	$C_{trough,ss}$b (ng/mL)
Sunitinib	Predicted	23.7	147	33.4
	Observed	24.5	110	38.8
	Predicted/Observed Ratio	0.97	1.34	0.86
SU012662	Predicted	3.17	14.3	15.4
	Observed	3.16	14	17.33
	Predicted/Observed Ratio	1	1.02	0.89
Sunitinib+SU012662	Predicted	26.87	161	48.8
	Observed	27.73	125	56.1
	Predicted/Observed Ratio	0.97	1.29	0.87

AUC0-8=area under the concentration-time curve from time 0 to 8 hours; Cmax=maximum observed plasma concentration; Ctrough=pre-dose plasma concentration during multiple dosing; Ctrough,ss=trough plasma concentration at steady state; SimCYP=physiologically-based pharmacokinetic modelling software.
b. Observed is Ctrough on Day 28.

Assessment of the MAH's response

The MAH performed the requested analysis. The ratios of the predicted versus observed dose-corrected exposure values following trial simulations with the dose of 20 mg/m2 were very closed to the ones obtained with the dose of 15 mg/m^2.

Conclusion

Issue resolved

Question 5

SimCYP Simulation

An in depth discussion on the proposed dose reported in the SmPC is needed:

a) *Population PK and PK-PD analysis (PMAR-EQDD-A618w-Other-366, using pooled data from paediatric and adult patients) conclusions: Based on the PK, safety, and efficacy trial simulation results, a starting dose of ~15 mg/m2/day appears to be inadequate; however, a starting dose of ~25 mg/m2/day is predicted to be more appropriate in pediatric patients with GIST and provides comparable plasma drug exposures, and subsequently safety, and efficacy to those in adult patients with GIST treated at 50 mg/day on Schedule 4/2. Although the starting dose of 15 mg/m2 was selected as the starting dose for the GIST pediatric study A6181196, based on the Phase 1 data from heavily pre-treated pediatric patients with CNS tumours (solid tumours), the option for intra-patient dose escalation to 22.5 mg/m2 and subsequently to 30 mg/m2 was allowed to ensure maximum plasma drug exposure for each individual patient;*

b) *Population PK analysis (PMAR-EQDD-A618b-DP4-846, using data from paediatric patients) conclusions: Based on the final PK model predictions, a sunitinib dose of approximately 20 mg/m2/day in paediatric patients with GIST aged 6-17 years would be expected to lead to similar total plasma exposures for sunitinib and SU012662 as compared to adult patients with GIST on 50 mg/day, on Schedule 4/2;*

c) *PBPK analysis conclusions: Based on the simulated exposures in different ages groups of paediatrics patients, the sunitinib dose that will lead to predicted steady-state total plasma exposure over the dosing interval (i.e. steady-state AUC) similar to what has been observed in adults with GIST (1233 ng•hr/mL for sunitinib, 551 ng•hr/mL for SU012662, and 1822 ng•hr/mL for the total active moieties) at 50 mg once daily (QD) is 17 mg/m2, 20 mg/m2, and 24 mg/m2 for sunitinib; 28 mg/m2, 27 mg/m2, and 26 mg/m2 for SU012662; 20 mg/m2, 22 mg/m2, and 25 mg/m2 for the total active moieties, respectively, for the age groups 2 to 5, 6 to 11, and 12 to 17 years old.*

d) *In the Summary of Clinical Pharmacology Studies 25 mg/m2/day and 20 mg/m2/day are reported into two different sections as dose predicted to provide comparable sunitinib exposure to those in adult patients with GIST treated at 50 mg QD on schedule 4/2.*

e) *The MTD calculated in study ADVL0612 was lower compared to the doses reported above: MDT for pediatric patients without previous exposure to anthracyclines or cardiac irradiation was indeed established to be 15 mg/m2 schedule 4/2. Although the MAH noted that in some cases patients were able to escalate sunitinib dose (e.g. in study A6181196), there is a concern of safety with doses higher than the MTD. The MAH should take this data into account in its discussion.*

Given all the above considerations, the indication of the dose appears confounding, therefore, further discussion and analyses are requested.

Summary of the MAH's response

The determination of the dose in pediatric patients with GIST, providing comparable exposures to those in adult patients with GIST at 50 mg on Schedule 4/2, were made using 3 different analyses and approaches.

a. As part of the population PK and PK-PD analysis (PMAR-EQDD-A618w-Other-366, using pooled data from paediatric and adult patients), only data from one pediatric study in patients with solid tumors were available to be included in the pooled dataset. The remaining data included adult data in patients with GIST and solid tumors. As part of the final population PK model for sunitinib and SU012662, Tumor Type (Solid Tumor vs GIST) was one of the variables identified as significant covariates on CL/F and subsequently was used in extrapolation of PK parameters in pediatric patients with GIST (PMAR-EQDD-A618w-Other-366 PKPD – Published Part A Sections 6.2.1 and 6.2.2). Based on the final PK model, sunitinib (and SU012662) extrapolated CL/F in pediatric patients with GIST was predicted to be higher than that in pediatric patients with solid tumors. Therefore, in the absence of PK data in pediatric patients with GIST at the time of the analysis, it was assumed that the higher CL/F observed in GIST vs Solid Tumors in adults was also applicable to that in pediatric patients [Note: this assumption was not later confirmed as part of the integrated population PK analysis (PMAR-EQDD-A618b-DP4-846)].

b. In contrast to the initial population PK analysis (ie, PMAR-EQDD-A618w-Other-366), the integrated population PK analysis (PMAR-EQDD-A618b-DP4-846, using data from only pediatric patients) was based on only pediatric PK data and included PK data in both GIST and solid tumor patients (2 pediatric solid tumor studies and 1 pediatric GIST study). Contrary to the initial analysis, which was mainly based on adult data, this analysis did not identify Tumor Type (GIST vs. Solid Tumor) as a significant covariate on CL/F. Based on this analysis, due to the lack of Tumor Type effect on CL/F in pediatric patients, the CL/F values estimated for pediatric GIST patients were comparable to that in Solid Tumor patients and mainly driven by differences in body surface area (PMAR EQDD-A618b-DP4-846 Section 6.2 and 6.3). Therefore, the difference in the dose projections based on the initial analysis and the integrated analysis (ie, 25 mg/m2 vs 20 mg/m2) could be in part due to the absence of Tumor Type effect (GIST vs Solid Tumor) on CL/F in pediatric patients.

c. In the PBPK analysis (SimCYP Report, using physiochemical properties, preclinical, and clinical adult data), the PK of sunitinib and its active metabolite was predicted/simulated based on a hybrid approach (bottom up and top down approaches) using both physiochemical properties and pre-clinical data (ie, bottom up) as well as adult clinical PK data (top down). Based on the SimCYP PBPK model, the PK predictions/simulations for pediatric patients appeared to be consistent with the observed data in both solid tumors and GIST patients with the geometric mean ratios of observed vs predicted for the majority of the PK parameters Cmax, AUC, and Ctrough falling within the 0.8 to 1.25 range. Similarly, the dose projections appeared to be within approximately 25% of the dose estimated by the integrated population PK analysis (ie, 20 mg/m2). Assuming an under-prediction of approximately 15% (Response to Question 3), the revised projected doses (ie, 19 mg/m2 for 6-11 years and 21 mg/m2 for 12-17 years) would be even closer (ie, within approximately 5%) to the dose estimated by the integrated pop PK analysis (ie, 20 mg/m2). Therefore, in both scenarios, the dose projections by SimCYP approach support the 20 mg/m2 dose determined by the integrated population PK analysis.

d. Considering that the integrated population PK analysis included data from 3 pediatric studies (instead of only 1) in both GIST and solid tumors patients (instead of only solid tumors), the dose projection in pediatric patients with GIST based on the integrated population PK analysis, instead of the initial analysis, was selected as the proposed dose in pediatric patients with GIST (please also refer to Responses to Questions 5a and 5b for further details). It is also important to note that in the absence of a Tumor Type effect on CL/F in pediatric patients (ie, CL/F in GIST being similar to CL/F in solid tumors), the approximated population CL/F value based on the initial analysis, for the integrated population PK analysis Solid Tumor/GIST patient population, appears to be comparable to the population CL/F value from the integrated population PK analysis (ie, 24.2 L/h vs 24.0 L/h for sunitinib and 10.9 L/h vs 11.1 L/h for SU012662), further confirming the inherent consistency in CL/F projections and consequently dose projections in pediatric patients with GIST/solid tumors between

both analyses.

e. Based on the dose escalation study in pediatric patients with solid tumors, the maximum tolerated dose was determined to be 15 mg/m2. The MTD projection was done in heavily pretreated pediatric patients with solid tumors and the majority of them with CNS tumors. In Study A6181196, although the starting dose was 15 mg/m2, it was escalated in 5/6 patients to 22.5 mg/m2 and in 2 out of 5 escalated further to 30 mg/m2. The average dose across the study was close to 20 mg/m2 (ie, 19.07 mg/m2; Study A6181196 CSR Section 12.1.1). In addition, based on the published case studies from Janeway et al and Rutkowski et al (Retrospective Analysis of Medical Records) in patients where the dose per body surface data were available, the median (minimum-maximum) dose (ie, starting or average daily dose) per body surface area was 28 (17-36) mg/m2. In the majority of the patients (ie, 12 out of 15 patients), the dose was higher than 20 mg/m2 and was tolerated well. Therefore, based on available safety data from Study A6181196 and published case reports, the starting or average daily doses of 20 mg/m2 should be well tolerated in pediatric patients with GIST.

Based on the above, the MAH would like to confirm that there are no confounding factors in determination of the projected dose in pediatric patients with GIST. The SmPC statement in regards to the dose of approximately 20 mg/m2 is in reference to the dose in pediatric patients expected to provide exposures similar to that obtained in adult patients with GIST, based on the integrated population PK analysis. In addition, based on available safety data from Study A6181196 and published case reports, the safety profile of the starting or average daily doses of 20 mg/m2 was manageable in pediatric patients with GIST. In conclusion, supportive evidence from 3 different analyses and from the available pediatric safety data in patients with GIST indicates that the 20 mg/m2 dose is a tolerable dose in children aging 6-17 years and provides similar drug plasma exposures compared to those in adult patients with GIST at 50 mg on Schedule 4/2.

Assessment of the MAH's response

The difference between the initial population PK analysis (pooled data from adult and paediatric patients) and the integrated population PK analysis (only paediatric data) is the inclusion of Tumor type as covariate on CL/F. In the first analysis it resulted to be significant, in the second one not. The integrated population PK analysis was selected as final analysis to be used to calculate the dose in pediatric patients expected to provide exposures similar to that obtained in adult patients with GIST at 50 mg on Schedule 4/2.

Regarding the MTD, which is reported in SmPC, this was defined to be 15 mg/m^2 on schedule 4/2 for the paediatric population (without risk factors for cardiac toxicity) based on the phase I dose-escalation study ADVL0612. As stated by the MAH in its response, the MTD projection in ADVL0612 study was done in heavily pretreated pediatric patients mainly with CNS tumors. In addition, the starting dose in both clinical trial A6181196 and ACNS1021 was 15 mg/m^2 (based on the MTD) with the option to escalate the dose based on toxicity: in A6181196 some patients were able to receive up to 30 mg/m^2 (data on how many patients escalated has not been found for ACNS1021 study). Further, the MAH noted that in the majority of the patients on the published case studies, the dose was higher than 20 mg/m^2. The information that children received starting or average daily doses of 20 mg/m^2 is not emerging from the SmPC, therefore it appears somewhat misleading to report that the MTD is 15 mg/m^2, and that 20 mg/m^2 is the dose in pediatric patients expected to provide exposures similar to that obtained in adult patients with GIST.

The MAH should propose wording in the appropriate sections of the SmPC to describe the dosages of

Sutent received by paediatric patients in the clinical setting (e.g. 15 mg/m2 as starting dose, use of increased doses etc.) in order to explain the apparent contradiction between MTD and wording on 20 mg/m^2 . **(OC)**

Conclusion

Issue partially solved

Clinical safety

Question 6

Based on the data provided, several TEAEs of electrolyte disturbances (i.e., hypo/hypercalcemia, hypophosphatemia, hypo/hyperkaliemia, hyponatriemia, hypermagnesemia), also with high severity grade, have been reported across clinical trials with sunitinib in children (e.g. in Study A6181196: hypophosphatemia G3; in Study ADVL0612, G3 hyponatriemia, G3 hypophosphatemia, G3 hyperkaliemia; in study ACNS1021 hypocalcemia G4 and hyponatriemia G3). In various cases they are reported as related to sunitinib. It is noted that no electrolyte imbalances are reported as ADR of sunitinib in the SmPC section 4.8. The MAH should discuss this finding, and evaluate how to eventually reflect relevant information for paediatric patients in the SmPC.

Summary of the MAH's response

Upon review of the TEAEs of electrolyte disturbances in paediatric studies, 9 out of the 70 patients reported 11 Grade 3 TEAEs [hypophosphatemia (4), hyperkalaemia (3), hyponatraemia (2), hypokalaemia (2)] with sunitinib in A6181196 and ADVL0612 studies. Most of these TEAEs were non-serious and resolved at the time of latest reported outcome. Of these 11 TEAEs, 6 TEAEs of electrolyte disturbances [G3 hypophosphatemia (4), G3 hyponatraemia (1), G3 hypokalemia (1)] were considered either possibly or probably related to sunitinib by the investigator. In 3/6, the TEAEs were serious and reported as resolved. On review of the case of serious G3 hyponatraemia (2007092810), the MAH considers hyponatraemia was confounded by the presence of a paraneoplastic syndrome of inappropriate antidiuretic hormone secretion (SIADH) secondary to progressive lung disease and was likely related to metastatic disease under study. Of note, this patient developed G3 hyponatraemia 10 days post sunitinib discontinuation. Upon review of serious TEAEs of G3 hypophosphatemia and G3 hypokalemia that were reported in a patient with refractory/recurrent neuroblastoma in the case 2007039720, the MAH considers that the patient's progressive underlying disease Central Nervous System (CNS) pathology may have contributed to the occurrence of these events.

In study ACNS1021, no TEAEs of electrolyte disturbances were reported. Three patients reported laboratory abnormalities of G4 hypocalcaemia (2) based on total calcium levels. Ionized calcium was not reported and these were not reported as TEAEs. One patient had a laboratory abnormality of G3 hypokalemia which was not reported as TEAE. Please note, there was no laboratory abnormality of G3 hyponatraemia. Overall, since most of the patients with TEAEs of electrolyte disturbances had highly progressive CNS tumors, it is suggested that the underlying disease may have contributed to the development of these laboratory abnormalities. The TEAEs of electrolyte disturbance reported in these studies were manageable and well-tolerated in this patient population. Thus, the MAH proposes that the currently proposed text in the updated SmPC appropriately represents the safety information regarding TEAEs of electrolyte disturbances from these studies.

Assessment of the MAH's response

The MAH reviewed the TEAEs of electrolyte disturbances occurred in paediatric studies, reporting that

9/70 (13%) patients reported 11 Grade 3 TEAEs [hypophosphatemia (4), hyperkalaemia (3), hyponatraemia (2), hypokalaemia (2)]; 6/11 were considered probably or possibly related to sunitinib, and 3/6 of them were serious and resolved. The three SAEs (hypophosphatemia, hypokalaemia, hyponatraemia) were considered confounded by advanced primary tumor and paraneoplastic syndrome (SIADH). In study ACNS1021, the 3 episodes of electrolyte disturbances reported (G4 hypocalcemia (2 episodes) and G3 hypokaliemia (1 event)) were reported on laboratory values and not as TEAE, and no further information regarding possible relationship with study drug as evaluated by investigator are available.

It is noted that SmPC 4.8 section includes the information that, for A6181196, Grade 3 adverse drug reactions reported were hypophosphatemia, (neutropenia and thrombocytopenia) in 1 patient each (16.7%). Based on the MAH's review of the grade ≥3 electrolyte disturbances described, no further information is considered needed in the SmPC.

Conclusion

Issue solved

12. 2nd Request for supplementary information

12.1. Other concerns

Clinical aspects

1. The MAH should propose wording in the appropriate sections of the SmPC to describe the dosages of Sutent received by paediatric patients in the clinical trials/case series (e.g. 15 mg/m2 as starting dose, use of increased doses etc.) in order to explain the apparent contradiction between MTD (15 mg/m2) and wording on 20 mg/m2.

User testing

2. Q6 (Please name three very common side effects that may occur with Sutent) has a long list of answers that could increase the possibility of a positive results. Moreover, it is not clear how the answer is scored in case the participant listed only one or two side effects. This aspect should be clarified.
3. Q9 (What should a breast-feeding woman consider before she starts taking Sutent?) has two possible answers (She should tell her doctor. She should not breast-feed during treatment with Sutent. Optional: If she is breast-feeding, she should ask her doctor or pharmacist for advice before taking this medicine). The first answer represents the focus since breast-feeding woman should clearly understand that breast-feeding must be stopped before she starts treatment with Sutent. Since it is not possible to check the answers due to the lack of a detailed summary of individual responses, it should be clarified if a positive outcome was registered in case only the optional answer was given.
4. Regarding questions for which a "difficulty" or "very difficulty" score in finding the information was reported, a clarification is needed, since there is a discrepancy between data reported in table 14 and those reported in tables 8 and 9.
5. Q4 (Suppose you are treated for GIST (Gastrointestinal stromal tumour). What is the usual dose?) registered the "very difficult finding" score. The wording used in the PL section 3 is: "Your doctor will prescribe a dose that is right for you, depending on the type of cancer to be treated. If you are being treated for GIST or MRCC, the usual dose is 50 mg once daily taken for 28 days (4 weeks), followed by 14 days (2 weeks) of rest (no medicine), in 6-week cycles. If you are being treated for pNET, the usual dose is 37.5 mg once daily without a rest period".
6. In order to better identify the information regarding the dose indicated for each tumor type in the PL, a bulleted list could be used to distinguish the two possible dose regimens.

13. Assessment of the responses to the 2nd Request for Supplementary Information

13.1 Other concerns

Clinical aspects

Question 1

The MAH should propose wording in the appropriate sections of the SmPC to describe the dosages of Sutent received by paediatric patients in the clinical trials/case series (e.g. 15 mg/m2 as starting dose, use of increased doses etc.) in order to explain the apparent contradiction between MTD (15 mg/m2) and wording on 20 mg/m2.

Summary of the MAH's response

The MAH agrees with the Rapporteur's recommendation and Section 5.2 of the SmPC has been updated to read as follows (text in "tracked changes" mode):

Pharmacokinetic properties:

Furthermore, based on an integrated population PK analysis of pooled data from the 3 paediatric studies (2 paediatric solid tumor studies and 1 paediatric GIST study; ages: 6 years to 11 years and 12 years to 17 years), baseline body surface area (BSA) was a significant covariate on apparent clearance of sunitinib and its active metabolite. Based on this analysis, a dose of approximately 20 mg/m^2 daily ~~(BSA range: 1.10-1.87 m2)~~ in paediatric patients, with BSA values between 1.10 and 1.87 m^2, is expected to provide plasma exposures to sunitinib and its active metabolite comparable (between 75 and 125% of the AUC) to those in adults with GIST administered sunitinib 50 mg daily on Schedule 4/2 (AUC 1233 ng.hr/mL).

In paediatric studies, the starting dose of sunitinib was 15 mg/m^2, which in paediatric patients with GIST increased to 22.5 mg/m^2 and subsequently to 30 mg/m^2 (not to exceed the total dose of 50 mg/day) based on individual patient safety/tolerability. Furthermore, according to the published literatures in paediatric patients with GIST, the calculated starting dose ranged from 16.6 mg/m^2 to 36 mg/m^2, increased to doses as high as 40.4 mg/m^2 (not exceeding the total dose of 50 mg/day).

Assessment of the MAH's response

The MAH modified the SmPC as per CHMP request. The wording is considered overall acceptable for this section, although a minor rewording to specify that the starting dose of 15 mg/m2 was based on the identified MDT is suggested, as follow (additional words highlighted in yellow):

Section 4.8

In **these** paediatric patients without previous exposure to anthracyclines or cardiac irradiation, the maximum tolerated dose (MTD) has been identified (see section 5.1).

Section 5.2

In paediatric studies, the starting dose of sunitinib was 15 mg/m^2 ***(based on the MTD identified in the Phase 1 dose-escalation study, see section 5.1),*** *which in paediatric patients with GIST increased to 22.5 mg/m^2 and subsequently to 30 mg/m^2(not to exceed the total dose of 50 mg/day) based on individual patient safety/tolerability. Furthermore, according to the published literatures in paediatric patients with GIST, the calculated starting dose ranged from 16.6 mg/m^2 to 36 mg/m^2, increased to doses as high as 40.4 mg/m^2 (not exceeding the total dose of 50 mg/day).*

Conclusion

Issue solved, provided the rewording of sections 4.8 and 5.2 as suggested.

User Testing

Question 2

User testing Q6 (Please name three very common side effects that may occur with Sutent) has a long list of answers that could increase the possibility of a positive results. Moreover, it is not clear how the

answer is scored in case the participant listed only one or two side effects. This aspect should be clarified.

Summary of the MAH's response

In the case only 1 or 2 side effects are listed, the question is repeated and rated "*sufficiently understood*" or "*not understood*" depending on the answer.

Finding scores are not affected as the participant found the sought paragraph. Usually, if a participant found the information but gives an incomplete answer, he/she misunderstood the question.

Assessment of the MAH's response

The MAH's response can be considered acceptable, however, as a general rule, in order to better assess the results of UT, it is preferable that a detailed summary of individual responses is submitted.

Conclusion

Issue solved

Question 3

User testing Q9 (What should a breast-feeding woman consider before she starts taking Sutent?) has two possible answers (She should tell her doctor. She should not breast-feed during treatment with Sutent. Optional: If she is breast-feeding, she should ask her doctor or pharmacist for advice before taking this medicine). The first answer represents the focus since breast feeding woman should clearly understand that breast feeding must be stopped before she starts treatment with Sutent.

Since it is not possible to check the answers due to the lack of a detailed summary of individual responses, it should be clarified if a positive outcome was registered in case only the optional answer was given.

Summary of the MAH's response

If, after repetition of the question, only the optional answer is given, the question is rated *"not found/not understood".*

Optional answer is an information for the interviewer, so that the interviewer knows that if a participant additionally gives the optional answer, the answer must not be rated as incorrect.

Assessment of the MAH's response

See comment on question 2.

Conclusion

Issue solved

Question 4

Regarding questions for which a "difficulty" or "very difficulty" score in finding the information was reported, a clarification is needed, since there is a discrepancy between data reported in table 14 and those reported in tables 8 and 9.

Summary of the MAH's response

Table 14 of the user testing report shows the detailed ease of finding results, independent of participants comments. In tables 8 and 9 individual questions are only listed if the participants provide a comment, independently of the finding or comprehension score.

Assessment of the MAH's response
Issue solved

Question 5

Q4 (Suppose you are treated for GIST (Gastrointestinal stromal tumour). What is the usual dose?) registered the "very difficult finding" score. The wording used in the PL section 3 is: "Your doctor will prescribe a dose that is right for you, depending on the type of cancer to be treated. If you are being treated for GIST or MRCC, the usual dose is 50 mg once daily taken for 28 days (4 weeks), followed by 14 days (2 weeks) of rest (no medicine), in 6-week cycles. If you are being treated for pNET, the usual dose is 37.5 mg once daily without a rest period".

In order to better identify the information regarding the dose indicated for each tumor type in the PL, a bulleted list could be used to distinguish the two possible dose regimens.

Summary of the MAH's response

The MAH has updated the Package Leaflet accordingly.

Assessment of the MAH's response
Issue solved

Additional changes to the SmPC made by the MAH

As per Rapporteur's comment, Section 5.1 of the SmPC has been updated to include the efficacy data related to Study A6181196. In addition, the sentence related to the publications has been rephrased to avoid duplication of the text (changes highlighted in "track changes mode"):

"Evidence from a Phase 1/2 study of oral sunitinib conducted in 6 paediatric patients with GIST aged 13 years to 16 years who received sunitinib on Schedule 4/2, at doses ranging between 15 mg/m^2 daily and 30 mg/m^2 daily, and available published data (20 paediatric or young adult patients with GIST) indicated that sunitinib treatment resulted in disease stabilization in 18 of 26 (69.2%) patients, either after imatinib failure or intolerance (16 patients with stable disease out of 21), or de novo/after surgery (2 patients with stable disease out of 5). In ***~~this~~ the*** *Phase 1/2 study,* ***stable disease and disease progression was observed in 3 out of 6 patients each (1 patient received new adjuvant and 1 patient received adjuvant imatinib, respectively). In the same study,*** *4 out of 6 patients (66.7%) experienced grade 3-4* ***treatment-related adverse events (****Grade 3 hypophosphatemia, neutropenia, and thrombocytopenia in 1 patient each and a Grade 4 neutropenia was reported in 1 patient).*

In addition, the publications reported the following Grade 3 adverse drug reactions experienced by 5 patients: fatigue (2), gastrointestinal adverse drug reactions (including diarrhoea) (2), haematologic adverse drug reactions (including anaemia) (2), cholecystitis (1), hyperthyroidism (1), and mucositis (1)."

The MAH would like also to inform that in Section 4.8 and Section 5.1 the text was corrected as some events are not adverse drug reactions but treatment related treatment emergent adverse events.

Assessment of the MAH's response

The MAH's proposal is accepted.

☐ 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