Office of Hematology & Oncology Products
Combined Clinical and Clinical Pharmacology Review
Pediatric Exclusivity Request and Changes in Pediatric Labeling

NDA:	21938
Supplement number:	36
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Product:	Sunitinib (Sutent)
Sponsor:	Pfizer
Reviewers:	Michael Brave, (clinical) Huiming Xia (clinical pharmacology) Junshan Qiu (pharmacometrics)
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Executive Summary

This supplemental New Drug Application provides for the addition of pediatric information from a Phase 1 trial ADVL0612, a Phase 2 trial ACNS1021, and an integrated population pharmacokinetics (PK) and pharmacodynamics (PD) analysis into Section 8.4 of the Package Insert. The Applicant is not seeking an indication in the pediatric population, as the efficacy, safety, and clinical pharmacology of sunitinib in children do not support a favorable benefit/risk profile. Because these data are the results of a commitment by the Applicant to study sunitinib in the pediatric population as agreed in a final pediatric written request (PWR), the Applicant requests that the Agency consider the information provided as the basis for granting additional marketing exclusivity, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act.

This review finds that the Applicant has met all the requirements of the Written Request. This was discussed at the Pediatric Exclusivity Board and was found to be acceptable. This review recommends that descriptions of the Phase 1 and Phase 2 trials and the integrated population PK and PK/PD analysis be added to Section 8.4 of the Package Insert, as shown in italics below.

8.4 Pediatric Use

The safety and effectiveness of SUTENT in pediatric patients have not been established. *Safety and pharmacokinetics of sunitinib were assess in an open-label study (NCT00387920) in 29 pediatric patients with refractory solid tumors who were 2 years* (b) (4) *. In addition, efficacy, safety and pharmacokinetics of sunitinib was assessed in another open-label study (NCT01462695) in 27 pediatric patients with high-grade glioma or ependymoma* (b) (4) *The maximum tolerated dose (MTD) normalized for body surface area (BSA) was lower in pediatric patients compared to adults. Sunitinib was poorly tolerated in*

pediatric patients. The occurrence of dose-limiting cardiotoxicity prompted an amendment of the NCT00387920 study to exclude patients with previous exposure to anthracyclines or cardiac radiation. No responses were reported in patients in either of the trials.

Apparent clearance and volume of distribution normalized for BSA for sunitinib and its active major metabolite were lower in pediatrics as compared to adults.

The effect on open tibial growth plates in pediatric patients who received SUTENT has not been adequately studied. See Juvenile Animal Toxicity Data below.

Juvenile Animal Toxicity Data

Physeal dysplasia was observed in cynomolgus monkeys with open growth plates treated for ≥3 months (3 month dosing 2, 6, 12 mg/kg/day; 8 cycles of dosing 0.3, 1.5, 6.0 mg/kg/day) with sunitinib at doses that were >0.4 times the RDD based on systemic exposure (AUC). In developing rats treated continuously for 3 months (1.5, 5.0, and 15.0 mg/kg) or 5 cycles (0.3, 1.5, and 6.0 mg/kg/day), bone abnormalities consisted of thickening of the epiphyseal cartilage of the femur and an increase of fracture of the tibia at doses ≥5 mg/kg (approximately 10 times the RDD based on AUC). Additionally, caries of the teeth were observed in rats at >5 mg/kg. The incidence and severity of physeal dysplasia were dose related and were reversible upon cessation of treatment; however, findings in the teeth were not. A no-effect level was not observed in monkeys treated continuously for 3 months, but was 1.5 mg/kg/day when treated intermittently for 8 cycles. In rats the no-effect level in bones was ≤2 mg/kg/day.

A new section, 'Section 2.6 Dose Modification for End-Stage Renal Disease (ESRD) Patients on Hemodialysis' was created to reflect the dose adjustment recommendation for ESRD paitents on hemodialysis, which was originally located in Section 8.7 Renal Impairment. Furthermore, editorial changes have been made to update the labeling language in Section 8.6 Hepatic Impariment, Section 8.7 Renal Impariment, Section 12.2 Pharmacodynamics, and Section 12.3 Pharmacokinetics.

Clinical Review

Background

On 18 April 2011, the Applicant and the FDA agreed on the requirements for a pediatric written request (PWR) for sunitinib. Two clinical studies were required as a result of the agreed PWR:

- ADVL0612 (NCT00387920): A phase 1 study of sunitinib in 35 patients 3-21 years of age with refractory solid tumors.

- ACNS1021 (NCT01462695): A phase 2 study of sunitinib in 25 patients 3-20 years of age with recurrent, refractory or progressive high-grade glioma and ependymoma tumors.

Key primary endpoints were to be safety and dose-finding in the Phase 1 trial, and response rates in the Phase 2 trial. In addition, data from both studies were to be combined and analyzed using non-linear mixed-effect modeling to explore exposure-response relationships for measures of safety and effectiveness. Reports of both studies were to be submitted to the FDA by January 1, 2019 to possibly qualify for pediatric exclusivity under Section 505A of the Federal Food, Drug, and Cosmetic Act.

Both clinical studies were sponsored by the National Cancer Institute (NCI) and conducted by the Children's Oncology Group (COG). The format and content of this sNDA were discussed with the Agency at a pre-NDA meeting on 6 March 2015. This sNDA contains data in Modules 1, 2, and 5. No nonclinical or chemistry, manufacturing and controls updates are required for this sNDA.

Issues Regarding Data Integrity and Submission Quality

On September 25, 2018, COG informed Pfizer that the COG database used in these studies:

- Did not track database corrections in a 21CRF Part 11 compliant manner; and
- Did not have an Investigator acknowledgement page.

Changes were documented on the COG database on an Excel spreadsheet. Each change was clearly identified, but the reason for the change and the previous value was unknown. The Applicant submitted case report forms (CRFs) for patients for whom narratives were required by the FDA from Study ACNS 1021. In the PDF images provided to FDA, two sets of images are present per patient because two separate databases were used. One database was managed by the COG that held CRF data and one was managed by Pfizer that contained dosing diary data. Following a request by the Agency, the Applicant submitted COG CRFs for Study ADVL0612. The Audit Trial within the Pfizer-managed CRFs clearly identified the changes to and addition of laboratory addresses. The Audit Trail within the COG-managed CRFs clearly identified each change, but not the reason for the change or the previous value/datum.

Pfizer also stated that COG sent queries to the sites by e-mail and that information on the queries or the reason for these queries is not available.

No sites were audited by Pfizer.

For the Phase 1 trial, all adverse events (AEs) were reported on the CRFs. For the Phase 2 trial, only Adverse Event Expedited Reporting System-reportable events were included on the CRFs. These reportable events include Grade 1-5 events requiring at least 24 hours hospitalization and Grade 3-5 events regardless of hospitalization.

While these irregularities are of concern, the Applicant is not seeking a pediatric indication. Further, these issues have been identified in previous applications containing data from cooperative groups, including applications in which an indication is sought. A decision was made to rely on the safety and efficacy data provided in the COG CRFs.

Sources of Clinical Data

The application was submitted electronically, and consists of draft labeling changes, complete clinical study reports, and supporting datasets, and literature references.

Trial ADVL0612

ADVL0612 was a Phase 1 study of sunitinib of patients 2 to 21 years of age with refractory solid tumors for which there was no therapy proven to prolong survival with an acceptable quality of life. The trial enrolled 35 patients who had adequate renal (GFR ≥ 70 ml/min/1.73 m^2 or met a pre-defined serum creatinine level based on age/gender) and hepatic function (total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, SGPT (ALT) ≤ 110 U/L, and serum albumin ≥ 2 g/dL). Among the 35 patients, 29 were ages 2 to <17 years.

Sunitinib was administered once daily (QD) for 4 weeks followed by 2 weeks off (administered orally as intact capsule or as capsule content sprinkled over applesauce or yogurt).

The primary objective was to determine the maximum tolerated dose (MTD), recommend a Phase 2 dose of sunitinib, and characterize the sunitinib pharmacokinetics (PK) in children with refractory solid tumors. Dose-limiting toxicity (DLT) was defined as Grade 4 hematological toxicity or Grade 3 non-hematological toxicity with certain exceptions.

In adults, sunitinib is administered as 50 mg orally daily for 4 weeks with a 2-week rest or 37.5 mg orally daily. The 50 mg dose in adults corresponds to ~ 30 mg/m^2. For Parts A and B, the dose was rounded to the nearest 12.5 mg and for Part C, the dose was rounded to the nearest 6.25 mg.

Part A of the study enrolled and treated 12 patients. The first 6 patients were treated with sunitinib 20 mg/m^2 (dose level 1). All had received at least 2 chemotherapy regimens. Three DLTs were seen and included:

- Grade 2 systolic dysfunction in a patient who received prior doxorubicin 150 mg/m^2 and had a decrease in ejection fraction from 61% to 43%;
- Grade 4 neutrophil count on Day 29 which resolved on Day 52; and
- Grade 3 fatigue, decreased weight/appetite, dehydration, and electrolyte abnormalities and Grade 2 hypotension and hypothyroidism.

The dose was deescalated, and 6 patients were treated with sunitinib 15 mg/m^2 (dose level -1). All had received at least 1 chemotherapy regimen and 4 had also received radiation therapy. Three DLTs were seen and included:

- Grade 3 heart failure and Grade 2 acute coronary syndrome and left ventricular dysfunction in a patient who had received doxorubicin 367 mg/m^2 and 16.2 Gy to the lungs as well as radiation to the rib and spine;
- Grade 3 elevation in ALT; and
- Grade 3 hyponatremia.

The protocol was amended to exclude patients with previous anthracycline or cardiac radiation exposure.

Part B treated 11 patients. The first 8 patients received sunitinib 15 mg/m^2. Prior therapy included: none (N=3), radiation (N=4), and chemotherapy or chemotherapy + radiation (N=4). Two of these patients had DLTs:

- Grade 3 kidney stones, bilaterally in a patient with ganglioma and a minimally elevated uric acid level; and
- Grade 4 neutropenia and Grade 2 QT prolongation

Tthe dose was escalated and 3 patients received sunitinib 20 mg/m^2. One patient had received chemotherapy, one radiation, and the remaining patient had received multiple prior therapies. Two of the 3 patients had DLT including:

- Grade 4 hyperuricemia (associated Grade 2 diarrhea, Grade 1 dehydration); and
- Grade 4 intracranial hemorrhage, Grade 4 vagus nerve disorder, and Grade 5 aspiration in a patient with an underlying pontine glioma.

The MTD of sunitinib in children without prior cardiac radiation or anthracycline exposure was determined to be 15 mg/m^2 QD for 28 days followed by 14 days off, as compared to the MTD of 30 mg/m^2 QD for 28 days followed by 14 days off in adults.

Part C treated 12 patients with sunitinib 15 mg/m^2. Prior therapy included: chemotherapy and radiation (N=8), chemotherapy (N=2), and radiation (N=2). Part C provided further information on the AE profile of sunitinib 15 mg/m^2 and examined the pharmacokinetics of intact capsules and opened sunitinib capsules sprinkled on applesauce or yogurt (N = 3).

Dose-limiting toxicities in 12 patients included:

- Grade 4 intracranial hemorrhage and hypoxia in a patient with gliobastoma multiforme
- Grade 3 palmar-plantar erythrodysesthesia
- Grade 3 back pain and dizziness in a patient with glioblastoma multiforme

Toxicities after Cycle 1 which met the criteria for DLT included: Grade 3 pneumotosis intestinalis (considered unrelated), Grade 3 alkaline phosphatase (related), and Grade 3 proteinuria (related).

The tables below provide an overview of all adverse events on this trial. In the Phase 1 trial, 3 patients were agen 2-5, 11 age 6-11, and 21 age 12-21 years. A total of 12 treated patients in Part A reported 197 all causality AEs, 11 treated patients in Part B reported 129 all causality AEs, and 12 treated patients in Part C reported 244 all causality AEs. One patient in the sunitinib 20 mg/m^2 group of Part B experienced a Grade 5 AE ((b) (6) (underlying pontine glioma) experienced Grade 5 aspiration following an intracranial hemorrhage which the investigator assessed as possibly treatment related).

Table 1. Treatment-Emergent Adverse Events

	Part A			Part B			Part C	Total
	15 mg/m^2	**20 mg/m^2**	**Total**	**15 mg/m^2**	**20 mg/m^2**	**Total**	**15 mg/m^2**	
Patients (n)	6	6	12	8	3	11	12	23
AEs (n)	109	88	197	88	41	129	244	326
Patients with AEs (n, %)	6 (100.0)	6 (100.0)	12 (100.0)	8 (100.0)	3 (100.0)	11 (100.0)	12 (100.0)	23 (100.0)
Patients with Gr 3-4 AEs (n, %)	5 (83.3)	5 (83.3)	10 (83.3)	4 (50.0)	3 (100.0)	7 (63.6)	11 (91.7)	17 (73.9)
Patients with Gr 5 AEs (n, %)	0	0	0	0	1 (33.3)	1 (9.1)	4 (33.3)	1 (4.3)

Table 2. Treatment-Emergent AEs Reported by >3 Patients

	All Grades	Grade 3-5
Part A – Sunitinib 15 mg/m^2 (n = 6)		
Any	6 (100%)	5 (83.3%)
Platelet count decreased	5 (83.3%)	0
Hypercalcemia	4 (66.7%)	0
Lymphocyte count decreased	4 (66.7%)	3 (50.0%)
White blood cell count decreased	4 (66.7%)	0
Part A – Sunitinib 20 mg/m^2 (n = 6)		
Any	6 (100%)	5 (83.3%)
AST increased	5 (83.3%)	0
Neutrophil count decreased	5 (83.3%)	4 (66.7%)
White blood cell count decreased	5 (83.3%)	3 (50.0%
Platelet count decreased	4 (66.7%)	0
Part B – Sunitinib 15 mg/m^2 (n = 8)		
Any	8 (100%)	4 (50.0%)
Hypophosphatemia	4 (50.0%)	1 (12.5%)
Neutrophil count decreased	4 (50.0%)	2 (25.0%)
Vomiting	4 (50.0%)	1 (12.5%)
Part B – Sunitinib 20 mg/m^2 (n = 3)		
Any*	3 (100%)	3 (100%)
Part C – Sunitinib 15 mg/m^2 (n = 12)		
Any	12 (100%)	11 (91.7%)
Fatigue	8 (66.7%)	2 (16.7%)
ALT increased	6 (50%)	0
Anemia	6 (50%)	1 (8.3%)

	All Grades	Grade 3-5
Hypermagnasemia	6 (50%)	0
Lymphocyte count decreased	6 (50%)	2 (16.7%)
Neutrophil count decreased	6 (50%)	2 (16.7%)
White blood cell count decreased	6 (50%)	0
Hypercalcemia	5 (41.7%)	0
Hypertension	5 (41.7%)	0
Abdominal pain	4 (33.3%)	1 (8.3%)
Ataxia	4 (33.3%)	3 (25.0%)
Death	4 (33.3%)	4 (33.3%)
Dizziness	4 (33.3%)	1 (8.3%)
Headache	4 (33.3%)	0
Hyperglycemia	4 (33.3%)	1 (8.3%)
Hypocalcemia	4 (33.3%)	0
Hypokalemia	4 (33.3%)	0
Nausea	4 (33.3%)	1 (8.3%)
Platelet count decreased	4 (33.3%)	0
Vomiting	4 (33.3%)	0

* No individual AE was reported by >2 patients in this part

Reviewer's comment: The BSA normalized recommended Phase 2 dose is lower in children than adults (15 vs. 30 mg/m^2 QD). Two potential reasons are: 1) decreased clearance of sunitinib in children; and 2) poor tolerability due to extensive prior treatment. The exposure following a 20 mg/m^2 dose in children achieved comparable exposure (

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Table 3) as a 50 mg dose (corresponding to approximately 30 mg/m^2) in adults (

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Table 4). However, the clinical results suggested that the sunitinib 20 mg/m^2 dose is not tolerable in children. Among the 9 patients who received sunitinib 20 mg/m^2, 7 had received at least two chemotherapy regimens. This may have contributed to the poor tolerance in children.

The most common adverse reaction in adults were seen in the pediatric population but were not included in the table above since they did not occur in more than 3 patients within each part of the trial. In general, the adverse event profile in children was similar to adults. Given the small patient numbers and the use of prior cardiotoxic therapy, it is difficult to determine whether administration of sunitinib resulted in increased cardiotoxicity in children. The incidence of heart failure is 3% in adults.

Plasma levels of sunitinib and its active metabolite SU012662 were evaluated on Day 1 of Cycle 1 prior to administration and at 1, 2, 4, 6, 8-10 hours after the Day 1 dose. In patients > 10 kg, plasma levels of sunitinib were also obtained 24-28 and 48-52 hours after the Day 1 dose. The tables below provide the PK parameters of sunitinib in children at dose of 20 mg/m^2 (

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Table 3), at dose of 15 mg/m^2 (Table 7) and adults (

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Table 4).

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Table 3. Summary of Sunitinib, SU012662 and Total Drug PK Parameters Following Sunitinib Oral Doses of 20 mg/m² as Intact Capsule in Children

PK Parameter	Study Part A (Intact Capsule) Mean (CV%) [Median] n	Study Part B (Intact Capsule) Mean (CV%) [Median] n
Sunitinib		
t_{max} (hr)	8.0 (8.0–8.0) 1a	NA
C_{max} (ng/mL)	26.3 (NA) [26.3] 1	NA
AUC_{24} (ng·hr/mL)	432 (NA) [432] 1	NA
AUC_{48} (ng·hr/mL)	665 (NA) [665] 1	NA
C_{trough} D7 (ng/mL)	35.7 (33) [34.1] 6	45.2 (24) [46.9] 3
C_{trough} D14 (ng/mL)	34.6 (35) [29.7] 6	43.4 (38) [43.4] 2
C_{trough} D21 (ng/mL)	38.9 (34) [37.4] 6	35.9 (43) [35.9] 2
C_{trough} D28 (ng/mL)	46.4 (47) [41.8] 6	47.3 (NA) [47.3] 1
SU012662		
t_{max} (hr)	8.0 (8.0–8.0) 1a	NA
C_{max} (ng/mL)	5.25 (NA) [5.25] 1	NA
AUC_{24} (ng·hr/mL)	103 (NA) [103] 1	NA
AUC_{48} (ng·hr/mL)	201 (NA) [201] 1	NA
C_{trough} D7 (ng/mL)	15.9 (49) [13.6] 6	16.6 (47) [14.5] 3
C_{trough} D14 (ng/mL)	17.0 (46) [13.6] 6	23.7 (64) [23.7] 2
C_{trough} D21 (ng/mL)	19.0 (61) [14.4] 6	23.9 (46) [23.9] 2
C_{trough} D28 (ng/mL)	25.2 (75) [16.8] 6	21.9 (NA) [21.9] 1
Total Drug		
t_{max} (hr)	8.0 (8.0–8.0) 1a	NA
C_{max} (ng/mL)	31.6 (NA) [31.6] 1	NA
AUC_{24} (ng·hr/mL)	537 (NA) [537] 1	NA
AUC_{48} (ng·hr/mL)	869 (NA) [869] 1	NA
C_{trough} D7 (ng/mL)	51.6 (35) [47.8] 6	61.8 (25) [69.6] 3
C_{trough} D14 (ng/mL)	51.7 (37) [45.1] 6	67.0 (47) [67.0] 2
C_{trough} D21 (ng/mL)	57.8 (41) [49.3] 6	59.8 (44) [59.8] 2
C_{trough} D28 (ng/mL)	71.6 (55) [64.0] 6	69.2 (NA) [69.2] 1

Table 4. Summary of PK Parameters in Adult patients with Solid Tumor

Pharmacokinetic Parameters	Arithmetic Mean (CV %) [Median]			
	Schedule 2/2		Schedule 4/2	
	50 mg daily	75 mg daily	25 mg daily	50 mg daily
Cycle 1, Day 1	n=15	n=5	n=3	n=15
C_{max} (ng/mL)	23.7 (35) [23.9]	39.7 (35) [33.6]	11.2 (40) [12.6]	28.9 (36) [28.2]
DN-C_{max} (ng/mL)	23.7 (35) [23.9]	26.5 (35) [22.4]	22.5 (40) [25.2]	28.9 (36) [28.2]
AUC_{0-24} (ng*hr/mL)	385 (38) [401]	612 (25) [573]	186 (37) [218]	430 (35) [417]
DN-AUC_{0-24} (ng*hr/mL)	385 (38) [401]	408 (25) [382]	372 (37) [436]	430 (35) [417]
T_{max} (hr) [a]	6.0 (3.0, 12.0)	6.0 (3.0, 12.0)	10.0 (6.2, 12.0)	5.1 (2.9, 8.3)
Cycle 1, Day 14	n=14	n=5	n=2 [b]	n=15
C_{max} (ng/mL)	92.5 (57) [86.1]	138 (32) [144]	24.3, 31.0	90.2 (41) [86.9]
DN-C_{max} (ng/mL)	92.5 (57) [86.1]	91.9 (32) [96.0]	48.6, 62.0	90.2 (41) [86.9]
AUC_{0-24} (ng*hr/mL)	1706 (52) [1462]	2734 (33) [2875]	500, 673	1697 (42) [1745]
DN-AUC_{0-24} (ng*hr/mL)	1706 (52) [1462]	1823 (33) [1916]	999, 1346	1697 (42) [1745]
C_{trough} (ng/mL)	65.4 (58) [53]	117 (43) [122]	14.0, 25.3	59.6 (51) [58.9]
CL/F (L/hr)	37.9 (58) [34.2]	30.3 (36) [26.1]	37.2, 50.0	36.7 (57) [28.7]
T_{max} (hr) [a]	6.1 (2.0, 20.0)	8.0 (0.0, 24.0)	4.1, 5.9	6.1 (4.1, 12.3)
Cycle 1, Day 28	N/A	N/A	n=3	n=10
C_{max} (ng/mL)	N/A	N/A	46.9 (60) [33]	82.4 (34) [87.5]
DN-C_{max} (ng/mL)	N/A	N/A	93.9 (60) [66]	82.4 (34) [87.5]
AUC_{0-24} (ng*hr/mL)	N/A	N/A	943 (59) [697]	1425 (34) [1588]
DN-AUC_{0-24} (ng*hr/mL)	N/A	N/A	1887 (59) [1394]	1425 (34) [1588]
C_{trough} (ng/mL)	N/A	N/A	36.5 (44) [31.7]	55.7 (40) [59.0]
CL/F (L/hr)	N/A	N/A	32.4 (47) [35.9]	40.7 (49) [31.5]
T_{max} (hr) [a]	N/A	N/A	3.0 (3.0, 12.0)	5.4 (0.0, 10.2)

Source: CSR of Study RTKC-0511-005, Table 7, page 78.

The BSA-normalized CL/F median values were lower by 21% for sunitinib and 30% for SU012662 in pediatric patients as compared to adult patients (Table 5 and Table 6). Correspondingly, a lower dose is needed in pediatric patients than adults to achieve similar plasma exposures. Based on the BSA-normalized CL/F values, doses of approximately 21 mg/m^2 (ie, 26.6*22.6/28.8) and 19 mg/m^2 (ie, 26.6*10.9/15.5) in pediatric patients would provide the same level of total plasma exposures of sunitinib and SU012662 as those in adults at the 50 mg dose (ie, 50 mg/1.88 m^2 = 26.6 mg/m^2). As a result, a sunitinib dose of approximately 20 mg/m^2 would be expected to provide the comparable exposures as that in adults at the 50 mg dose.

Table 5. Median (Min-Max) Values for BSA-normalized Sunitinib PK Parameters for Pediatric and Adult Patients

Parameters	Pediatrics	Adults
N	59	275
BSA, m^2	1.47 (0.66-2.14)	1.88 (0.818-2.96)
CL/F (L/hr)	22.4 (8.30-64.9)	36.1 (13.5-129)
BSA-normalized CL/F[a] (L/hr)	22.6 (14.5-51.9)	28.8 (9.50-111)
Vc/F (L)	995 (331-2578)	2169 (588-6928)
BSA-normalized Vc/F[b] (L)	1063 (699-1745)	1549 (354-13965)

a. Calculated as Population PK predicted individual CL/F (L/hr)/ (1+0.557*(Individual BSA-1.47))
b. Calculated as Population PK predicted individual Vc/F (L)/((Individual BSA/1.47) $^{1.47}$)

Table 6 Median (Min-Max) Values for BSA-normalized SU012662 PK Parameters in Pediatric and Adults Patients

Parameters	Pediatrics	Adults
N	59	275
BSA, m^2	1.47 (0.66-2.14)	1.88 (0.818-2.96)
CL/F (L/hr)	10.4 (2.27-43.5)	19.0 (6.82-103)
BSA-normalized CL/F[a] (L/hr)	10.9 (3.58-34.8)	15.5 (5.84-67.5)
Vc/F (L)	902 (180-2963)	2709 (548-15685)
BSA-normalized Vc/F[b] (L)	1014 (388-2885)	1806 (414-23428)

a. Calculated as Population PK predicted individual CL/F (L/hr)/ ((Individual BSA/1.47)$^{0.843}$)
b. Calculated as Population PK predicted individual Vc/F (L)/((Individual BSA/1.47) $^{1.72}$)

Note: the BSA normalization equations were adopted from population PK final model equations (Population PK report PMAR-EQDD-A618f-DP4-893). Source: 'Response to the information request' SDN 1344, 3/4/2019.

The PK of sunitinib capsules sprinkled on applesauce or yogurt (N=12) was similar to that of the intact capsule (N=23) (Table 7). Both sunitinib and its active metabolite SU012662 reached steady state concentrations by Day 14 of Cycle 1.

Reviewer's note: Three out of 12 pediatirc patients who received the sunitinib capsule contents sprinkled on applesauce or yogurt switched to the intact capsule. Therefore, trough samples collected from these 3 patients after formulation switch were excluded from the Part C only summary descriptive statistics representing the sprinkled capsule content formulation.

Table 7. 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 (Parts A & B) and 15 mg/m^2 as Sprinkled Capsule Content on Applesauce or Yogurt (Part C)

PK Parameter	Sprinkled Capsule Study Part C 15 mg/m^2 Mean (CV%) [Median] n	Intact Capsule Study Parts A and B Combined 15 and 20 mg/m^2 Mean (CV%) [Median] n	Geometric Mean Ratio Part C vs. Parts A & B
Sunitinib			
t_{max} (hr)	4.0 (4.0–8.0) 12a	8.0 (2.0–48.0) 9a	NA
C_{max} (ng/mL)	21.5 (35) [23.6] 12	21.8 (57) [17.2] 9	1.01
AUC_{24} (ng·hr/mL)	355 (37) [357] 12	334 (43) [275] 9	1.06
AUC_{48} (ng·hr/mL)	547 (37) [572] 12	556 (33) [552] 9	0.96
C_{trough} D7 (ng/mL)	28.3 (41) [30.8] 10	31.2 (36) [33.2] 23	0.88
C_{trough} D14 (ng/mL)	33.6 (41) [30.7] 9	33.0 (46) [28.3] 20	1.03
C_{trough} D21 (ng/mL)	31.1 (45) [30.0] 6	31.5 (46) [33.5] 19	1.03
C_{trough} D28 (ng/mL)	34.1 (56) [27.9] 4	38.4 (51) [31.8] 15	0.91
SU012662			
t_{max} (hr)	6.0 (4.0–24.0) 11a·b	8.0 (4.0–48.0) 9a	NA
C_{max} (ng/mL)	4.81 (73) [3.80] 12b	3.70 (57) [2.92] 9	1.30c
AUC_{24} (ng·hr/mL)	88.3 (66) [74.3] 12b	60.5 (60)[43.3] 9	1.46c
AUC_{48} (ng·hr/mL)	162 (58) [152] 12b	124 (54) [84.8] 9	1.31c
C_{trough} D7 (ng/mL)	11.6 (44) [11.3] 10	12.6 (38) [10.9] 23	0.88
C_{trough} D14 (ng/mL)	16.0 (76) [12.7] 9	16.0 (49) [13.4] 20	0.91
C_{trough} D21 (ng/mL)	14.0 (31) [14.4] 6	16.8 (54) [14.5] 19	0.91
C_{trough} D28 (ng/mL)	14.3 (52) [14.0] 4	18.6 (50) [14.4] 15	0.75
Total Drug			
t_{max} (hr)	4.0 (4.0–8.0) 12a	8.0 (2.0–48.0) 9a	NA
C_{max} (ng/mL)	25.8 (37) [27.4] 12	25.4 (55) [21.2] 9	1.03
AUC_{24} (ng·hr/mL)	444 (37) [473] 12	395 (44) [314] 9	1.11
AUC_{48} (ng·hr/mL)	711 (36) [745] 12	680 (35) [714] 9	1.03
C_{trough} D7 (ng/mL)	39.9 (41) [42.3] 10	43.8 (32) [41.7] 23	0.87
C_{trough} D14 (ng/mL)	49.6 (48) [43.4] 9	49.0 (42) [40.7] 20	0.99
C_{trough} D21 (ng/mL)	45.1 (39) [44.4] 6	48.2 (44) [46.3] 19	0.98
C_{trough} D28 (ng/mL)	48.4 (54) [41.9] 4	57.1 (46) [55.6] 15	0.84

Source: CSR of Study ADVL0612, Table 16, Page 77.

No PK and PD modeling and simulations were performed in this study. The results of exploratory correlation analyses suggested moderate to strong correlation between exposure (sunitinib, SU012662, or total Drug Day 28 C_{trough} values) and known pharmacological targets in children (including soluble, circulating endothelial cells-related, or circulating endothelial progenitor-related biomarkers).

No patient achieved a complete response (CR) or partial response (PR). Stable disease was observed in 1 (8.3%), 3 (27.3%), and 2 (16.7%) patients in Part A, Part B, and Part C of the study, respectively.

Trial ACNS1021

ACNS1021 was a Phase 2 study in patients 3-20 years of age with recurrent, refractory or progressive high-grade gliomas or ependymomas. All patients received sunitinib 15 mg/m^2 QD for 4 weeks followed by 2 weeks off. The primary objective was to estimate the objective response rate (ORR), confirmed 8 weeks after the initial response assessment by central review. Predose plasma levels of sunitinib and its active metabolite SU012662 were obtained on Days 1, 7, 14, and 28 of Cycle 1 and Days 1 and 28 of Cycle 2. Optional postdose PK profiles for sunitinib and SU012662 were

obtained on Day 1 of Cycle 1 prior to drug administration and at 2, 4, 6-8, and 24 hours post Day 1 dose from a selected number of pediatric patients from both gliomas or ependymomas groups.

A total of 29 evaluable patients were enrolled: 16 with glioma and 13 with ependymoma. Among the 29 patients, 27 were ages 2 to < 17 years with 3 patients age 2-5, 10 age 6-11, and 16 age 12-21. The enrolled patients have adequate renal (GFR ≥ 70 ml/min/1.73 m^2 or meet pre-defined serum creatinine level based on age/gender) and hepatic functions (total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, both SGOT (AST) and SGPT (ALT) ≤ 2.5 x ULN for age). The most frequent prior therapies were chemotherapy multi-agent systemic (7 patients [43.8%] and 7 patients [53.8%] in the glioma group and ependymoma group, respectively) and radiotherapy NOS (10 patients [62.5%] and 4 patients [30.8%] in the glioma group and ependymoma group, respectively).

Pharmacokinetic samples were collected from 24 patients who received intact capsule out of total 29 enrolled patients. The single- and the multiple- dose plasma exposures to sunitinib and its active metabolite appeared to be comparable between the glioma group as compared to the ependymoma group (Table 8). Plasma levels of both sunitinib and its active metabolite SU012662 appears to be reached steady state by Day 14. The steady state exposure of sunitinib and its active metabolite appears to be slightly higher than those in the Phase 1 Study ADVL0612 (Table 7).

Table 8. 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

The observed higher C_{max} after single-dose and AUC_{0-24} as well as the steady state C_{trough} in children with solid tumors appear to be higher by 78%-80% for sunitinib and 80%-98% for SU012662 (

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Table 4), indicating potentially lower CL/F per BSA in children as compared to adults. This observation was consistent with the BSA-normalized CL/F and Vc/F comparison and correlative analyses suggesting a lower volume of distribution and a shorter half-life in children from Phase 1 PK study ADVL0612.

The mean plasma vascular endothelial growth factor (VEGF) level did not significantly change from Day 1 to Day 14. There was a 20% decrease in mean VEGF receptor 2 levels from Day 1 to Day 14 and Day 28.

No patient achieved a CR or PR. Four patients, 2 with glioma and 2 with ependymoma, had stable disease.

The table below provides an overview of AEs in patients participating in ACNS1021. There were 5 deaths due to disease progression during the treatment period. The datasets do not record whether an AE led to permanent discontinuation. Overall, 22 (75.9%) of 29 patients developed treatment-emergent adverse events. Frequently reported AEs were neutropnil count decreased (6 [21%]) and, in 3 patients each (10.3%), hemorrhage intracranial, hydrocephalus, neoplasm progression, and seizure.

Table 9. Treatment Emergent AEs in ACNS1021 – Safety Population

	High-Grade Glioma (n = 16)	**Ependymoma (n = 13)**	**Total (n = 29)**
Number of AEs	31	20	51
Patients with AEs	13 (81.3%)	9 (69.2%)	22 (75.9%)
Patients with SAEs	10 (62.5%)	3 (23.1%)	13 (44.8%)
Patients with Grade 3-4 AEs	11 (68.8%)	7 (53.8%)	18 (62.1%)
Patients with Grade 5 AEs	5 (31.3%)	0	5 (17.2%)

Table 10. Treatment-Emergent AEs Reported by ≥2 Patients in ACNS1021 - Safety Population

	All Grades	**Grade 3-5**
High-Grade Glioma (n = 16)		
Any	13 (81.3%)	12 (75.0%)
Neoplasm progression	3 (18.8%)	3 (18.8%)
Seizure	3 (18.8%)	3 (18.8%)
Fatigue	2 (12.5%)	1 (6.3%)
Hemorrhage intracranial	2 (12.5%)	1 (6.3%)
Headache	2 (12.5%)	1 (6.3%)
Hydrocephalus	2 (12.5%)	2 (12.5%)
Ependymoma (n = 13)		
Any	9 (69.2%)	7 (53.8%)
Neutrophil count decreased	5 (35.8%)	5 (38.5%)
Paresthesia	2 (15.4%)	1 (7.7%)

Reviewer's comment: The AE profile in this trial is dominated by events related to the patient's underlying CNS malignancy. The safety profile of sunitinib in children at 15 mg/m^2 appeared generally consistent with its known safety profile of 50 mg (~ 30 mg/m^2) in adults.

Population PK-PD analysis

PMAR-EQDD-A618f-DP4-893 was a population PK-PD analysis of pooled PK and PD data from ADVL0612 and ACNS1021. Based on the prior knowledge and modeling experience with sunitinib, a 2-compartment model with first-order absorption (nonlinear mixed effects modeling [NONMEM] subroutine ADVAN4) with lag time was used as the initial model to fit to sunitinib and SU012662 concentrations. Covariate Model Building process starts by including a group of pre-defined potential covariates based on prior experience. These covariates were tested for significance in a stepwise manner to obtain the full model which was then subjected to a backward elimination step.

In the PK-PD analyses, transit compartments in series with feedback loop model and the indirect response model was used to explore the exposure-response relationship between sunitinib concentration and safety endpoints such as absolute neutrophil count, platelet count, lymphocyte count, ALT and AST. Relationships between the average daily plasma exposures up to time of worst common terminology criteria for adverse events (CTCAE v4) and the incidence rate were explored for categorical safety endpoints such as hand foot syndrome, fatigue, and others.

These analyses concluded:

- The PK of sunitinib and SU012662 in pediatric patients with solid tumors were adequately characterized using a 2-compartment PK model with first order absorption and lag time.
- Using a stepwise covariate selection procedure, the effect of BSA on CL/F and Vc/F was significant ($p \leq 0.001$) for sunitinib and SU012662. The effect of adding other covariates (age, race, baseline ECOG performance status, or sex) on CL/F or Vc/F was not significant ($p > 0.001$).

The WR required collection of data concerning known or suspected toxicities of sunitinib in adults. Analyses of each of these toxicities are provided below.

Thyroid Dysfunction

The WR asked the Applicant to monitor for thyroid dysfunction. In the Phase 1 trial, thyroid stimulating hormone (TSH) was to be obtained at baseline and Day 28 of odd-numbered cycles. In the Phase 2 trial, TSH was to be obtained at baseline, the end of Week 6, and on Day 1 of even-numbered cycles.

In the Phase 1 trial, Grade 1-2 hypothryoidism was reported in 5 and Grade 1 hyperthyroidism in 2 patients. On treatment, TSH values and the normal range were available for 15 patients. Two had TSH > 10 times the upper limit of normal (ULN). The normal range was not available for an additional patient who appeared to have a TSH > 10xULN. Among the 3 patients with TSH > 10x ULN, 2 were reported to be hypothyroid. Among the 2 patients reported to be hyperthyroid, 1 had a TSH > 10xULN and the other had normal TSH levels throughout the trial.

In the Phase 2 trial, there were no reports of AEs associated with thyroid dysfunction (see above concerning reportable AEs). On treatment, the TSH value and normal range were available for 14 patients. One patient had a TSH 3-10xULN. No patients had a TSH below the lower limit of normal (LLN).

Reviewer's Comments: Hypothyroidism was reported in 16% of adults with renal cancer. This appears to be similar to the incidence in pediatric patients.

Cardiac Dysfunction

The WR asked the Applicant to monitor electrocardiograms (EKG) and echocardiograms/ MUGAs. In the Phase 1 trial, EKGs and echocardiograms were to be obtained at baseline and on Day 28 of Cycles 1 and 2. In the Phase 2 trial, EKGs were to be obtained at baseline, between Weeks 4 and 6 of Cycles 1 and 2, and then every 3 cycles, if previous EKGs were normal. Echocardiograms were not obtained on the Phase 2 trial. The Applicant provided only baseline EKGs and echocardiograms.

Many of the cardiac AEs in the Phase 1 trial are outlined in the discussion of DLT. In the Phase 1 trial, 7 patients had a cardiac AE including: heart failure/left ventricular dysfuntion (N=3), QT prolongation (N=3), acute coronary syndrome (N=1), sinus tachycardia (N=4), and sinus bradycardia (N=1). There is 1 report of Grade 1 asystole which is said to be ongoing in a patient with sinus bradycardia. On treatment, 4 patients had an on-treatment ejection fraction (EF) (N=1) or shortening fraction (SF) (N=3) less than the LLN. The decrease in EF was Grade 2. One of the 3 patients had a decrease in SF > 10 % compared to baseline. One of these 4 had a follow up value which was above the LLN. Among the 3 patients with reports of heart failure/left ventricular dysfunction, all had a decrease in EF/SF to below the LLN and below baseline. None of the patients had a Grade 2-4 QTc prolongation.

In the Phase 2 trial, there were no reports of cardiac AEs. Only baseline EKGs and echocardiogram results were provided. These are not helpful in the assessment of the effect of sunitinib.

***Reviewer's Comment**: In adults, heart failure has been reported in 3% of patients receiving sunitinib. In an adjuvant trial in renal cancer in adults, the number of patients with a Grade 2 decrease in EF was identical in the sunitinib and placebo arms. In this Phase 1 trial in pediatric patients, 3/35 (8.6%) patients had a report of heart failure or left ventricular systolic dysfunction while 4/35 (11.4%) had a decrease in EF or SF. Given the small number of patients and the use of prior anthracyclines and radiation in the pediatric patients, the incidences cannot be directly compared.* (b) (4)

concerning cardiovascular events included in the package insert notes that patients with a cardiac event within the previous 12 months have been excluded from studies of sunitinib and that patients with prior anthracycle use or cardiac radiation have been excluded from some studies.

Bone Growth

The WR asked the Applicant to monitor the effect of sunitinib on growing bones. In the Phase 1 trial, X-rays of the tibial growth plate were required at baseline and, if open, on Day 28 of odd-numbered cycles. In the Phase 2 trial, X-rays of the tibial growth plate were required at baseline and, if open, on Day 1 of even-numbered cycles.

In the Phase 1 trial, on-treatment X-rays of the tibial growth plate were provided for two patients. The first patient showed no change over 9 cycles following by fusion of the growth plates consistent with the patient's age. The second patient had radiographs showing possible early widening, but the radiologist also commented that this may be an oblique view.

In the Phase 2 study, no information was provided on X-rays of the tibial growth plate.

Reviewer's Comment*: The information collected is insufficient to make a determination concerning the effect of sunitinib on bone growth.* (b) (4)

Blood Pressure

The WR asked the Applicant to monitor the effect of sunitinib on blood pressure (BP). In the Phase 1 trial, Grade 1-2 hypertension was reported in 10 patients. In the Phase 2 trial, there were no reports of on-treatment hypertension (see information on reportable AE collection above). In pediatric patients, the CTCAE v4 defines Grade 3 hypertension as systolic $\geq$ 160 or diastolic $\geq$ 100 and Grade 4 as hypertensive crisis. No patients on the Phase 1 trial met Grade 3 or 4 criteria. For the Phase 2 trial, no datasets containing the blood pressure measurements were provided.

Reviewer's Comment*: In the Phase 1 trial, sunitinib did not appear to be associated with the development of Grade 3-4 hypertension.*

Written Request Items and their Adequacy

Written Request Items	***Information Submitted/Sponsor's Response***
Types of studies/Study Design: Phase 1 study: Single-arm, dose-finding and pharmacokinetic study of oral sunitinib in pediatric patients with refractory solid tumors Phase 2 study: Single-arm study to assess safety and tolerability, pharmacokinetic profile, cumulative toxicities, response rate and progression-free survival when sunitinib is administered over multiple courses to pediatric and young adult patients with central nervous	 Phase 1 study: ADVL0612 is entitled, A Phase 1 Study of Sunitinib (SU11248), an Oral Multi-Targeted Tyrosine Kinase Inhibitor, in Children with Refractory Solid Tumors Phase 2 study: ACNS1021 is entitled, A Phase II Study of Sunitinib in Recurrent, Refractory or Progressive High-Grade Glioma and Ependymoma Tumors in Pediatric and Young Adult Patients.

Written Request Items	Information Submitted/Sponsor's Response
system tumors.	
Reviewer's Comment: *The applicant's study designs fulfill this requirement.*	
Indication(s) to be studied: Phase 1 study: refractory solid tumors	**Indication(s) studied:** Phase 1 study: Key inclusion criteria included • Age: ≥ 2 years and < 21 years at the time of study entry. • Diagnosis: Histologic verification of solid malignancy at original diagnosis except in patients with intrinsic brain stem tumors or optic pathway gliomas. Patients with recurrent or refractory solid tumors were eligible, including primary CNS tumors or patients with known CNS metastases. In patients with primary CNS tumors or known CNS metastases, there must have been no evidence of intracranial hemorrhage on magnetic resonance imaging (MRI), including gradient echo sequences. • Disease status: Patients had either measurable or evaluable disease. • Therapeutic options: Patient's current disease state must have been one for which there was no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.
Phase 2 study: central nervous system tumors • Stratum A: Recurrent/progressive/ refractory malignant high-grade glioma (i.e., anaplastic astrocytoma, glioblastoma multiforme [e.g., giant cell and gliosarcoma types], anaplastic oligodendroglioma, anaplastic oligoastrocytoma, or anaplastic ganglioglioma) within the brain, with or without spinal cord disease. • Stratum B: recurrent or progressive ependymoma (including ependymoma variants) within the brain with or without spinal cord disease.	Phase 2 study: Key inclusion criteria included • Age: ≥ 18 months and < 22 years at the time of enrollment. • Diagnosis: Patients must have been diagnosed with ependymoma or high grade glioma (World Health Organization Grade III/IV): o Stratum A: Recurrent/progressive/ refractory malignant glioma (i.e., anaplastic astrocytoma, glioblastoma multiforme [including giant cell and gliosarcoma types], anaplastic oligodendroglioma, anaplastic oligoastrocytoma or anaplastic ganglioglioma) within the brain with or without spinal cord disease. o Stratum B: Recurrent/progressive/ refractory ependymoma (including ependymoma variants) within the

Written Request Items	*Information Submitted/Sponsor's Response*
	brain with or without spinal cord disease (patients with diffuse intrinsic pontine glioma were not eligible). • A histological diagnosis from either the initial presentation or at the time of recurrence was required. Patients had to have radiographically documented measurable disease in the brain, defined as at least 1 lesion that could be accurately measured in at least 2 planes.
Reviewer's Comment: *The applicant's eligibility criteria fulfill this requirement.*	
Age group and population in which study will be performed: Both studies were to be conducted in children (2 to 5 years and 6 to 11 years) and adolescents and young adults (12 to 21 years).	ADVL0612 enrolled patients 3 –21 years of age. ACNS1021 enrolled patients 3 –20 years of age.
Reviewer's Comment*: The eligibility criteria and patient ages fulfill this requirement.*	
Number of patients to be studied or power of study to be achieved: Phase 1 Study: Thirty-five evaluable patients will be enrolled. Descriptive statistics will be used. Phase 2 Study • Stratum A (recurrent or progressive high-grade gliomas): Using a Simon's minimax design, 16 patients will be accrued in the first stage, and if ≥ 2 patients among the first 16 patients have a response, then the stratum will be open to Stage 2 and accrual will continue until 25 evaluable patients have been treated • Stratum B (refractory, recurrent, or progressive ependymomas): Using a Simon's minimax design, 13 patients will be accrued in the first stage, and if ≥ 1 patient among the first 13 patients has a response, then the stratum will be open to Stage 2 and accrual will continue until 20 evaluable patients have been treated	Phase 1 Study: A total of 35 patients were enrolled. Phase 2 Study: A total of 29 evaluable patients (16 in Stratum A [Stage 1] and 13 in Stratum B [Stage 1]) were enrolled,
Reviewer's Comment: *The number of patients treated on each study fulfills this requirement.*	
Entry criteria:	

Written Request Items	***Information Submitted/Sponsor's Response***
Phase 1 study: refractory solid tumors	The Phase 1 study enrolled 35 patients, including 16 males and 19 females, age 2 to 21 years, with a variety of refractory solid tumors for which there was no known curative therapy or therapy proven to prolong survival with an acceptable quality of life. Patients had either measurable or evaluable disease
Phase 2 study: central nervous system tumors • Stratum B Recurrent/progressive/refractory malignant high-grade glioma (i.e., anaplastic astrocytoma, glioblastoma multiforme [e.g., giant cell and gliosarcoma types], anaplastic oligodendroglioma, anaplastic oligoastrocytoma, or anaplastic ganglioglioma) within the brain, with or without spinal cord disease • Stratum B recurrent or progressive ependymoma (including ependymoma variants) within the brain with or without spinal cord disease	The phase 2 study enrolled 29 patients, including 18 males and 11 females, age 2 to 17 years. Patients in Stratum A had anaplastic astrocytoma, glioblastoma multiforme, or anaplatic oligodendroglioma, and patients in Stratum B had ependymoma. A histological diagnosis from either the initial presentation or at the time of recurrence was required. Patients had to have radiographically documented measurable disease in the brain, defined as at least 1 lesion that could be accurately measured in at least 2 planes.
Reviewer's Comments; *The patients enrolled fulfilled the eligibility criteria.*	
Clinical endpoints: Phase 1 Study: Safety and tolerability, dose-finding (maximum tolerated dose and recommended phase 2 dose), pharmacokinetics, and antitumor effects of oral sunitinib.	Phase 1 study: Summaries and descriptive analyses and listings are provided for: • Dose Limiting Toxicities • Treatment-Emergent, All Causality Adverse Events • Treatment-Emergent, Treatment-Related Adverse Events • Serious Adverse Events • Deaths • Laboratory Values • Vital signs including blood pressure, electrocardiogram, and physical findings During Part A of the study, a total of 12 patients were enrolled and treated (6 patients were treated with sunitinib 20 mg/m^2; the dose was then deescalated, and 6 patients were treated with sunitinib 15 mg/m^2). After observing cardiac related dose limiting toxicity in Part A of the study, the protocol was amended to exclude patients with previous

Written Request Items	*Information Submitted/Sponsor's Response*
	anthracycline or cardiac radiation exposure. Based on Part B of the study, the MTD and the recommended Phase 2 dose for sunitinib in children without previous cardiac radiation or anthracycline exposure was 15 mg/m^2 QD for 28 days followed by 14 days off treatment. Plasma levels of sunitinib and its main active metabolite (SU012662) were measured at baseline and during treatment. The CSR provides an overview of the PK parameters determined.
Phase 2 Study: Objective response rate (partial response or complete response > 8 weeks), safety and tolerability, pharmacokinetic profile, cumulative toxicities when administered over multiple courses to pediatric and young adult patients, and progression-free survival. For phase 1 and phase 2 studies, relevant pharmacokinetic endpoints must be derived. An approach such as optimal sparse sampling in all patients with rich sampling in a sub-group is recommended. Such data must then be appropriately analyzed using validated methods such as nonlinear mixed effects modeling.	Phase 2 study: • No patient achieved a CR or PR. A total of 4 patients, 2 each in the glioma and ependymoma groups, had stable disease. • Median PFS was 2.3 months (95% CI: 0.8, 2.8) in the glioma group and 2.7 months (95% CI: 1.2, 2.9) in the ependymoma group. • No new safety signals were identified with sunitinib use in this patient population. The safety profile of sunitinib in children was consistent with the known safety profile in adults and adverse events were c in cally manageable. Summaries, descriptive analysis, and listings are provided for: o Treatment-Emergent, All Causality Adverse Events o Treatment-Emergent, Treatment-Related Adverse Events o Serious Adverse Events o Deaths o Laboratory Values • The CSR provides an overview of the PK parameters determined in the study
Data from the Phase 1 and Phase 2 studies must be combined to develop pharmacokinetic and pharmacodynamic (PK-PD) models to explore exposure-response relationships for measures of safety and effectiveness.	A Population PK-PD analysis of pooled data from Studies ADVL0612 and ACNS1021 concluded: • The PK of sunitinib and SU012662 in pediatric patients with solid tumors were wel characterized using two-compartment PK models with first order absorption and lag time. • Following stepwise covariate selection

Written Request Items	*Information Submitted/Sponsor's Response*
	procedures, the effect of BSA on CL/F and Vc/F was selected (p≤0.001) for sunitinib and SU012662; and the effect of addition of other covariates (i.e., age, race, performance status, or sex) on CL/F or Vc/F was not selected (p>0.001). • There was a higher probability of AEs with higher average plasma sunitinib concentrations. • The PK-PD relationship for different safety endpoints was mainly driven by sunitinib plasma exposures and was not affected by body size or other baseline covariates. • Due to lack of efficacy, the FDA indicated that the sponsor did not need to conduct a PK/PD analysis for efficacy (see meeting minutes dated March 17, 2015).
Reviewer's Comment: *The studies collected sufficient information concerning the activity, safety, and pharmacokinetics of sunitinib in children to fulfill this requirement. Grade 1-5 adverse events should have been collected on the Phase 2 trial.*	
Timing of assessments: if appropriate Not applicable	**Timing of assessments:** Not applicable
Drug specific safety concerns: The most common sunitinib-related adverse reactions (≥20%) are fatigue, asthenia, diarrhea, nausea, mucositis/stomatitis, vomiting, dyspepsia, abdominal pain, constipation, hypertension, rash, hand-foot syndrome, skin discoloration, altered taste, anorexia and bleeding. In addition, the following less common, but potentially serious, risks are noteworthy: Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid pregnancy, cardiovascular risks (decreased left ventricular ejection fraction, prolonged QT intervals and Torsade de Pointes, hypertension), hemorrhagic events, hepatic dysfunction/hepatic failure, thyroid dysfunction, and adrenal hemorrhage. Rare (<1%) reports exist of subjects presenting with seizures and radiological evidence of reversible posterior	The investigator recorded all observed or volunteered AEs, the severity of the events, and the investigator's opinion of the relationship to the study treatment. Monitoring of cardiovascular safety: • Phase 1 Study: Electrocardiograms and echocardiograms were performed pre-study and at the end of Week 4 of Cycles 1, 2, 3, 6, 9, 12, 15, and 18. o Three patients who received 15 mg/m^2 and 2 patients who received 20 mg/m^2 of sunitinib developed an increase in QTc of 30-60 msec. One of the 3 patients who received 15 mg/m^2 sunitinib also had a QTc interval of 450 msec. Changes in the QTc of 30-60 msec are not included in CTCAE v4. o In Part A of the study, 1 patient in the sunitinib 15 mg/m^2 dose group showed absolute decrease in shortening fraction of 10% points from baseline. This patient

Written Request Items	*Information Submitted/Sponsor's Response*
leukoencephalopathy syndrome (RPLS), pancreatitis, and venous thromboembolic events. In addition, potential effects on long bones and caries of the teeth were seen in animal studies. Safety monitoring for cardiovascular safety, thyroid dysfunction, and effects of sunitinib on growing bones should be monitored using appropriate studies (i.e., electrocardiogram, echocardiogram or MUGA scan, blood pressure monitoring, laboratory assessments, radiographs).	experienced cardiac DLTs in Cycle 1 (Grade 3 cardiac failure, Grade 2 acute coronary syndrome, and Grade 2 left ventricular dysfunction). Part A of the study, 1 patient in the sunitinib 20 mg/m^2 dose group showed absolute decrease in shortening fraction of 9% points from baseline. This patient experienced cardiac DLTs in Cycle 1 (Grade 2 left ventricular dysfunction). o There were no reports of torsades or ventricular arrhythmias. • Phase 2 Study: ECGs were performed at baseline and Cycles 1 and 2, then every 3 cycles thereafter. Additional ECGs were performed as clinically indicated. The CSR does not present ECG results. There were no adverse event reports of cardiac dysfunction, torsades, or ventricular arrhythmias. Monitoring of thyroid function: o Phase 1 Study: TSH was measured at baseline, at the end of Week 4 in Cycle 1, Day 1 and the end of Week 4 in Cycle 2, and the end of Week 4 of odd-numbered cycles thereafter. o Hypothyroidism was reported in 5 patients and hyperthyroidism in 2 patients. o Three patients had a TSH > 10xULN. o Phase 2 Study; TSH was measured at baseline, the end of Week 6 (Cycle 1), Day 1 of even-numbered cycles starting with Cycle 4, and at the end of treatment. o There were no reports of Grade 3-5 thyroid-related AEs. o One patient had a TSH 3-10xULN. Monitoring effects on growing long bones o Phase 1 Study: o A plain anteroposterior radiograph of the tibial growth plate was measured at baseline. If found closed, no additional radiograph

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	required; otherwise, the test was to be repeated at Day 28 of odd-numbered cycles. o Of 35 patients treated, 23 had open tibial growth plates at baseline. Of the 6 patients with open tibial growth plates who received > 1 dose, only 2 completed Cycle 3. Patient 782618 received 9 cycles. X-rays on Days 133 and 218 showed no change, while a radiograph on Day 406 showed the distal femoral physes to be less distinct and beginning to fuse. This patient was age 12 at entry and girls typically have closure of the growth plate by age 14. Patient 773927 received 18 cycles. X-rays up to D 282 showed no change. On Day 534, possible widening was seen relative to baseline. On D 618, slight widening was reported, but there was also a comment that this may be due to oblique views • Phase 2 Study: o A plain AP radiograph of the tibial growth plate was measured at baseline. If found closed, no additional radiograph required; otherwise, the test was to be repeated every even-numbered cycle starting with Cycle 4. Evidence of growth plate thickening was to be further checked via MRI of the knee and adequate consultations with orthopedic surgeon. o Tibial growth plate assessment results are not available, and no growth analyses were performed. Data on toxicity related to growing bones were to be reported as AEs and/or SAEs, however none were reported. o Only 1 patient received 4 or more cycles (Patient 1010820366).
Reviewer's Comment: *The applicant collected sufficient safety information from the Phase 1 trial to fulfill the Written Request. Echocardiograms, EKGs, and tibial growth plate assessments*	

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as well as Grade 1-5 adverse events should have been collected from the Phase 2 trial.	
Drug information: • Dosage form: 6.25, 12.5, 25, 37.5 and 50 mg capsules. For patients not able to take intact capsules orally, the dose will be administered as "sprinkles" (contents of capsule) mixed with applesauce or yogurt • Route of administration: Oral • Regimen: intermittent dosing (4 weeks on drug followed by 2 weeks off) at 15 mg/m2/day, the pediatric MTD from the Phase 1 study in pediatric patients with solid tumors. • Use an age-appropriate formulation in the studies described above. If the studies you conduct in response to this Written Request demonstrate this drug will benefit children, then an age-appropriate dosage form must be made available for children. This requirement can be fulfilled by developing and testing a new dosage form for which you will seek approval for commercial marketing. If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Development of a commercially-marketable formulation is preferable. Any new commercially marketable formulation you develop for use in children must meet agency standards for marketing approval.	Phase 1 Study: For Parts A and B, drug doses were rounded to the nearest 12.5 mg. For Part C, drug doses were rounded to the nearest 6.25 mg. After the capsule content sprinkled on applesauce or yogurt from all capsules was swallowed, the patient was instructed to drink 60 mL of water or apple juice. Phase 2 Study: Patients received sunitinib 15 mg/m^2 as capsules in 6-week cycles. Each 6-week cycle comprised sunitinib taken orally QD for 28 days followed by a 14-day rest period. 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. Patients had their first disease status evaluation after 2 cycles (12 weeks) of therapy and prior to every odd-numbered cycle. Sunitinib could be taken without regard to meals. For patients not able to swallow intact capsules, the capsules may have been opened and the contents mixed with apple sauce or yogurt immediately prior to oral or gastric tube ingestion. Sunitinib powder was determined to be stable for at least 30 minutes when sprinkled on top of apple sauce or yogurt. As the studies did not demonstrate efficacy, the Sponsor is not seeking an indication. Thus, a commercially marketable formulation was not developed.
Reviewer's Comments: *In the absence of drug activity, the development of a pediatric formulation of sunitinib was not required. The applicant's studies on sunitinib powder (mixed with food) were adequate.*	
Statistical information (statistical analyses of the data to be performed): Phase 1 Study: Descriptive statistics will be used.	 Phase 1 study: A minimum of 3 evaluable patients were entered at each dose level in

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Phase 2 Study • Stratum A recurrent or progressive high-grade gliomas) Sunitinib will be deemed unsuitable of further investigation in this patient population if the true response rate is less than 10%, and the study design will have 90% statistical power for a true response rate of 30%. These parameter settings coupled with type I and II error rates set at 10% lead to a sample size of 25 patients based on a Simon's minimax design. Sixteen (16) patients will be accrued in the first stage, and if ≥ 2 patients among the first 16 patients have a response, then the stratum will be open to Stage 2 and accrual will continue until 25 evaluable patients have been treated and assessed for response. With this study design, if the "true" response rate is 10%, then the probability that the trial will stop early is 0.515 (51.5%). However, if the "true" response rate is 30%, then there is only a 0.026 (2.6%) probability that the trial will be terminated in Stage 1. Descriptive statistics will be used. • Stratum B: refractory, recurrent, or progressive ependymomas): Sunitinib will be deemed unsuitable of further investigation in this patient population, if the true response rate is less than 5%, and the study design will have 90% statistical power for a true response rate of 25%. These parameter settings coupled with type I and II error rates set at 10% lead to a sample size of 20 patients based on a Simon's minimax design. Thirteen (13) patients will be accrued in the first stage, and if ≥ 1 patient among the first 13 patients has a response, then the	this single-stratum study. A minimum of 15 and a maximum of 60 evaluable patients were to be enrolled in the study. Phase 2 study: Simon's minimax 2-stage design was employed to determine the sample size. The Type I error rate was set to be 0.1 and the power 90%. For Stratum A, the null and alternative hypotheses were as follows: H_0: ORR ≤ 10% vs H_a: ORR ≥ 30%. For Stratum B, the null and alternative hypotheses were as follows: H_0: ORR ≤ 5% vs H_a: ORR ≥ 25%. For Stratum A, 16 eligible and evaluable patients were to be accrued in the first stage. If at least 2 patients had objective response, then this stratum would enter the second stage to accrue an additional 9 patients. Otherwise the stratum would be closed at the end of the first stage due to the lack of evidence for adequate efficacy. A maximum of 25 eligible and evaluable patients would be accrued for this stratum. At the end of the second stage, if at least 5 patients had objective response, it would be considered as evidence of efficacy for further clinical investigation. For Stratum B, 13 eligible and evaluable patients were to be accrued in the first stage. If at least 1 patient had objective response in the first stage, then this stratum would enter the second stage to accrue an additional 7 patients. Otherwise the stratum would be closed at the end of the first stage due to the lack of evidence for adequate efficacy. A maximum of 20 eligible and evaluable patients would be accrued for this stratum. At the end of the second stage, if at least 3 patients had objective response, it would be considered as evidence of efficacy for further clinical investigation.

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stratum will be open to Stage 2 and accrual will continue until 20 evaluable patients have been treated and assessed for response. With this study design, if the 'true' response rate is 5%, there is a 0.513 (51.3%) probability of ending the trial during stage 1. However, if the 'true' response rate is 25%, then there is only a 0.0238 (2.38%) probability that the trial will be terminated in Stage 1. Descriptive statistics will be used	
Reviewer's Comments: Given the lack of activity of sunitinib in pediatric patients, the number of patients enrolled, and the analysis of these patients was sufficient.	
Labeling that may result from the studies: The sponsor must submit proposed pediatric labeling to incorporate the findings of the studies. Under section 505A(j) of the Act, regardless of whether the studies demonstrate that sunitinib malate is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the studies. Under section 505A(k)(2) of the Act, the sponsor must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the studies.	A proposed update to the Sutent USPI providing discussion of the results of the pediatric studies is provided in Module 1.14 of this submission.
Reviewer's Comments: *Pediatric labeling was submitted and Section 8.4 of the package insert was revised.*	
Format of reports to be submitted: Full study reports (including data sets and individual data listings) will be submitted to the Agency addressing the issues outlined in this request with full analysis, assessment, and interpretation. Even if the study fails, we need full study reports with data to support study conclusion. In addition, the reports will include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific	Full CSRs, including all applicable appendices, are provided for both studies. Annual Reports and Period Adverse Drug

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Islander or White. For ethnicity one of the following designations should be used for each pediatric patient: Hispanic/Latino or Not Hispanic/Latino. Under section 505A(d)(2)(B) of the Act, when the sponsor submits the study reports, the sponsor must submit all postmarketing adverse event reports regarding this drug that are available at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the Guidance for Industry E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs and the Guidance addendum. You are encouraged to contact the reviewing Division for further guidance. Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the FDA website at http://www.fda.gov/CDER/REGULATORY/ersr/Studydata.pdf and referenced in the FDA Guidance for Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UC M072349.pdf.	Experience Reports are up to date for NDA 21938. Study data were submitted electronically according to the SDTM standard published by the CDISC.
Timeframe for submitting reports of the studies: Reports of the above studies must be submitted to the Agency on or before January 1, 2019.	The studies were submitted to the Agency on November 8, 2018.

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Reviewer's Comments: Study reports were submitted prior to January 2019.	

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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I concur with the overall assessment of consultants and review team