Phase I Study of Oral Sonidegib (LDE225) in Pediatric Brain and Solid Tumor and a Phase II Study in Children and Adults with Relapsed Medulloblastoma

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Abstract

Background and Purpose: Hedgehog (Hh) signaling activation has been identified in medulloblastoma (MB) tumors. Sonidegib (LDE225) is a potent, selective Hh inhibitor of SMOOTHENED. This study explored the safety and pharmacokinetics (PK) of sonidegib in children with relapsed/recurrent tumors followed by a phase II trial in pediatric and adult patients with relapsed MB to assess tumor response.

Patients and Methods: Pediatric patients aged $\geq$1 to <18 years were included according to a Bayesian design starting at 372mg/m^2 of continuous once daily oral sonidegib. Tumor samples were analyzed for Hh pathway activation using a validated 5-gene Hh signature assay. In phase II, pediatric patients were treated at the recommended phase II dose (RP2D) while adults received 800 mg daily.

Results: Sixteen adult (16 MB) and 60 pediatric (39 MB, 21 other) with an age range of 2-17 years were enrolled at 233, 372, 425 and 680mg/m^2 (declared the RP2D and with systemic exposure and toxicity profiles similar to the adult dose). The 5-gene Hh signature assay showed that the 4 complete response patients (2 pediatric and 2 adult) and 1 partial response (adult) all had Hh‑activated tumors, while 5 patients with activated Hh had either stable disease (n = 3) or progressive disease (n = 2). No patients with Hh-negative signatures (n = 50) responded.

Conclusions: Sonidegib was well tolerated and the RP2D in pediatric patients was 680 mg/m^2 once daily. Five of the 10 MB patients with activation of the Hh pathway demonstrated prolonged complete or partial responses.

Key Words: Medulloblastoma, sonic hedgehog, SMO, PTCH, phase I, phase II, pediatric, adult

Significance (NEW: 150-word summary of the importance of the study (maximum)

Recurrent or progressive medulloblastoma continues to have a poor prognosis. Four major molecular subgroups have been identified; the sonic hedgehog variants are characterized by upstream mutations in hedgehog, patch, smoothened (which can be inhibited by targeting smoothened) as well as downstream activation of Gli and SuFu. Sonidegib (LDE225) is an oral, once daily, highly selective smoothened inhibitor that we demonstrate to be well tolerated and with significant activity in both adult and pediatric patients with activation of the Hh pathway. Minor creatine phosphokinase elevation and effects on growth plates were the only significant toxicities observed. Patients lacking upstream activation of the pathway do not respond and based on these results, can be spared undergoing a therapy that will not provide benefit. By contrast, these findings provide a treatment option for the recurrent/progressive medulloblastoma patients with Hh-activated tumors and this approach could be ideally suited to incorporation into upfront treatment protocols.

Introduction

Significant advances in the treatment of medulloblastoma have occurred over the last three decades. For children over the age of three, maximal safe surgery, craniospinal radiation and multiagent chemotherapy have resulted in excellent outcomes for those with standard-risk features[1] and improved survival for patients with high-risk disease.[2] Unfortunately, cure comes at a significant cost for these patients due to deleterious effects on growth, hormones, vascularity, induction of secondary tumors and most importantly, cognition.[3] Strategies that attempt to avoid the side effects of radiation therapy using high-dose chemotherapy and stem cell rescue have also been widely evaluated and effective in some but not all patients.[4] Better therapies are therefore needed to reduce toxicity in all age groups. Approximately 30% of patients with medulloblastoma will experience a recurrence and for these patients, long-term survival is very poor, independent of salvage regimen, with a median survival of approximately 12 months.[5] Novel agents are desperately needed for these patients.

Recent advances in the molecular characterization of medulloblastoma have resulted in the identification of 4 major subgroups, largely defined by the developmental pathway activated.[6] One of these pathways, called the sonic hedgehog (Hh) pathway, is an important developmental signaling cascade responsible for the proliferation of cerebellar granule neuron precursors[7-9] that has been strongly implicated in the development of approximately 25% of pediatric and 70% of adult medulloblastoma cases. In the absence of Hh ligand binding, the Hh receptor Patched (PTCH) acts as a negative regulator of the Hh pathway by inhibiting Smoothened (SMO), a G-protein coupled receptor-like signal transducer. Hh signaling is activated when a Hh ligand binds to PTCH, releasing its inhibition of SMO. Activated SMO initiates a downstream signaling cascade via a complex of cytosolic proteins, involving suppressor of fused (SUFU), a negative regulator of Hh signaling. The signaling cascade activates Glioma-associated oncogene (GLI) transcription factors, which translocate to the nucleus and induce Hh-pathway target gene expression.[10,11] Mutations in *PTCH*, *SUFU*, and *SMO* lead to constitutive activation of the Hh pathway in MB.[12,13] A validated, five-gene Hh signature reverse transcriptase-polymerase chain reaction (RT-PCR) assay demonstrated a strong association between Hh pathway activation and tumor response.[14] Inhibition of the Hh pathway in fetal development results in defective neural proliferation and holoprosencephaly with a single midline eye (cyclops).[15] Over activation of the pathway by contrast has been identified to cause excessive cellular proliferation and germline mutation of *PTCH* can result in a number of morphogenic defects and increased tumor formation including basal cell carcinoma, rhabdomyosarcoma and medulloblastoma and is referred to as Gorlin's or basal cell nevoid carcinoma syndrome.[16] Sonic hedgehog signaling, either sporadic or as part of the syndrome, most commonly results from persistent activation through mutations of *PTCH* or *SMO* although approximately 25% of Hh-driven tumors have mutations downstream of *SMO*.[17] The Hh subgroup is reported to comprise 65%, 15%, and 72% of MBs in infants (≤ 3 years of age), children (4-15 years), and adults (≥ 16 years), respectively.[6,18] Patients with Hh

activation have an approximately 70% 5-year event-free survival; those with an associated p53 mutation have an outcome of only 20%.[19]

Inhibition of the Hh pathway has been reported using sonidegib in an adult phase I trial[20] and in adult and pediatric patients with vismodegib.[21] Sonidegib (LDE225) is an oral selective antagonist of the Hh pathway that acts by inhibiting SMO at low nanomolar concentrations, thereby suppressing the growth of Hh, PTCH and SMO driven tumors.[22,23] In the first-in-human phase 1 dose-escalation study of sonidegib in adult patients with advanced solid tumors, three of nine patients (33%) with MB achieved objective tumor responses according to RECIST 1.0 and FDG-PET.[20] We now report the results from the pediatric phase 1 dose-escalation study of sonidegib in children with advanced solid tumors potentially dependent on Hh signaling, including patients with relapsed or refractory MB. Safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity were assessed. The maximum tolerated dose (MTD) or the recommended phase 2 dose (RP2D) to be used for future studies of sonidegib in children was determined. In the phase 2 study of sonidegib, the RP2D (625 mg/m^2/day) for children and 800 mg for adults was tested in recurrent/relapsed medulloblastoma patients.

Materials and Methods

Patients

Children between the ages of 1 and 18 years of age with a histologically confirmed diagnosis of MB, rhabdomyosarcoma, neuroblastoma, hepatoblastoma, high-grade glioma, or osteosarcoma who had progressed despite standard therapy, or for whom no standard therapy was available, were eligible for the phase I component of the study. Drug was provided by Novartis Pharmaceutical in 50 mg, 100 mg, 200 mg and 250 mg capsules. Drug was dispensed at the start of every 28-day cycle and was administered once daily, at approximately the same time, preferably in the morning. Patients who were unable to swallow whole capsules were provided instructions for handling open capsules to be taken with a small amount of food – applesauce or yoghurt. Drug was required to be stored in the refrigerator (2-8 ℃, 36-46°F) and at room temperature one hour before the dosing time to make the capsule contents easier to prepare. Patients were assessed weekly for the first 8 weeks, then monthly after. In the phase 2 component, for both adult and pediatric patients, recurrent or relapsed medulloblastoma patients were eligible. Other eligibility criteria included: Karnofsky performance status score of ≥ 60 for patients older than 10 years of age or a Lansky Play scale of ≥ 50 for patients 10 years of age or younger. Adequate renal function (serum creatinine ≤ 1.5 x upper limit of normal [ULN] for age or creatinine clearance or radioisotope glomerular filtration rate ≥ 1.17 mL/s/1.73 m^2), liver function (bilirubin ≤ 1.5 x ULN for age, serum alanine aminotransferase [ALT]/serum glutamic pyruvic transaminase ≤ 5 x ULN for age, serum aspartate aminotransferase [AST]/ serum

glutamic oxaloacetic transaminase ≤ 5 x ULN for age, serum albumin ≥ 20 g/L), and bone marrow function (peripheral absolute neutrophil count [ANC] ≥ 1.0 x 10^9/L, platelet count ≥ 80 x 10^9/L, and hemoglobin ≥ 8 g/dL). Consent to provide archival or fresh tumor sample for PD analyses was required if material was available. Patients with impaired cardiac function or clinically significant cardiac disease, gastrointestinal dysfunction, neuromuscular disorders associated with creatinine phosphatase (CPK) elevation, or any other concurrent severe and/or uncontrolled medical conditions were excluded from the trial. Strenuous exercise was to be avoided while taking sonidegib to prevent significant increases in plasma CPK levels. Treatment with strong inhibitors or inducers of cytochrome P450 (CYP) 3A4/5 or drugs metabolized by CYP2B6 or CYP2C9, which have a narrow therapeutic index, was prohibited during the study. Patients not on a stable dose of corticosteroid or those on enzyme-inducing anticonvulsants that were prohibited during the study were not eligible; drugs recognized to cause rhabdomyolysis (HMG CoA inhibitors [statins], clofibrate, and gemfibrozil) were also prohibited (pravastatin was allowed with extra monitoring if essential to control hyperlipidemia). All patients/legal guardians provided written consent and assent where appropriate. The trial was conducted in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations, and with the ethical principles laid down in the Declaration of Helsinki. The study protocol and amendments were reviewed and approved by the Institutional Review Board/Independent Ethics Committee/Research Ethics Board of each site.

Study design

This international multisite open label study (NCT01125800) included a phase I dose-escalation and safety expansion in children with relapsed/refractory MB or other tumors potentially dependent on the Hh pathway. The protocol was amended to include a dose expansion component to assess the preliminary efficacy in children and adults with relapsed/refractory MB. The primary objective of the dose-escalation phase was to determine the MTD or RP2D and dose-limiting toxicities (DLTs) of sonidegib. Secondary objectives included characterization of the safety, tolerability, and pharmacokinetic (PK) profile of sonidegib, and assessment of preliminary antitumor activity (objective response rate [ORR]), Hh gene expression signature, and mutational status of Hh pathway genes (*SMO, PTCH, SUFU*). Other planned objectives including analysis of pharmacodynamic (PD) effects of sonidegib on Hh pathway biomarkers (*GLI1, PTCH1, cyclin D1*) in tumor cells from cerebrospinal fluid (CSF), correlation between tumor response and expression of the Hh gene signature, effects of sonidegib on bone markers in serum samples, and a determination of PK/PD and PK/safety relationships were not completed due to lack of tumor material available. For the phase II component of the trial, the primary objective was to assess the efficacy of sonidegib, as determined by radiographic response in recurrent or progressive MB patients. The secondary aims included a planned assessment of the mechanisms of de novo resistance by analysis of *GLI2* amplifications and downstream mutations, such as *SuFu*. CSF concentrations of sonidegib were also to be assessed if available. The secondary objectives could not be completed due to lack of sufficient patient material.

Successive cohorts of pediatric patients (minimum of 3) were treated with oral sonidegib starting at 372 mg/m^2 once daily in 28-day cycles. Patients were considered evaluable if they were treated with at least 75% of the planned doses of sonidegib within the first 6 weeks of treatment and had completed sufficient safety evaluations and/or if they experienced a DLT during the first 6 weeks of treatment. Dose-escalations were based on an adaptive Bayesian logistic regression model with overdose control.[24,25] A DLT was defined as an adverse event (AE) or abnormal laboratory value considered to be ≥ grade 3 according to the common terminology criteria for adverse events (CTCAE), version 4.0 that was related to sonidegib. The MTD or RP2D was defined as the highest tolerated dose at which at least 6 patients had been assessed. Once the MTD or RP2D was established, an additional 6 patients were treated at the MTD and/or RP2D to further characterize the safety and tolerability of sonidegib. A MB enrichment phase allowed the enrollment of additional patients with MB into previously tested, well-tolerated doses to further characterize sonidegib treatment in MB. Patients continued treatment until disease progression, unacceptable toxicity, death, or as per investigator discretion. Once the phase I and cohort expansion was completed, additional pediatric patients were enrolled on the phase II component of the trial. Adult patients were eligible for entry into the phase II component from the outset as the RP2D for this group had already been determined.[20]

Safety Assessments

Safety assessments included monitoring and recording of all AEs, serious AEs (SAEs), laboratory evaluations, physical examination, vital signs, weight, and electrocardiogram recordings. AEs were graded according to the CTCAE, version 4.0 guidelines and were monitored throughout the study and until 30 days following the last dose. Due to increased serum CPK levels observed in the first-in-human phase 1 study of sonidegib in adults with advanced solid tumors,[20] additional CPK monitoring was implemented throughout the study. In addition, because inhibition of the Hh pathway has been shown to cause premature growth plate closure in preclinical mouse models,[26] bone x-rays and dental assessments were conducted throughout the study.

Pharmacokinetics (PK)

Blood Sample Collection and Handling: Whole blood samples (1 mL) were collected throughout the phase I study. Serial blood samples were collected on day 1 and day 22 of cycle 1 at pre-dose and 0.5, 1, 2, 4, 7, and 24 hours post-dose. Blood samples were also collected pre-dose on days 8, 15, and 28 of cycle 1 and on day 1 of each cycle from cycle 3, or anytime a CSF sample was collected. For patients on the phase II component of the trial, trough levels were assessed during cycle 1 (on days 1, 2, 8, 15, 22, 23 and 28) and cycles 2-18 (on day 1). Samples were processed and frozen at ≤ –70°C. Preparation and analysis of plasma samples was performed as previously published.[20]

PK Assessments: PK parameters including area under the plasma concentration-time curve from time zero to 24 hours [$AUC_{0\text{-}24h}$], peak plasma concentration [C_{max}], and time to reach C_{max}

[T_{max}]) were calculated using noncompartmental methods with Phoenix WinNonlin version 6.2 (Pharsight, Mountain View, CA, USA).

Tumor Assessments

Tumor response was assessed every 8 weeks by the Neuro-Oncology Criteria of Tumor Response (central nervous system [CNS] tumors)[27,28] and the Response Evaluation Criteria In Solid Tumors v1.0 (non-CNS tumors).[29] Assessments continued until disease progression or the start of a new antineoplastic agent. For all patients with CNS disease, neurological assessments including determination of consciousness level, mental status, speech, vision fundus (papilledema), cranial nerves (III, IV, VI, other), motor, sensory, and gait or limb ataxia were completed within 1 week of each tumor response evaluation.

Pharmacodynamics

Formalin-fixed paraffin-embedded archival tumor samples from any time-point (diagnosis or relapse) and fresh tumor samples (when available) from preplanned, treatment-related surgical resections or biopsies were subjected to gene expression analysis (five-gene Hh signature RT-PCR assay[14]/markers of pathway activation). In consenting pediatric patients, blood samples (maximum of 5 mL) were also collected pre-dose on days 1, 15, and 28 of cycle 1, day 28 of cycle 2, and at the end of treatment for bone marker analyses.

Statistical analyses

Patient demographics, safety, pharmacokinetic, and response data were summarized using descriptive analyses. Data included all patients and all time points until off therapy.

Results

Demographics

Sixty pediatric patients were enrolled (59 on the phase I/dose expansion and 1 on phase II), including 39 patients with MB, with a median age of 12 (range 2–17) years. In the phase II, 16 adult patients with medulloblastoma were included. Baseline characteristics and disease history, including tumor histology/cytology, previous tumor directed therapies, and performance status (Karnofsky/Lansky) of patients enrolled are listed in Table 1.

Safety

The median treatment exposure for all pediatric and adult patients was 55 days (range, 2-289 days) and 97 days (range, 34-511 days), respectively. The most common treatment-related AEs in children included fatigue, muscle spasms, increased CPK, myalgia and vomiting (Table 2 and

Supplemental Table 2) and were similar to those observed in adults (increased CPK, myalgia, muscle spasms, nausea and increased alanine aminotransferase (ALT). The only DLT observed was a reversible grade 4 CPK elevation which occurred in one pediatric patient with rhabdomyosarcoma treated at 372 mg/m^2, which occurred at the end of the first cycle of therapy. This patient was discontinued due to progressive disease (PD) after 35 days on treatment and without renal dysfunction or muscle symptoms. Dose levels were reduced to 233 mg/m^2 for the next 6 patients and then re-escalated to 372 mg/m^2. An additional 15 patients were treated at 372 mg/m^2 in the dose-escalation (n = 10) or MB enrichment (n = 5) phases without DLTs. Furthermore, no DLTs were observed in patients enrolled in the dose-escalation or MB enrichment phases at doses of 425 mg/m^2 (n = 6) and 680 mg/m^2 (n = 4), therefore, the MTD was not reached and the RP2D was determined to be 680 mg/m^2 once daily. Grade 1/2 and grade 3/4 CPK elevation occurred in 7 and 2 pediatric patients, respectively, and in 2 and 5 adults, respectively. No concurrent renal dysfunction was observed in any pediatric patients who experienced CPK elevations. Evidence of growth plate closure was observed in 3 pediatric patients (wrist cartilage closure, knee cartilage closure, and knee subchondral condensation within growth plate; Figure 1).

Dose reduction or interruptions occurred in 7 pediatric patients. These events were grade 2 confusional state, grade 3 convulsion, and grade 3 disorientation in one patient; confusional state and agitation (both grade 3) in one patient; and grade 4 convulsion, grade 3 hypersensitivity, grade 3 hypophosphatemia, grade 3 vomiting, and grade 2 lethargy, each in one patient each). The investigator considered the hypersensitivity to be related to study drug; the remainder of these events were considered unrelated to study drug by the investigators. The patient with agitation and confusional state had GBM; the other patients had MB. Six adult patients had one or more AEs that required dose adjustment or interruption: grade 4 increased CPK and grade 3 increased ALT in one patient; grade 4 increased CPK in one patient; increased ALT and increased aspartate aminotransferase (AST) (both grade 4) in one patient; grade 3 increased CPK and grade 1 increased bilirubin in one patient; grade 3 increased CPK in 2 patients. The adult patient whose dose was adjusted for grade 3 increased CPK and grade 1 increased bilirubin also discontinued study drug as a result of grade 2 increased CPK. With the exception of increased bilirubin, all of these events were considered to be related to study drug.

Four pediatric patients discontinued treatment because of AEs that included grade 4 hydrocephalus, grade 3 pleural effusion (both considered unrelated to therapy), grade 2 chondropathy and grade 1 epiphyseal disorder (both considered related to therapy). Three adult patients discontinued study drug as a result of grade 4 respiratory distress, grade 3 femur fracture (both felt unrelated to treatment) and grade 2 increased CPK (considered related to therapy). Thirteen pediatric and two adult patients died while receiving sonidegib or within 30 days of the last dose. All were due to progressive disease except in one adult, where the cause of death was listed as acute respiratory distress.

Pharmacokinetics

PK parameters including $AUC_{0\text{-}24h}$, C_{max}, and T_{max} were determined during cycle 1 (Table 3) for pediatric patients. Median T_{max} for all doses on day 1 occurred at 2 to 4 hours (range 0.5 – 7) and at 2 hours (range 0-7) on day 22. T_{max} was reached independent of dose level and declined in a bi-exponential manner. C_{max} and $AUC_{0\text{-}24h}$ increased dose-proportionally at both day 1 and day 22. Most patients discontinued treatment prior to achieving steady state although sonidegib continued to accumulate past cycle 2 in most patients for whom data was available. Inter-patient coefficient of variation for C_{max} and $AUC_{0\text{-}24h}$ on day 1 was 38.5 to 74.6% and 42.5 to 74.2%, respectively, and not significantly different on day 22. The PK data for adults was similar to those previously reported.[20] The trough sonidegib and LGE899 concentrations were generally within the range observed in adult patients with advanced basal cell carcinoma.[20].

Efficacy

The overall response rate in the entire pediatric (n = 60) or adult (n = 16) populations were 2/60 (3.3% - CI 0.4, 11.5) and 3/16 (18.8% - CI 4.0, 45.7) respectively. In patients with SHH activated MB (n = 10/60 pediatric and adult patients tested), 5 responses were observed (50%), all in patients that had received prior radiation therapy as part of their upfront treatment for medulloblastoma. Only patients with MB responded (2 complete responses [CRs] at doses of 372 and 425 mg/m2 for the pediatric patients and 2 CRs as well as 1 PR in adults at 800 mg; Figure 2). Stable disease (SD) was observed in 11 (5 pediatric and 6 adult patients, all with medulloblastoma). One pediatric patient was discontinued from the study after 7 days due to hydrocephalus; the remaining 53 pediatric and 7 adult patients had PD. Both responding pediatric patients stopped treatment after 9 months when in CR. Duration of response of a total of 21 months was observed for the 11 year-old female treated at 372 mg/m^2 and the 4 year-old female treated at 425 mg/m^2 is still in remission at time of writing the manuscript (duration of 49 months in Dec 2016). For the adult patients, duration of response for the two CRs were 1.6 and 8.7 months and the duration of response for the PR was 4.8 months. Progression free and overall survival was not evaluated as the phase II component of this study was terminated early (n = 17) in order to proceed to a randomized phase III trial of this agent in patients with SHH MB.

Biomarkers: Tumor responses were associated with Hh pathway activation as identified by the five-gene signature (upregulation of GLI1, SHROOM2, SPHK1, PDLIM3 and down-regulation of OTX2) RT-PCR assay.[14] Three of 47 pediatric patients (at the 372, 425 and 680mg/m2 dose levels) and 7 of 13 adult tumors tested (all treated at 800mg) were positive on the 5-gene assay. All signature positive patients had MB. This included both pediatric patients with CR as well as the 2 CR and 1 PR identified in adults. None of the 50 patients with Hh pathway non-activated tumors demonstrated a response to therapy (SD, n = 4; PD, n = 39; discontinued therapy before first evaluation, n = 5; unknown, n = 2). Assessment of serum bone markers including C-terminal telopeptide of type I collagen (CTx), tartrate resistant acid phosphatase 5b (TRAP5b), osteoprotegerin (OPG), osteocalcin (OC), bone specific alkaline phosphatase (BSAP) and

procollagen 1 N-terminal peptide (P1NP) demonstrated decrease from baseline in bone formation and in bone resorption markers across all dose levels (see Supplemental Table 1). Neither tumors (n = 47) nor cells from CSF samples (n = 2) could be analyzed for mutations in the Hh pathway genes *SMO*, *PTCH*, and *SUFU.* Skin biopsies were optional (in phase I only) and no patients provided samples for analysis.

Discussion

Oral once daily sonidegib was well tolerated in children with advanced solid tumors and demonstrated antitumor activity in pediatric and adult patients with relapsed MB with Hh pathway activated signature. The recommended phase 2 dose is 680 mg/m^2 orally once daily to a maximum of 800 mg.

Common treatment-related AEs were similar to those observed in the phase 1 study of sonidegib in adults with advanced solid tumors[20] and have been observed with other SMO inhibitors.[30,31] Elevated blood creatinine phosphokinase (CPK) without evidence of organ impairment was common. Dose-limiting grade 4 CPK elevation was observed in 1 patient with rhabdomyosarcoma. All events were of skeletal muscle origin based on total CPK/CPK-MB ratio. Significant CPK elevation observed in pediatric patients on this study occurred less frequently (5/60 or 8.3%) than that observed in adults (5/16 or 31.3%).[20] The reason for this difference is unknown.

Due to the known role of Indian hedgehog (IHh) in bone development and the on-target growth plate effects observed with Hh pathway inhibitors in preclinical animal models,[26] use of Hh pathway inhibitors in pediatric patients has potential risks. Therefore, patients in this trial were monitored for growth plate effects. In addition to changes in serum bone markers suggesting some impact of Hh inhibition, three bone related toxicities of potential importance were identified. A 4 year old female reported narrowing of the epiphyseal plate of the phalanx on day 133 and a subchondral condensation in the area of the growth plate on day 169. As a result of these, drug was discontinued. An 8 year old male patient had widening of the distal femur epiphyseal growth plate on day 57 and an 11 year old female patient was noted to have knee cartilage closure on day 56 and wrist cartilage closure on day 196 which resulted in discontinuation of drug. No bone growth defects were reported in the clinical trial of vismodegib,[21] although only 4 patients had a response, all were above the age of 17 at the time of treatment and thus not at a developmental stage where growth plate effects could be evaluated. Based on the results from this study, further evaluation of growth plate effects in pediatric patients treated with Hh pathway inhibitors is clearly warranted. Since Hh associated MB is common in young infants, particular caution should be exercised before considering adding Hh targeted treatment to this subgroup of patients.

Sonidegib exposure increased with increasing doses in a linear manner in the dose range of 233 to 680 mg/m^2. Steady state was not achieved within the first two cycles of treatment. Sonidegib exposure in children is consistent with that observed previously in adults for equivalent mg/m^2 doses.[20] Sonidegib demonstrated antitumor activity in patients with relapsed SHH MB. No activity was observed in non-SHH MB or other tumor types that have been associated with activation of the Hh pathway, although this may have resulted from the fact that none of the patients with non-MB tumors happened to have Hh activation as defined by the 5-gene signature. Two children and two adults achieved CRs (Figure 3) and one adult achieved a PR. All five patients had tumors with evidence of activated Hh pathway as determined by the five-gene signature RT-PCR assay.[14] The remaining patients with activated Hh pathway had PD. Lack of response in these patients may have been due to a mutation downstream of SMO although due to lack of material, was not tested. Five and 24 patients with MB had either SD or PD, respectively. None of these patients had tumors with activated Hh pathway. The significance of stable disease in the response assessment of medulloblastoma remains unclear as patients with known recurrent disease can demonstrate very slow progression that in the early assessment can mimic stable disease.[32] These findings should be taken into consideration when assessing response in clinical trials of patients with medulloblastoma. Five patients with MB did not have their tumors analyzed; one patient was removed from the study prior to tumor response assessment due to hydrocephalus. All of the patients with other solid tumors had PD and were found to have Hh non-activated tumors. In the phase 1 study in adults, activated Hh pathway determined using the five-gene signature assay was strongly associated with tumor response in patients with MB[14] and basal cell carcinoma.[20] The study described here adds further credence to the validity of the five-gene signature assay. The 50% (5 of 10) radiographic response rate observed in this combined phase I/II cohort of pediatric and adult patients is higher than reported for vismodegib, another Hh targeted agent, where 4 of 26 patients (15%) had a response.[21] Whether this difference is related to the CNS penetration of the two agents, or is a result of the mixture of patients with mutations upstream versus downstream of smoothened between the two studies is not known and neither study was able to obtain sufficient material in enough patients to complete these mutational analyses.[21]

There is a strong unmet need for medulloblastoma patients with high-risk (e.g. metastatic SHH or MYCN-amplified SHH MB), very high-risk disease (e.g. SHH with TP53 mutation) and recurrent or relapsed MB.[19] Targeted therapies and patient selection diagnostics are needed to improve survival and quality of life in this patient population. This study has demonstrated that the use of Hh pathway-targeted therapies can be beneficial in patients with Hh pathway-activated relapsed MB. Particular attention however must be taken in younger patients with incomplete maturation of the skeletal system.

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Tables

Table 1. Patient demographics and baseline disease characteristics

Variable	Pediatrics N = 60	Adults N=16
Age, median (range)	12 (2–17)	34 (18-66)
≤ 10 years	23 (38.3%)	0
> 10 years	37 (61.7)	16 (100%)
Body surface area (m^2), median (range)	1.2 (0.6–2.7)	1.8 (1.1-2.7)
Gender, n (%)		
Male	37 (61.7)	7(43.8)
Female	23 (38.3)	9 (56.3)
Race		
Caucasian	45 (75)	14 (87.5)
Asian	4 (6.7)	1 (6.3)
Black	4 (6.7)	0
Other or missing (not specified)	7 (11.7)	1 (6.3)
Stage at initial diagnosis, n (%)		
Karnofsky status[a,b] / Lansky Play score[c], n (%)	37 (62) / 23 (38)	16 (100) / NA
100	15 (25) / 11 (18.3)	0 / NA
90	6 (10) / 6 (10)	8 (50) / NA
80	7 (11.7) / 4 (6.7)	5 (31.3) / NA
70	3 (5) / 2 (3.3)	1 (6.3) / NA
<70	5 (8) / 0	2 (12.5) / NA
Not applicable (≤ 10 years) / Not applicable (>10 years)	23 (38.3) / 37 (61.7)	0 (0) / 16 (100%)
Histology/cytology, n (%)		
Medulloblastoma	39 (65)	16 (100)
Glioblastoma multiforme	5 (8.3)	0
Osteosarcoma	5 (8.3)	0
Rhabdomyosarcoma	4 (6.8)	0
Neuroblastoma	3 (5.0)	0
Hepatoblastoma	1 (1.7)	0
Anaplastic astrocytoma	1 (1.7)	0
Oligoastrocytoma	1 (1.7)	0
Gliomatosis	1 (1.7)	0
Time from initial diagnosis of primary site to start of study (months), median (range), n = 60	35.63 (8.6–111.6)	70.72 (15.9-210.9)
Time since most recent relapse/recurrence to start of study (months), median (range), n = 60	0.94 (0.3–7.2)	1.61 (0.2-20.7)
Prior therapy, n (%)		
Surgery	59 (98.3)	16 (100)
Radiotherapy	49 (81.7)	16 (100)

Chemotherapy	60 (100.0)	15 (93.8)

[a] Karnofsky missing for 1 (1.7) patient.
[b] Karnofsky performance status was used for patients > 10 years of age.
[c] Lansky performance status was used for patients ≤ 10 years of age.

Table 2: Adverse events suspected to be study drug related, by preferred term, maximum grade and treatment (> 3% All Children or > 10% adults; Safety Analysis Set)

Preferred Term	Sonidegib Daily Dose, mg/m^2								All Children N = 60		Adults 800 mgN = 16	
	233 n = 11		372 n = 16		425 n = 11		680 n = 22					
	All grade n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Total	8 (72.7)	1 (9.1)	13 (81.3)	2 (12.5)	9 (81.8)	0	14 (63.6)	2 (9.1)	44 (73.3)	5 (8.3)	13 (81.3)	6 (37.5)
Fatigue	5 (45.5)	0	4 (25.0)	0	2 (18.2)	0	1 (4.5)	0	12 (20.0)	0	1 (6.3)	0
Muscle spasms	2 (18.2)	0	4 (25.0)	0	3 (27.3)	0	2 (9.1)	0	11 (18.3)	0	4 (25.0)	0
Blood creatine phosphokinase increased	1 (9.1)	0	1 (6.3)	0	2 (18.2)	0	5 (22.7)	2 (9.1)	9 (15.0)	2 (3.3)	7 (43.8)	5 (31.3)
Myalgia	0 ()	0	0	0	4 (36.4)	0	5 (22.7)	0	9 (15.0)	0	5 (31.3)	0
Vomiting	2 (18.2)	1 (9.1)	1 (6.3)	0	3 (27.3)	0	3 (13.6)	0	9 (15.0)	1 (1.7)	1 (6.3)	0
Nausea	3 (27.3)	0	2 (12.5)	0	2 (18.2)	0	1 (4.5)	0	8 (13.3)	0	4 (25.0)	0
Alopecia	0	0	1 (6.3)	0	3 (27.3)	0	1 (4.5)	0	5 (8.3)	0	0	0
Arthralgia	1 (9.1)	0	1 (6.3)	0	2 (18.2)	0	1 (4.5)	0	5 (8.3)	0	0	0
Pain in extremity	1 (9.1)	0	1 (6.3)	0	3 (27.3)	0	0	0	5 (8.3)	0	0	0
Madarosis	1 (9.1)	0	1 (6.3)	0	2 (18.2)	0	0	0	4 (6.7)	0	0	0
Anemia	0	0	0	0	3 (27.3)	0	0	0	3 (5.0)	0	0	0
Asthenia	0	0	1 (6.3)	0	1 (9.1)	0	1 (4.5)	0	3 (5.0)	0	2 (12.5)	0
Decreased appetite	0	0	0	0	2 (18.2)	0	1 (4.5)	0	3 (5.0)	0	2 (12.5)	0
Headache	1 (9.1)	0	1 (6.3)	0	1 (9.1)	0	0	0	3 (5.0)	0	0	0
Aspartate aminotransferase increased	0	0	1 (6.3)	0	1 (9.1)	0	0	0	2 (3.3)	0	1 (6.3)	1 (6.3)
Blood creatinine increased	0	0	0	0	1 (9.1)	0	1 (4.5)	0	2 (3.3)	0	0	0
Diarrhea	0	0	1 (6.3)	0	1 (9.1)	0	0	0	2 (3.3)	0	3 (18.8)	0
Nail disorder	1 (9.1)	0	0	0	1 (9.1)	0	0	0	2 (3.3)	0	0	0
Neutrophil count decreased	0	0	0	0	1 (9.1)	0	1 (4.5)	0	2 (3.3)	0	0	0
Pain	0	0	0	0	1 (9.1)	0	1 (4.5)	0	2 (3.3)	0	0	0
Pain in jaw	0	0	0	0	2 (18.2)	0	0	0	2 (3.3)	0	0	0

Toothache	2 (18.2)	0	0	0	0	0	0	0	2 (3.3)	0	0	0
Alanine aminotransferase increased	0	0	1 (6.3)	0	0	0	0	0	1 (1.7)	0	4 (25.0)	2 (12.5)

Table 3. Sonidegib plasma exposure in pediatric patients at days 1 and 22 of cycle 1 by dose cohort

Sonidegib Dose Level (Once Daily)	Cycle 1, Day 1			Cycle 1, Day 22		
	C_{max} (ng/mL) n mean (SD)	AUC_{0-24h} (ng*hr/mL) n mean (SD)	T_{max} (h) n median (min;max)	C_{max} (ng/mL) n mean (SD)	AUC_{0-24h} (ng*hr/mL) n mean (SD)	T_{max} (h) n median (min;max)
233 mg/m^2	11 191 (82)	11 1982 (737)	11 4.0 (1.1;6.8)	9 769 (496)	9 10,590 (4163)	9 2.0 (1.0;7.0)
372 mg/m^2	15 246 (211)	15 2194 (1592)	15 2.0 (1.0;7.0)	12 944 (553)	14 15,431 (10,433)	12 2.1 (1.0;4.3)
425 mg/m^2	10 642 (487)	11 5309 (3247)	10 2.9 (0.5;7.0)	9 1122 (737)	9 17753 (11552)	9 2.0 (0.7;7.0)
680 mg/m^2	17 618 (403)	19 5118 (2658)	17 2.1 (1.0;4.1)	15 1930 (678)	15 32623 (11671)	15 2.0 (0.0;7.1)

Figures

Figure 1. Growth plate closure in 11-year-old patient treated at 372 mg/m^2

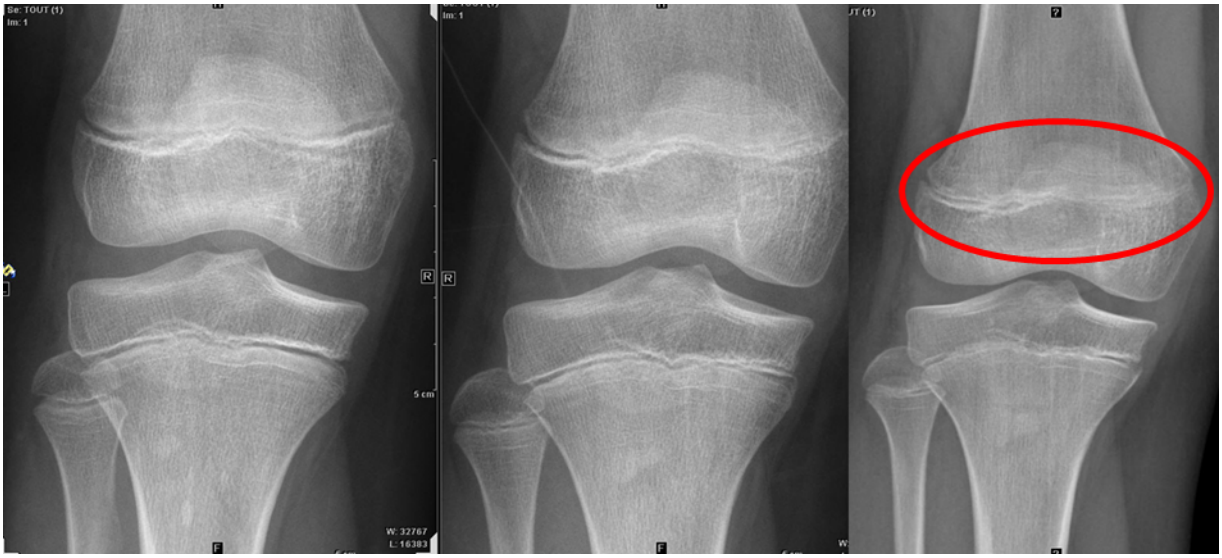
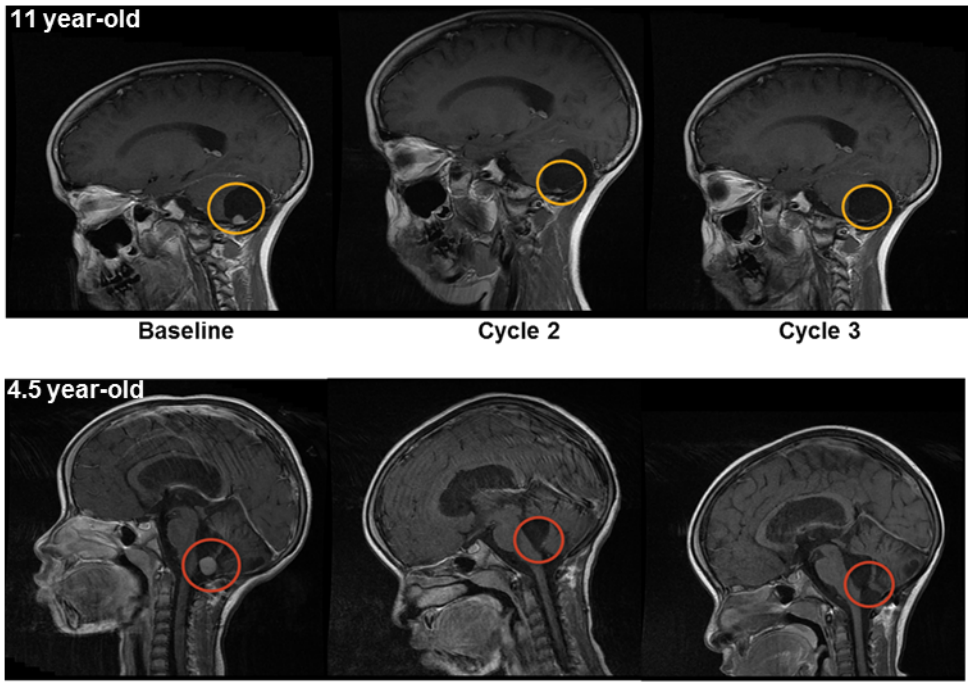


Figure 2. Complete tumor responses in 11 and 4.5 year-old children with medulloblastoma



Supplemental Table 1: Summary of mean change from baseline in bone markers by dose cohorts and visits Mean change from baseline (SD)

Parameter	Sonidegib Dose			
Cycle and day	233 mg/m2	372 mg/m2	425 mg/m2	680 mg/m2
Bone resorption markers				
OPG				
Cycle 1 D15	0.122 (0.56)	0.039 (1.43)	-0.051 (0.83)	0.00 (0.45)
Cycle 1 D28	0.317 (0.83)	0.421 (1.42)	-0.166 (0.72)	0.121 (0.66)
Cycle 2 D28	-0.097 (0.22)	-0.008 (1.46)	0.821 (1.23)	0.043 (0.42)
CTX				
Cycle 1 D15	-0.142 (0.42)	-0.065 (0.41)	-0.206 (0.16)	0.160 (0.37)
Cycle 1 D28	-0.198 (0.26)	-0.123 (0.37)	0.094 (0.28)	-0.089 (0.33)
Cycle 2 D28	-0.080 (0.09)	-0.062 (0.45)	-0.217 (0.32)	-0.099 (0.25)
TRAP 5b				
Cycle 1 D15	0.859 (2.16)	0.787 91.58)	0.150 (0.14)	0.938 (1.92)
Cycle 1 D28	0.422 (1.43)	-0.520 (1.81)	-0.591 (2.09)	0.089 (1.40)
Cycle 2 D28	-0.226 (1.77)	-1.628 (1.11)	-4.105 (3.61)	-1.269 (0.77)
Bone formation markers				
BSAP				
Cycle 1 D15	4.795 (13.93)	-5.956 (7.88)	-12.312 (8.65)	-8.095 (7.69)
Cycle 1 D28	5.724 (25.31)	-13.340 (15.16)	-21.855 (21.075)	-14.449 (8.39)
Cycle 2 D28	-3.855 (9.55)	-34.393 (34.64)	-50.133 (35.19)	-24.197 (17.69)
OC				
Cycle 1 D15	1.464 (4.6044)	-2.579 (15.433)	-3.462 (12.2130)	-2.720 (19.5484)
Cycle 1 D28	1.481 (8.93)	-6.513 (17.08)	-5.957 (20.11)	1.263 (25.85)
Cycle 2 D28	-1.165 (7.16)	-14.170 (18.80)	-9.377 (35.39)	-28.993 (41.00)
P1NP				
Cycle 1 D15	44.111 (70.22)	-0.916 (102.24)	-7.840 (38.68)	-63.441 (179.20)
Cycle 1 D28	13.146 (45.61)	1.96 (193.07)	-55.550 (152.05)	-81.611 (215.05)
Cycle 2 D28	-12.050 (34.58)	-89.917 (67.80)	-119.467 (228317)	-229.990 (221.15)

BSAP = bone-specific alkaline phosphatase; CTx = C-terminal telopeptide of type 1 collagen; OC = osteocalcin; OPG = osteoprotegerin; P1NP = procollagen 1 N-terminal peptide; SD = standard deviation; TRAP5b = tartrate resistant acid phosphatase 5b

Supplemental Table 2: Adverse events, regardless of study drug relationship, by preferred term, maximum grade, and treatment (≥ 10% of all children or Adults; Safety Analysis Set)

Preferred term	Sonidegib Daily Dose, mg/m^2								All Children N = 60		Adults N = 16	
	233 N = 11		372 N = 16		425 N = 11		680 N = 22					
	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
Total	11 (100.0)	9 (81.8)	16 (100.0)	8 (50.0)	11 (100.0)	5 (45.5)	22 (100.0)	16 (72.7)	60 (100.0)	38 (63.3)	16 (100.0)	9 (56.3)
Vomiting	5 (45.5)	1 (9.1)	9 (56.3)	0	7 (63.6)	1 (9.1)	17 (77.3)	5 (22.7)	38 (63.3)	7 (11.7)	2 (12.5)	0
Headache	6 (54.5)	1 (9.1)	8 (50.0)	2 (12.5)	4 (36.4)	2 (18.2)	11 (50.0)	3 (13.6)	29 (48.3)	8 (13.3)	2 (12.5)	0
Fatigue	5 (45.5)	0	7 (43.8)	1 (6.3)	3 (27.3)	0	6 (27.3)	1 (4.5)	21 (35.0)	2 (3.3)	1 (6.3)	0
Nausea	5 (45.5)	1 (9.1)	4 (25.0)	0	3 (27.3)	0	8 (36.4)	0	20 (33.3)	1 (1.7)	4 (25.0)	0
Constipation	1 (9.1)	0	6 (37.5)	0	4 (36.4)	0	3 (13.6)	0	14 (23.3)	0	2 (12.5)	0
Muscle spasms	2 (18.2)	0	4 (25.0)	0	5 (45.5)	0	2 (9.1)	0	13 (21.7)	0	4 (25.0)	0
Pain in extremity	2 (18.2)	0	6 (37.5)	0	4 (36.4)	0	1 (4.5)	1 (4.5)	13 (21.7)	1 (1.7)	0	0
Myalgia	1 (9.1)	0	2 (12.5)	1 (6.3)	4 (36.4)	0	5 (22.7)	0	12 (20.0)	1 (1.7)	5 (31.3)	0
Abdominal pain	1 (9.1)	0	3 (18.8)	0	2 (18.2)	0	5 (22.7)	1 (4.5)	11 (18.3)	1 (1.7)	1 (6.3)	0
Decreased appetite	1 (9.1)	1 (9.1)	2 (12.5)	1 (6.3)	4 (36.4)	1 (9.1)	4 (18.2)	1 (4.5)	11 (18.3)	4 (6.7)	3 (18.8)	0
Ataxia	2 (18.2)	2 (18.2)	2 (12.5)	0	2 (18.2)	1 (9.1)	4 (18.2)	1 (4.5)	10 (16.7)	4 (6.7)	0	0
Blood creatine phosphokinase increased	1 (9.1)	0	1 (6.3)	0	2 (18.2)	0	6 (27.3)	2 (9.1)	10 (16.7)	2 (3.3)	8 (50.0)	5 (31.3)
Cough	3 (27.3)	0	1 (6.3)	0	5 (45.5)	0	1 (4.5)	0	10 (16.7)	0	3 (18.8)	0
Diarrhea	2 (18.2)	0	5 (31.3)	0	2 (18.2)	0	1 (4.5)	0	10 (16.7)	0	4 (25.0)	0
White blood cell count decreased	2 (18.2)	1 (9.1)	2 (12.5)	0	3 (27.3)	0	3 (13.6)	0	10 (16.7)	1 (1.7)	1 (6.3)	0
Arthralgia	2 (18.2)	0	3 (18.8)	1 (6.3)	3 (27.3)	0	1 (4.5)	0	9 (15.0)	1 (1.7)	0	0
Lymphocyte Count decreased	2 (18.2)	1 (9.1)	1 (6.3)	1 (6.3)	3 (27.3)	1 (9.1)	3 (13.6)	2 (9.1)	9 (15.0)	5 (8.3)	1 (6.3)	1 (6.3)
Anemia	0	0	2 (12.5)	0	4 (36.4)	0	2 (9.1)	0	8 (13.3)	0	0	0
Asthenia	2 (18.2)	1 (9.1)	4 (25.0)	1 (6.3)	1 (9.1)	0	1 (4.5)	0	8 (13.3)	2 (3.3)	3 (18.8)	0
Convulsion	0	0	2 (12.5)	1 (6.3)	2 (18.2)	1 (9.1)	4 (18.2)	3 (13.6)	8 (13.3)	5 (8.3)	1 (6.3)	0
Hyponatremia	1 (9.1)	1 (9.1)	3 (18.8)	0	1 (9.1)	1 (9.1)	3 (13.6)	1 (4.5)	8 (13.3)	3 (5.0)	0	0

Pruritus	2 (18.2)	0	3 (18.8)	0	1 (9.1)	0	2 (9.1)	1 (4.5)	8 (13.3)	1 (1.7)	0	0
Aspartate Aminotransferase increased	0	0	2 (12.5)	0	2 (18.2)	0	2 (9.1)	0	6 (10.0)	0	1 (6.3)	1 (6.3)
Confusional state	1 (9.1)	0	2 (12.5)	1 (6.3)	1 (9.1)	1 (9.1)	2 (9.1)	2 (9.1)	6 (10.0)	4 (6.7)	1 (6.3)	0
Dry skin	0	0	2 (12.5)	0	3 (27.3)	0	1 (4.5)	0	6 (10.0)	0	1 (6.3)	0
Neck pain	0	0	3 (18.8)	0	2 (18.2)	0	1 (4.5)	0	6 (10.0)	0	2 (12.5)	0
Neutrophil count decreased	0	0	2 (12.5)	0	2 (18.2)	0	2 (9.1)	0	6 (10.0)	0	0	0
Somnolence	0	0	3 (18.8)	2 (12.5)	1 (9.1)	1 (9.1)	2 (9.1)	2 (9.1)	6 (10.0)	5 (8.3)	0	0
Weight decreased	1 (9.1)	0	2 (12.5)	0	0	0	2 (9.1)	0	5 (8.3)	0	3 (18.8)	0
Gait disturbance	1 (9.1)	0	1 (6.3)	0	1 (9.1)	0	1 (4.5)	0	4 (6.7)	0	2 (12.5)	0
Stomatitis	1 (9.1)	0	1 (6.3)	0	1 (9.1)	0	0	0	3 (5.0)	0	3 (18.8)	0
Hiccups	1 (9.1)	0	0	0	0	0	0	0	1 (1.7)	0	3 (18.8)	0
Paresthesia	0	0	1 (6.3)	0	0	0	0	0	1 (1.7)	0	2 (12.5)	0
Upper respiratory tract infection	0	0	1 (6.3)	0	0	0	0	0	1 (1.7)	0	2 (12.5)	0

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