TRAMETINIB

PEDIATRIC ONCOLOGY ADVISORY COMMITTEE MEETING

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1. EXECUTIVE SUMMARY

Trametinib (GSK1120212 and previously known as JTP-74057) is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2. MEK1 and MEK2 are proteins in the MAP-kinase (MAPK) signal transduction pathway, which is critical for cell proliferation and survival. Specific oncogenic mutations in the upstream MAPK pathway proteins BRAF and RAS constitutively activate the MAPK pathway, thus driving tumor cell proliferation and dissemination. Although, inhibitors of BRAF have demonstrated clinical activity in tumors harboring activating BRAF mutation it is also known that these mutations predicts sensitivity to MEK inhibition. Several MEK inhibitors have entered into clinical trials for a variety of solid tumors. However, trametinib is the first MEK inhibitor which has demonstrated clinically significant activity in a randomized Phase III study and for which a New Drug Application (NDA) has been submitted for the treatment of unresectable or metastatic BRAF V600-mutation positive melanoma. Compared to most other MEK inhibitors in development, trametinib has a unique pharmacokinetic (PK) profile which provides prolonged exposure after once daily dosing with a low peak to trough concentration ratio with sustained levels of molecular target inhibition. Pre-clinically, trametinib has demonstrated potent cell growth inhibition in most BRAF or RAS mutation-positive tumor cell lines.

Trametinib is being evaluated in multiple tumor types and has shown anti-tumor activity in subjects with BRAF V600-mutation positive metastatic melanoma in a recent Phase III study. Trametinib is currently being developed both as monotherapy and in combination with other anti-cancer medications including cytotoxic drugs and targeted small-molecule inhibitors. Trametinib is not approved by any regulatory authority worldwide.

To date studies evaluating trametinib in children have not been conducted. In order to fulfill European regulatory requirements, a Pediatric Investigation Plan (PIP) for trametinib was approved by the European Medicines Agency (EMA) in first quarter of 2012. The approved PIP is a commitment to study trametinib in pediatric patients with solid malignant tumors with known or expected RAS, RAF or MEK pathway activation and to conduct a modeling study to extrapolate adult efficacy data to adolescent patients with melanoma containing BRAF V600 activating mutations. This pediatric development plan includes: (i) an ongoing study evaluating the relative bioavailability of trametinib tablets and the trametinib pediatric formulation following single-dose administration in adult subjects, (ii) a planned Phase I study in pediatric population (1 month to <18 years) with advanced solid tumors with activated MAPK pathway, (iii) a planned phase II study in pediatric population with tumor type selected based on initial activity observed in expansion cohorts in Phase I study and lastly (iv) a modeling study to extrapolate the observed adult efficacy data in BRAF V600-mutant melanoma to adolescent patients (12-17 years).

Despite well recognized challenges with conducting studies in children including a small number of pediatric subjects that could participate in clinical trials, GSK is committed to trametinib development for children with cancer. To ensure timely completion of the proposed plan, the sponsor has intention to conduct these trials in collaboration with cooperative groups.

2. TRAMETINIB REGULATORY HISTORY

GlaxoSmithKline (GSK) is currently conducting studies under an active investigational new drug (IND) application for trametinib filed with the FDA. Trametinib received orphan drug designation from the FDA for treatment of BRAF V600 mutation positive Stage IIb through IV melanoma, and additionally, trametinib received Fast Track Status "for the treatment of patients with BRAFV600K mutation-positive, unresectable or metastatic melanoma to demonstrate improved progression-free survival".

GSK partnered with bioMerieux in the co-development of a companion diagnostic assay to be available at the time of trametinib registration. In discussions with FDA's Center for Devices and Radiological Health (CDRH)/Office of In Vitro Diagnostics (OIVD) agreement was reached on the bridging requirements for the "investigational use only" (IUO) assay used in clinical trials to the final companion diagnostic for commercial use.

Trametinib is not approved for any indication in any market at this time. A New Drug Application (NDA) is currently under review with FDA for the treatment of patients with unresectable or metastatic melanoma with BRAF V600 mutation as detected by an FDA approved test. A marketing application has also been submitted in Canada. A complete analytical validation package was included in a Premarket Approval Application (PMA) filed by BioMerieux to CDRH/OIVD concurrently with the NDA to support the parallel registration of the companion diagnostic.

A Pediatric Investigation Plan (PIP) for trametinib was approved by the European Medicines Agency (EMA) in first quarter of 2012 and reflects a commitment to study trametinib in pediatric patients with solid malignant tumors with known or expected RAS, RAF or MEK pathway activation and to conduct a modeling study to extrapolate adult efficacy data to adolescent patients with melanoma containing BRAF V600 activating mutations. EMA granted a waiver for preterm and term newborn infants from birth to less than 28 days old on the grounds that these pediatric patients are not commonly afflicted with the advanced solid tumors described above and confirmed that the class waiver for the treatment of melanoma in age groups from 0 to less than 12 years old was applicable to trametinib. As an orphan drug, trametinib is exempt from Pediatric Research Equity Act (PREA). A Proposed Pediatric Study Request (PPSR) was recently submitted to the Agency.

3. CLINICAL DEVELOPMENT OF TRAMETINIB IN ADULTS IN CANCER INDICATIONS

The RAS/RAF/MEK/ERK (MAPK pathway) is a critical signal transduction cascade implicated in the uncontrolled proliferation of many human cancers as well as other chronic diseases, such as neurofibromatosis (NF). Normally, this pathway is activated by the binding of extracellular growth factors to membrane-bound growth factor receptors that leads to the activation of the critical signaling proteins in this cascade: RAS, RAF and MEK. Activated MEK then phosphorylates its only known substrates, the MAP kinases ERK1 and ERK2. Phosphorylated ERK dimerizes and translocates to the nucleus, where it is involved in cellular proliferation, nuclear transport, deoxyribonucleic acid (DNA) repair, nucleosome assembly, messenger ribonucleic acid (mRNA)

processing, and translation. In cancer, mutated oncogenic forms of RAF and RAS are one of the main mechanisms that lead to hyperactivation of MEK and ERK, resulting in increased cell proliferation, dissemination and survival. Mutated oncogenic forms of RAS are found in approximately 15% of all cancers [Davies, 2002]. The prevalence of RAS mutations varies across tumor types. KRAS mutations, specifically, are common in pancreatic, colorectal, endometrial, lung, cervical, and biliary tract cancer [Schubbert, 2007]. In addition, activating BRAF mutations have been identified at a high frequency in certain human cancers, including approximately 60% of cutaneous melanoma, approximately 50% of papillary thyroid, 5 to 20% of colorectal, approximately 30% of ovarian, approximately 26% of cisplatin-resistant germ cell tumors, and in 60% of cases of Langerhans cell histiocytosis (LCH) [Wellbrock, 2004; Honecker, 2009; Badalian-Very, 2010]. In patients with NF, RAS is hyper-activated due to loss of function of a tumor-supressor protein, neurofibromin, which may contribute to the increased susceptibility of these patients to the development of tumors such as optic pathway gliomas, malignant peripheral nerve sheath tumors (MPNST), neuroblastomas, and plexiform neurofibromas [Schubbert, 2007; Wetmore, 2010]

While activating mutations of MEK itself have not been identified in human cancers, MEK is thought to be an important drug target for treating cancer that may involve enhanced RAS/RAF signaling, because of its central role in the this pathway.

Trametinib, N-[3-[3-cyclopropyl-5-[(2-fluoro-4-iodophenyl)amino]- 6,8-dimethyl-2,4,7-trioxo-3,4,6,7-tetrahydropyrido[4,3-D]pyrimidin-1(2H)-yl]phenyl]acetamide, dimethylsulfoxide solvate, is a reversible, highly selective, allosteric inhibitor of mitogen-activated extracellular signal regulated kinase 1 (MEK1) and MEK2.

3.1. Pharmacokinetics in Adults

Trametinib pharmacokinetic data are available from the following clinical programs conducted in adults with advanced/metastatic cancer. Studies are completed and a clinical study report is available unless otherwise indicated as ongoing:

Clinical Pharmacology Studies:

- MEK113708: Phase I Absorption, Distribution, Metabolism and Excretion study
- MEK113709: Phase I Food Effect study
- MEK115064: Absolute Bioavailability study (ongoing)
- MEK115892: Relative Bioavailability study (ongoing)
- MEK114655: QTc study (ongoing)

Single Agent PK:

- MEK111054: Phase I (First-time-in-human) FTIH study
- MEK111759: Phase I in patients with leukemia (ongoing)
- MEK113583: Phase II in unresectable, BRAF V600-mutation positive melanoma (sparse sampling)
- MEK114267: Phase III in unresectable, BRAF V600-mutation positive melanoma (sparse sampling)

In addition, PK was also determined in clinical studies evaluating trametinib in combination with gemcitabine, dabrafenib, everolimus, docetaxel, pemetrexed, erlotinib and carboplatin as well as AKT and PI3K inhibitors in adult patients with cancer.

Single and Repeat Dose Pharmacokinetics: Following single-dose administration, plasma concentrations of trametinib peaked approximately 1 to 3 hours post-dose and decreased thereafter following a bi-exponential decline. Mean trametinib half-life ranged from 1.2 to 5.6 days, across the different dose cohorts. Following single oral doses, the dose-normalized PK parameters varied across individuals (>10-fold). In general, AUC(0-24) and Cmax values were dose proportional up to 6 mg. Mean variability (CV%) in exposure ranged from 12 to 69% for Cmax and 21 to 143% for AUC(0-∞) across all dosing regimens.

Following repeat-dosing, the AUC(0-τ) and Cmax increased in an approximately dose proportional manner. Trametinib accumulates with repeat dosing with a mean accumulation ratio at the recommended dose of 2 mg once-daily of 5.97 and a terminal half-life of 5.3 days. Steady state appears to be achieved by Day 15, with little difference in pre-dose (trough) concentration at the end of the dosing interval (Cτ), Cmax AUC(0-24) between Days 15 and 21. Following administration of 2 mg once-daily, geometric mean Cmax, AUC(0-τ) and pre-dose concentrations were 22.2 ng/mL, 370 hg*hr/mL and 12.1 ng/mL, respectively. The peak:trough ratio averaged 1.8 at the recommended dose of 2 mg once-daily. The intersubject variability was low (<28%) regarding AUC and Cmax.

Absorption and Food Effect: Trametinib is absorbed rapidly with median Tmax generally occurring 1.50 hours after single oral administration under fasting conditions. The absolute oral bioavailability of a single trametinib 2.0 mg tablet is moderate to high (72%) relative to a co-administered IV microdose. Single-dose administration of trametinib with a high-fat, high-calorie meal resulted in a 70% decrease in (Cmax) and a 10% decrease in (AUC(0-∞)) compared to fasted conditions. The clinical impact of the effect of food on trametinib exposure with repeat dosing is unclear. Trametinib is recommended to be administered under fasting conditions, either 1 hour before or 2 hours after a meal.

Metabolism: Trametinib is metabolized predominantly via deacetylation (non-CYP450 mediated) with secondary oxidation or in combination with glucuronidation biotransformation pathways.

Excretion: Fecal excretion is the major route of elimination.

Renal or Hepatic Impairment: Mild and moderate renal impairment had no effect on trametinib exposure. No data are available in patients with severe renal impairment. The pharmacokinetics of trametinib were characterized in 64 patients enrolled in clinical trials with trametinib who had mild hepatic impairment. Exposure to trametinib was not significantly different in these patients relative to patients with normal hepatic function. No data are available in patients with moderate or severe hepatic impairment.

Impact of Demographic Factors: Based on population PK analysis, sex and body weight were found to influence trametinib oral clearance (CL/F). Although smaller

female subjects are predicted to have higher exposure than heavier male subjects, these differences are unlikely to be clinically relevant and no dosage adjustment is warranted in adult population. Age also had no relevant clinical effect on trametinib pharmacokinetics. The PK of trametinib has not been studied in different ethnic groups. Race/ethnicity other than White was not represented in the population PK analysis.

Drug-Drug-Interaction: *In vitro* and *in vivo* data suggest that GSK1120212 is unlikely to affect the PK of other drugs and that the PK of trametinib is unlikely to be affected by other drugs. Trametinib is likely deacetylated via hydrolytic esterases which are not generally associated with drug interaction risk, nor is it a substrate of P-gp or BCRP.

3.2. Pharmacodynamics in Adults

Based on the adverse events (AEs) observed in the dose escalation phase of study MEK111054, the maximum tolerated dose of trametinib was established at 3.0 mg once daily, and the recommended Phase II dose (RP2D) was identified as 2.0 mg once daily. However, repeat administration of trametinib doses of 0.5, 1.0, and 2.0 mg once-daily in FTIH trial resulted in dose-dependent modulations in tumor biomarkers such as pERK (MAP-kinase pathway activity), KI-67 (proliferation), and p27 (apoptosis) in tumor tissue obtained from subjects with BRAF V600-mutation positive melanoma. The mean trametinib concentrations observed following repeat-dose administration of 2.0 mg once-daily exceeds the pre-clinical target concentration of 10.4 ng/mL over a 24-hr dosing interval, thereby providing sustained inhibition of the MEK pathway.

Exposure-response analyses in both the Phase II and III studies were conducted to support the dose recommended for treatment of subjects with BRAF V600 mutation positive melanoma. The range of exposure with continuous daily administration of trametinib is relatively narrow as drug exposures exhibit low variability after repeat dosing in patients and thus limit full exploration of exposure-response. Overall, subjects with higher exposure tended to have better response than those with lower exposure. This was shown based on PFS and tumor size data and a trend was observed with objective response, but this did not reach statistical significance.

3.3. Current Drug Development Plan for Indications in Adults

3.3.1. Melanoma

In the randomized, controlled, open-label, multicenter Phase III study MEK114267 (METRIC) trametinib has demonstrated statistically and clinically significant advantage over standard chemotherapy in subjects with metastatic BRAF V600 mutation positive melanoma. In this study, subjects (N = 322) who were treatment naïve or may have received one prior chemotherapy treatment in the metastatic setting were randomized 2:1 to receive trametinib (2 mg once daily) or a choice of two chemotherapies at the investigator's discretion (dacarbazine 1000 mg/m^2 every 3 weeks or paclitaxel 175 mg/m^2 every 3 weeks). Patients in the chemotherapy arm were allowed to cross-over to the trametinib arm after independent confirmation of progression. A statistically significant improvement in the primary efficacy endpoint of PFS in favor of trametinib (hazard ratio [HR] 0.45, 95% CI 0.33 to 0.63, $p<0.0001$) was observed in the ITT and across multiple sub-populations. In addition, treatment with trametinib as compared to standard

chemotherapy resulted in an increased overall response rate and longer overall survival. In this pivotal study, trametinib demonstrated an acceptable safety profile.

3.3.2. Other tumor types investigated in adults

Trametinib monotherapy has also been investigated in other tumor types including pancreatic cancer, NSCLC and AML.

3.4. Safety of Trametinib Administered to Adults

The safety of trametinib has been evaluated in an integrated population of 329 patients with metastatic melanoma treated with trametinib 2 mg orally once daily. The most common adverse reactions (>20%) associated with trametinib treatment include:

- Rash and related toxicities: overall rate of 87% of subjects with most frequently reported terms being rash (57% of subjects) and dermatitis acneiforme (22% of subjects)
- Gastrointestinal Adverse Events: diarrhea (50 % of subjects), nausea (22% of subjects)
- General Adverse Events: peripheral edema (27% of subjects)

Less frequent adverse events potentially associated with the mechanism of MEK inhibition and of clinical interest include:

- Cardiac Disorders: LVEF decrease 9% and hypertension (14%)
- Ocular Disorders: rare cases of central serous retinopathy and retinal vein occlusion; all unilateral to date.
- Hepatic Disorders: hepatic enzyme elevations (11%) ; no Hy's Law cases
- Pulmonary Disorders: Pneumonitis (<1%)

4. CLINICAL DEVELOPMENT OF TRAMETINIB IN PEDIATRICS

4.1. Introduction and Background

Based on the available pre-clinical and clinical data, trametinib demonstrated activity in adult tumors harboring activating BRAF or RAS-mutations. Hence, pediatric tumor with constitutive activation of MAPK pathway may be also sensitive to trametinib treatment and activation of this pathway is described in a variety of pediatric tumors.

Pediatric tumor harboring BRAF V600-mutations include:

- Langerhans cell histiocytosis (LCH) - 60% of a cohort of archival lesion samples obtained from children and adults with LCH [Badalian-Very, 2010]
- Melanoma -50% of cases of pediatric melanoma may involve BRAF V600E mutations, which is a proportion similar to that observed in adults [Daniotti, 2009].

- Papillary thyroid carcinoma - approximately 20% of cases in patients aged <20 years [Rosenbaum, 2005; Kumagai, 2004]
- Low- and high-grade gliomas:
    - gangliogliomas -50-60% [MacConaill, 2009; Dougherty, 2010; Schindler, 2011]
    - pilocytic astrocytomas - 2-12% [Forshew, 2009; Pfister 2008; MacConaill, 2009; Qaddoumi, 2009; Jacob, 2009; Dias-Santagata, 2011; Schindler, 2011]
    - high-grade astrocytomas - 30% [Schiffman, 2010; Basto, 2005]

In addition, more than 50% of juvenile pilocytic astrocytomas harbor the specific BRAF fusion gene KIAA1549-BRAF that constitutively activates wild-type BRAF and in consequence the MAPK-pathway. This fusion product has also been identified at a particularly high rate in cerebellar pilocytic astrocytoma specifically (>80%) [Horbinski, 2009; Jones, 2009; Jacob, 2009]. In a pre-clinical study the MEK1/2 small-molecule inhibitor AZD6244 has shown evidence of anti-tumour activity in a juvenile pilocytic astrocytoma xenograft model [Kolb, 2010].

Other pediatric tumors with activated RAS signaling and MAPK pathway activation:

- Neurofibromatosis-related malignancies - loss of neurofibronin function (NF1) leads to loss of neurofibromin activity that results in hyperactivation of Ras, which stimulates MEK, and then ERK activity [Boyd, 2009]. Patients with NF1 have an increased susceptibility to the development of a number of central nervous system tumors including: neurofibromas, astrocytomas (particularly optic pathway), and malignant peripheral nerve sheath tumors (MPNST) [Benesch, 2010]
- Neuroblastoma is the most common extracranial solid tumor in childhood, with half of cases being considered high-risk. Several reports suggest important role of MAPK pathway in the growth, dissemination or response to treatment of neuroblastoma;
    - ERK was shown to be highly phosphorylated in approximately 50% of a set of 116 primary neuroblastoma samples [Opel, 2007]
    - Interruption of MEK signaling with the small molecule inhibitor U0126 in preclinical models of neuroblastoma with NF-1 loss, results in restoration of responsiveness to retinoic acid [Holzel, 2010]
    - Amplification of MYCN oncogene has been reported to be associated with resistance to therapy and poor prognosis of neuroblastoma. Reports from pre-clinical studies have shown that IGF-I induces MycN expression at the RNA level and cell cycle progression through the IGF-IR/MEK/ mitogen-activated protein kinase (MAPK) pathway in KPN-RT human neuroblastoma cells [Chambery, 1999; Misawa, 2000].

Current standard of care therapies usually offer benefit in the initial systemic treatment of pediatric patients between the ages of 1 month and 17 years, with unresectable melanoma and low- or high-grade gliomas, as well as high risk LCH. However, active and tolerable treatment options are needed in the relapsed and recurrent treatment setting once the initial standard therapies have failed. Based on the specific mode-of-action, trametinib

may demonstrate clinical activity in tumors with known activations of the MAPK-pathway.

4.2. Nonclinical Studies

Nonclinical toxicology studies in juvenile male and female rats are in progress and data is being generated to support clinical investigation in children. The two ongoing studies, a rat juvenile tolerability study and a rat GLP juvenile toxicity study, will be completed prior to the initiation of pediatric clinical studies.

4.3. Pediatric Dose Rationale

In general, it is expected that developmental differences will not play a significant role in altering clinical tolerability of trametinib in infants, children and adolescents. However, juvenile rat PK exposures were approximately 2.5 fold higher than those observed in adult rats the recommended starting dose in the pediatric population will be based on 50% of the adult dose (1 mg or 0.0125 mg/kg once-daily dose).

For both adolescent patients aged ≥12 to <18 years and for children aged ≥2 to 11 years, the trametinib target starting dose will be scaled by body weight. Children aged ≥2 to 11 years may ultimately require a higher mg/kg to achieve exposures similar to adults. Several drugs that are approved for use in children have routinely demonstrated that young children have higher weight-adjusted drug clearance than older children and adults [Lamictal, 2010; Trileptal, 2009; Prilosec, 2011; Kaletra, 2011; Viracept, 2010]. Given the rapidly changing absorption, distribution, metabolism, and excretion processes in children <2 years old, it is difficult to predict the impact on trametinib exposure; initial doses will be scaled by body weight; for infants (1 to 6 months) the initial mg/kg dose will be 40% of the adult mg/kg dose.

4.4. Pediatric Formulation of Trametinib

An age-appropriate powder for oral solution formulation is being developed. The dosage form will be presented as a powder in an amber bottle with child resistant screw-cap closure. The solution will be prepared at the clinical site by reconstituting the powder with purified water to a solution for single or multiple use. The active drug used in the pediatric oral solution is the same as that used in the tablet formulation. It is designed to deliver a 0.05 mg dose of trametinib, as free base, in 1 mL of solution.

GSK is currently conducting a relative bioavailability study of this powder for oral solution in adults to develop an appropriate pediatric formulation.

4.5. On-going and Planned Studies Relevant to Development of Trametinib in Pediatric Indications

A total of 4 studies relevant to trametinib development for pediatric indication are on-going or planned. They are listed in Table 1 and described in more detail below. These proposed studies form the clinical core of the agreed PIP for trametinib.

Table 1 Studies Relevant to Pediatric Development of Trametinib

Study No.	Study Title	Study status	Main objective
MEK-PIP-01	Open-label, single agent, uncontrolled Phase I dose escalation trial to determine the safety, tolerability, pharmacokinetics and maximum tolerated dose of GSK1120212 in children from 1 month to less than 18 years of age with relapsed/refractory solid malignant tumors.	Planned	To evaluate pharmacokinetics of trametinib in pediatric patients To determine dose exposure relationship for various age groups To evaluate pharmacodynamic effects of trametinib on relevant biomarkers (including at least pERK) and the anti-tumor activity To evaluate acceptability and palatability of the age-appropriate powder for oral solution formulation and the acceptability of the film-coated tablets. To evaluate preliminary evidence of antitumor activity
MEK-PIP-02	Randomized, controlled, parallel-group Phase II trial to determine the safety and efficacy of GSK1120212 in children from 1 month to less than 18 years of age with solid malignant tumors with known or expected RAS/RAF/MEK pathway activation	Planned	To evaluate efficacy of trametinib compared with standard of care in selected pediatric tumor type from the Expansion Cohort phase of Phase I study To further evaluate safety and tolerability of trametinib in pediatric population
MEK-PEDS-03	An open-label study to assess the relative bioavailability of GSK1120212 tablets and the GSK1120212 pediatric formulation following single-dose administration to adult subjects.	Ongoing	To determine relative bioavailability of the trametinib powder for oral solution formulation relative to the film-coated tablet formulation
Modeling and Simulation	Measure to extrapolate efficacy to the pediatric population	Planned	To extrapolate observed adult efficacy data in BRAF V600-mutant melanoma to adolescent patients (12-17 years)

4.5.1. MEK-PIP-01 - Phase I dose escalation study

A two-part, open-label, Phase 1 dose escalation study of trametinib in pediatric patients (age 1 month – 17 years, inclusive) with advanced or relapsed recurrent solid tumors. The objective of the first part of the study will be to identify a safe and tolerable recommended Phase 2 dose(s) of trametinib that provides an exposure comparable to the exposure necessary for anti-tumor activity seen in adult BRAF V600 mutant melanoma.

The objective of the second part of the Phase 1 study is to gather additional safety and tolerability data for the recommended Phase 2 dose and also assess evidence of clinical activity in various pediatric solid tumor types known to have high frequency of RAS/RAF/MEK pathway activation. This will be accomplished by enrolling an estimated 40 patients at the recommended Phase 2 dose in four disease-specific cohort expansions (e.g., neuroblastoma, BRAF tandem-duplication juvenile pilocytic astrocytoma, LCH, and BRAF V600-mutant high-grade glioma). Final choice of specific tumor types for expansion cohorts will be based on available clinical and preclinical data. Each expansion cohort will enroll a minimum of 10 patients, and early evidence of clinical activity of trametinib in each cohort will be considered to be an objective (radiographic) response rate using standard and appropriate disease-specific response criteria of ≥10% (1 or more out of 10 patients in any given cohort).

4.5.2. MEK-PIP-02 – Randomized, controlled, parallel group phase II trial

A randomized (if feasible), controlled, parallel-group Phase 2 safety and efficacy study of trametinib in pediatric patients with an advanced/relapsed solid tumor diagnosis (excluding melanoma). The specific indication will be determined based on evidence of clinical activity generated in the dose escalation portion, and the various disease-specific cohort expansions in the Phase 1 study (≥10% objective response rate using disease-appropriate response assessment criteria), as described above. In the event that there are multiple indications that show evidence of activity, a single indication will most likely be chosen, based on a variety of factors including the extent of anti-tumor efficacy, size of patient population, and the ability to assess a clinically relevant endpoint (e.g. progression-free survival or overall survival). The number of patients foreseen for such a trial will depend on the indication under study as the response rates to existing salvage therapies varies broadly by disease. The most appropriate primary endpoint for the studied indication in this Phase II trial will be selected (progression-free survival, overall response rate or overall survival). The secondary endpoints will include safety and tolerability as well as PK.

4.5.3. MEK-PEDS-03 – Relative bioavailability trial

An open-label study is ongoing to assess the relative bioavailability of GSK1120212 tablets and the GSK1120212 pediatric formulation following single-dose administration to adult subjects. The purpose of this study is to evaluate the pharmacokinetic properties and bioavailability of the proposed GSK1120212 powder for oral solution formulation, relative to the tablet formulation in order to support the use of the pediatric formulation in the planned Phase 1 study in pediatric patients. Approximately 18 adult subjects (male or female) with histologically-or cytologically-confirmed diagnosis of a solid tumor malignancy that is not responsive to standard therapies; or for which there is no approved or curative therapy; or for subjects which refuse standard therapy, and who are able to swallow and retain oral medication will be enrolled.

4.5.4. Study 4 - Modeling and simulation study

This study is designed to demonstrate that the PK, PD and efficacy of trametinib in adolescent patients (aged from 12 to less than 18 years of age) with BRAF V600-mutant

melanoma are similar to that in adults with BRAF V600-mutant melanoma. It will provide efficacy assumptions in the pediatric population based on extrapolation. Data from Phase I dose escalation trial (MEK-PIP-01 study) as well as in house data and data from the literature detailing similarities and differences between adult and adolescent melanoma, including histopathology, molecular biology/pathology, incidence of BRAF-V600 mutations, disease presentation and prognosis as well as response to inhibitors of the RAS-, RAF- or MEK pathway will be used.

4.6. Adverse Events of Special Interest in Pediatric Trials

As there is no specific toxicity data in pediatric patients with advanced/metastatic cancer treated with trametinib, the general risk for ocular- and cardiac-related AEs is considered similar to those in the adult population. There may be developmental factors that would influence either of these toxicities, or generate unexpected toxicities. In absence of specific data, it is proposed to use the same In-/Exclusion criteria and per-protocol safety assessments established for ocular- and cardiac-related AEs in adult tumor patients for the pediatric tumor population.

4.7. Pediatric Investigation Plan

In first quarter of 2012, GSK and EMA agreed to a PIP that includes development of an age appropriate formulation, juvenile toxicity studies, and the studies described above.

4.7.1. Pediatric subsets to be studied in the PIP

GSK will evaluate trametinib in the following pediatric subsets:

- Infants and toddlers (1 to 24 months)

- Children (2 to 11 years)

- Adolescents (12 to 17 years)

Trametinib may provide another therapeutic option for pediatric patients with advanced solid tumors who experience relapse following treatment with at least one standard therapy.

The studies will not involve premature infants and newborn infants ≤28 days old because in the published pediatric medical literature, reports of solid tumors in premature infants or newborn infants <1 month of age are limited, although examples exist. Following initial treatment, any reoccurrences in such patients that would require additional therapies are inevitably observed after the first month of life.

4.8. Challenges in the Development of Trametinib for Pediatric Indications

The main challenge for the development of trametinib in the treatment of pediatric cancer patients is the rarity of these specific tumor types and thus the limited number of subjects who could participate in clinical trials. The small number of potential subjects impacts

endpoints, timelines and statistical power. Pediatric cooperative groups have advanced the treatment success for this population. GSK will seek the assistance of the pediatric cooperative groups in design and conduct of the Phase I and Phase II trials of trametinib.

Despite the difficulties inherent in drug development in pediatric oncology and the specific challenges with trametinib, GSK is committed to the improvement of treatment outcomes for children with cancer.

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