9 November 2017
EMA/CHMP/86716/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Mektovi

Note: The product name was changed to Balimek on the 13th November 2017

International non-proprietary name: binimetinib

Procedure No. EMEA/H/C/004052/0000

Note

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

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List of abbreviations

ADME	Absorption, distribution metabolism and excretion
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse events of special interest
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC_{0-12}	Area under the concentration-time curve from time 0 to 12 hours
$AUC_{tau,ss}$	Area under the concentration-time curve from time 0 to the end of the dosing interval tau at steady state
BCRP	Breast cancer resistance protein
BID	Twice-daily
BIRC	Blinded independent review committee
BRAF	V-raf murine sarcoma viral oncogene homolog B1
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence intervals
CK	Creatine kinase
CL/F	Apparent total clearance following oral administration
Cmax	Maximum observed plasma concentration
Cmax,ss	Maximum observed plasma concentration at steady state
Cmin,ss	Minimum observed plasma concentration at steady state
CrCL	Calculated creatinine clearance
CSP	Clinical study protocol
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Human cytotoxic T-lymphocyte antigen-4
CYP	Cytochrome P450
DCR	Disease control rate

DOR	Duration of response
DRESS	Drug reaction with eosinophilia and systemic symptoms
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EMA	European Medicines Agency
ESMO	European Society for Medical Oncology
EU	European Union
FAS	Full Analysis Set
HR	Hazard ratio
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
INR	International Normalized Ratio
IOP	Intraocular pressure
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention-to-Treat
IV	Intravenous(ly)
KM	Kaplan-Meier
KRAS	Kirsten rat sarcoma viral oncogene homolog
LDH	Lactate dehydrogenase
LLN	Lower limit of normal
LVEF	Left ventricular ejection fraction
MAA	Marketing Authorisation Application
MAP	Mitogen-activated protein
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase kinase
MEK162	Binimetinib
MUGA	Multi-gated acquisition
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not estimable

NRAS	Neuroblastoma RAS viral (v-ras) oncogene homolog
OCT	Optical coherence tomography
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein 1
pERK	Phosphorylated extracellular signal-regulated kinase
PFS	Progression-free survival
P-gp	Phosphorylated glycoprotein
PIP	Paediatric investigational plan
PK	Pharmacokinetics
PRO	Patient-Reported Outcome
PT	Preferred term
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumours
RP2D	Recommended Phase 2 dose
RPED	Retinal pigment epithelium detachment
RVO	Retinal vein occlusion
SAE	Serious adverse event
t1/2	Apparent terminal half-life
Tmax	Time to maximum observed plasma concentration
TNFα	Tumours necrosis factor alpha
TTR	Time to response
UGT	Uridine glucuronosyltransferase
ULN	Upper limit of normal
VTE	Venous thromboembolism
Vz/F	Volume of central distribution

1. Recommendation

Based on the review of the data on quality, safety and efficacy, the CHMP consider that the application for Mektovi, in the treatment of adult patients with unresectable or metastatic melanoma, with NRAS Q61 mutation, is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of questions.

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

- The efficacy of binimetinib in the proposed patient population is questionable compared to dacarbazine (1.3-month improvement in PFS along with an ORR of 15.2%). The assessment of questionable efficacy applies both on treatment naïve as well as on patients treated with prior immunotherapy. In the absence of an OS the limited improvement in PFS not considered clinically relevant. To further challenge the question whether improved PFS (and therefore, indirectly, higher ORR) constitutes actually a clinical benefit in the concrete context of the NEMO trial (a trial which allowed check point inhibitor/immunotherapy treatment once licensed after initiation of NEMO trial both prior to recruitment as well as post progression), two additional analyses/discussions are requested from the applicant.
- An unmet medical need for binimetinib, specifically targeting NRAS mutations in melanoma, has not been justified. The limited efficacy of binimetinib demonstrated and considering the clinical practice of treating these patients with relatively effective treatments for BRAF wild type melanoma, including checkpoint inhibitors and PD-1 inhibitors, does not support the claim that binimetinib fulfils an unmet medical need.
- Safety in the studied population is a concern due to poorer safety, including quicker deterioration of ECOG PS (including deterioration free survival [DFS]) with binimetinib compared to dacarbazine chemotherapy. The observed deleterious effects on longer term OS may be attributable to the (very) poor efficacy of binimetinib as compared to checkpoint inhibitors administered post progression to a relevant proportion of patients in the pivotal NEMO trial.
- Further, the proposed mechanism for efficacy in NRAS mutation positive melanoma appears mainly theoretical and non-clinical evidence provided to support the claim is not compelling. As highlighted by the applicant in the responses, the knowledge about NRAS mutation positive melanoma is evolving and there are conflicting reports in literature regarding prognosis and possible improved response to PD-1 (or more general checkpoint) inhibitors.

New active substance status

Based on the review of the data, the CHMP considers that the active substance, binimetinib, contained in the medicinal product, Mektovi, could be qualified as a new active substance provided that satisfactory responses are given to the concerns as detailed in the List of Questions.

2. Executive summary

2.1. Problem statement

2.1.1. Disease or condition

Pierre Fabre Médicament (Pierre Fabre) is submitting this Marketing Authorisation Application (MAA) in support of the following indication:

Mektovi is indicated for the treatment of adult patients with unresectable or metastatic melanoma with NRAS Q61 mutation.

2.1.2. Epidemiology

Malignant melanoma is the 19th most common cancer worldwide, with around 232,000 new cases (2% of the total) diagnosed in 2012 (Ferlay, 2013; Ferlay, 2015). Malignant melanoma is the ninth most common cancer in Europe, with more than 100,000 new cases (3% of the total) diagnosed in 2012 (Skin cancer incidence statistics). The European incidence of malignant melanoma varies from 3 to 5/100 000/year in Mediterranean countries to 12–25 (and rising) in Nordic countries.

2.1.3. Biologic features

Approximately 20% of patients with unresectable or metastatic melanoma have NRAS-mutation positive tumours; of these, substitutions at position Q61 of exon 2 account for approximately 90% of NRAS mutations (Jakob et al 2012; Colombino et al 2012; Lee et al 2011; Bucheit et al 2013). Metastatic melanoma patients with an NRAS mutation may represent a distinct clinical subset of melanoma with a more aggressive clinical course and shorter survival compared to wild-type and v-raf murine sarcoma viral oncogene homolog B1 (BRAF)-mutation positive melanoma (Devitt et al 2011; Eggermont and Robert 2011; Jakob et al 2012).

2.1.4. Clinical presentation, diagnosis and stage / prognosis

Literature data states that melanomas frequently harbour mutually exclusive BRAF or NRAS mutations (Jakob et al 2012; doi: 10.1002/cncr.26724). In the absence of a specific targeted treatment, NRAS-mutated melanoma is generally managed as BRAF wild-type disease.

The publication quoted by the applicant provides information as to clinical presentation and prognosis of as to (BRAF and) NRAS mutations tested melanoma patients:

> *"Overall, 677 patients with melanoma who had successful testing for both* BRAF *and* NRAS *were identified … Mutations in exon 15 of* BRAF *(only) were identified in 320 patients (47.3%), and* NRAS *mutations (only) were identified in 136 patients (20.1%). … Substitutions at positions 60 and 61 accounted for 82.4% of* NRAS *mutations, most frequently a glutamine to arginine/lysine/lysine substitution at position 61 (Q61R/K/L). Four patients (0.6%) had activating mutations in both* BRAF *and* NRAS*. Two hundred seventeen patients (32.1%) did not have a mutation in either* BRAF *exon 15 or* NRAS *exon 1 or 2 and are referred to as wild type (WT) for subsequent analyses.*
>
> *At the time of initial diagnosis of melanoma, patients with a* BRAF *mutation ("BRAF") were significantly younger (median age, 49.8 years) than patients with* NRAS *mutation ("NRAS") (median age, 55.7 years; P = .0008) or WT patients (median age, 59.5 years; P < .0001).*

There also was a significant association for mutation with race (P = .042), although there were very few non-Caucasian patients in this cohort (4.1%).

…

*The interval from the diagnosis of melanoma to the diagnosis of stage IV disease trended toward a shorter duration for the NRAS patients, but this difference was not statistically significant using 3-group or 2-group comparisons …. BRAF patients were younger than NRAS patients (*P = *.0047) and WT patients (*P < *.0001) at stage IV diagnosis.*

…

Tumour mutation status correlated with overall survival from the diagnosis of stage IV disease in the full cohort (n = 519) …. NRAS patients (n = 104) had significantly shorter median overall survival (15.5 months) than WT patients (n = 163; 23.5 months; P = *.02). The median overall survival of BRAF patients (n = 252; 24.2 months) did not differ from that of WT patients."*

However, the clinical data presented originally in this application, for melanoma patients with BRAF or NRAS (trial X2201), or NRAS q61 positive melanoma (NEMO trial), did not suggest a difference in general clinical presentation and prognosis between BRAF and NRAS mutation positive patients. Therefore, more information regarding the clinical presentation, diagnosis and stage/prognosis of patients with melanoma harbouring NRAS (Q61) mutation would be useful.

Meanwhile the applicant has made available further publication. Based on these, the applicant concludes now that "*other studies have failed to demonstrate any significant difference in OS or melanoma-specific survival in patients with NRAS-positive tumours as compared to those patients with wild-type tumours (Edlundh-Rose et al 2006; Ellerhorst et al 2011; Carlino et al 2014; Thomas et al 2015).*" Therefore, a difference in prognosis between NRAS positive and BRAF and/or NRAS wild type tumours, cannot be considered as established.

In addition, the applicant submitted post hoc subgroup analysis concerning frequency of concurrent BRAF mutations in the (NRAS Q61 mutation positive) population investigated in trial NEMO. Accordingly, these additional analyses can be considered as rather robust and reliable (for the population investigated for this application). In conclusion, the frequency pattern of BRAFm, NRASm, and their simultaneous occurrence in a tumour tissue sample, does not follow the pattern of two stochastically independent events. They simultaneous occurrence, however, has been confirmed also by the new sub-group analysis although at a lower than stochastically independent frequency.

2.1.5. Management

In Europe, mutation testing for treatable mutations is mandatory in patients with advanced disease (unresectable stage III or stage IV), and highly recommended in high-risk resected disease (stage IIc, stage IIIb–IIIc). Tumour tissues, preferentially of metastatic lesions, should be screened for mutations of BRAF V600. Reasonable approaches for BRAF-mutated melanomas include combinations of BRAF inhibitors with MEK inhibitors. BRAFi/MEKi inhibitor combos offer high response rates (70%) and rapid response induction associated with symptom control, with a progression-free survival (PFS) of ~12 months. Anti-PD1 therapy, and to a lesser extent ipilimumab, offer lower response rates in the range, but many responses are durable.

The ESMO guidelines state that if the melanoma is negative for BRAF V600 then further molecular testing can be carried out for NRAS, c-Kit (mucosal and acrolentigenous primaries) GNA11 or GNAQ (uveal primary); this helps to direct patients to the appropriate targeted treatment or clinical trial. (*ref: Dummer et al, ESMO guidelines, 2015*).

According to the applicant, no therapies have been approved in the EU specifically for patients with *NRAS* mutation-positive melanoma. In the absence of a specific targeted treatment, *NRAS*-mutated melanoma is generally managed as *BRAF* wild-type disease. Furthermore, the applicant claims an unmet medical need in NRASm+ melanoma with reference to the ESMO guideline. The ESMO (2015) guideline, in the overall context of BRAF wild type tumours, however sees some "early signals" in trial CMEK162X2201 (assessed within this application and published in Lancet) justifying subsequent (following BRAFm testing) NRAS testing in the following wording: "There are early signals from a phase II clinical trial that patients with metastatic melanomas, carrying NRAS mutation, may benefit from MEK kinase-inhibitor therapy [40]." Already the next sentence, to challenge the claim of the applicant, of this 2015 guidance, however, reads: "The additional analysis for PDL-1 expression helps to enrich the population of patients who benefit from anti-PD1 therapy, but is not powerful enough to exclude patients from anti-PD1 treatment [39, 41].

In patients with BRAF-wild-type (wt) disease, ipilimumab has been the standard treatment based on a survival benefit with a ~10% higher survival rate at 1, 2 and 3 years. Based on very recent randomised trial results, comparing anti-PD1 antibody therapies to ipilimumab, anti-PD1 antibody therapy is the preferred first-line treatment of patients with BRAF-wt disease. These therapies also demonstrate efficacy for patients with BRAF mutation positive melanoma. Anti-PD1 therapies are also recommended as a second-line treatment, after ipilimumab failure. The anti-PD1 antibody nivolumab was compared with the reference chemotherapy dacarbazine in a double-blind randomised clinical trial with BRAF-wt patients. This trial showed a 1-year survival rate of 72.9% in the nivolumab group, compared with 42.1% in the dacarbazine group (HR for death, 0.42; P < 0.001). Opdivo and Keytruda were approved for treatment of advanced melanoma in the EU on 19 June 2015 and 17 July 2015, respectively.

The therapeutic place, or line, of dacarbazine is, accordingly, currently not well defined.

2.2. About the product

Mektovi (binimetinib; also known as MEK162 or ARRY-438162) was invented by Array BioPharma and co-developed with Novartis. Array subsequently regained the rights to the molecule and is now working with Pierre Fabre Médicament on the co-development and commercialization.

Binimetinib is an orally bioavailable, selective and potent mitogen-activated protein (MAP) kinase kinase (MEK) 1 and MEK 2 inhibitor.

Pierre Fabre Médicament (Pierre Fabre) is submitting this Marketing Authorisation Application (MAA) in support of the following indication:

Mektovi monotherapy is indicated for the treatment of adult patients with unresectable or metastatic melanoma with NRAS Q61 mutation.

Proposed legal status: Mektovi is a medicinal product subject to restricted medical prescription.

Proposed dose: The recommended dose of binimetinib is 45 mg (three 15 mg tablets) orally taken twice daily (BID), equivalent to a total daily dose of 90 mg. For patients with moderate hepatic impairment (total bilirubin >1.5 and ≤3.0 times the upper limit of normal [ULN] and any aspartate aminotransferase [AST] value) or moderate renal impairment (creatinine clearance [CrCL] 30 to 59 mL/min) the recommended dose is 30 mg (two 15 mg tablets) orally taken BID.

Continuation of treatment is recommended until disease progression or development of unacceptable toxicity.

2.3. The development programme/compliance with CHMP guidance/scientific advice

The majority of clinical studies contributing data to this application dossier, including both studies contributing efficacy data (Study CMEK162A2301 and Study CMEK162X2201), were sponsored and conducted by Novartis Pharmaceuticals Corp. through the relevant data cutoff dates.

Accordingly, Novartis conducted interactions with regulatory agencies in the European Union (EU) and United States of America (USA) from 2012 through to October 2015. Key regulatory authority interactions are provided in Module 1.2.

A request for EMA Scientific Advice was submitted in October 2012 to discuss the proposed Phase 3 study, CMEK162A2301, which was intended to establish the safety and efficacy of binimetinib in patients with previously untreated, unresectable advanced or metastatic NRAS-mutation positive melanoma. Advice was requested on the planned patient population, study endpoints, comparator and the planned clinical pharmacology package. Since that time, an amendment was made to the protocol (7 April 2014) that allowed for recruitment of patients with prior first-line immunotherapy in order to reflect the current characterizes retinal events. One of the questions raised by the Sponsor (Novartis) was whether a doubling in PFS represents a clinically meaningful improvement in that primary endpoint and could be considered as the basis for approval while the study was also powered for OS as a key secondary endpoint. The CHMP concluded that if the median PFS in the control arm is about 1.5 months, the assumed benefit would be the same (about 1.5 months) and questioned whether this benefit would outweigh the risks associated with treatment. Furthermore, the CHMP pointed out that the study was designed to capture a survival benefit HR of 0.67. If the median OS in the control arm was only about 8 months, a HR of 0.67 would translate into a survival benefit of about 4 months, indicating a discrepancy between the assumed PFS and OS benefits.

2.4. General comments on compliance with GMP, GLP, GCP

All pivotal toxicology studies and the safety pharmacology studies were conducted in accordance with GLP regulations.

The applicant states that the clinical studies were conducted according to GCP and to meet the ethical requirements of Directive 2001/20/EC.

No inspections of the drug substance manufacturing site, the drug product manufacturing site or the batch release site are considered necessary.

2.5. Type of application and other comments on the submitted dossier

- Legal basis

This application has been submitted in accordance with the Article 8(3), in the Directive 2001/83/EC, concerning a new active substance in the centralised procedure, i.e., with a dossier containing administrative, quality, non-clinical and clinical data.

In accordance with of Article 3(1) according to Regulation (EC) No 726/2004, referring to the mandatory scope (Annex 3- New active substance for mandatory indications), the application has been submitted as a centralised procedure application.

The product does not have orphan designation.

- Accelerated procedure

N/A

- Conditional approval

  N/A

- Exceptional circumstances

  N/A

- 1 year data exclusivity

  N/A

- Significance of paediatric studies

The paediatric subset from 0 to 12 years of age for the condition “Treatment of melanoma” is covered by an EMA class waiver.

Binimetinib has a PIP agreed concerning the treatment of melanoma in patients from the age group 12 years to less than 18 years. The indication targeted in the PIP is “Binimetinib in combination with encorafenib is indicated for the treatment of patients aged 12 years and older with unresectable or metastatic melanoma harbouring BRAF V600 mutations”. The measures include development of oral age-appropriate formulation (study 1); a multicentre, open-label study to assess pharmacokinetics, safety, tolerability, and preliminary evidence of antitumor activity of the combination of binimetinib and encorafenib in adolescents from 12 to 18 years with unresectable or metastatic BRAF V600 mutant melanoma (study 2); and modelling and simulation study to evaluate the use of the product in the treatment of melanoma in adolescents from 12 to less than 18 years of age with unresectable or metastatic BRAF V600 mutant melanoma. Issues considered to be of particular concern in the paediatric population include bone growth, soft tissue mineralisation and ocular toxicity. However, a deferral for the initiation of the modelling and simulation extrapolation, and a deferral for the study initiation in adolescents from 12 to 18 years of age is requested until after the data from clinical study in adults are available. Consequently the study results are to be available at a later point in time.

3. Scientific overview and discussion

3.1. Introduction

Binimetinib is a new chemical entity, proposed for the treatment of adult patients with unresectable or metastatic melanoma, with NRAS Q61 mutation.

3.2. Quality aspects

3.2.1. Active Substance

Binimetinib is presented as an anhydrous, crystalline free base for which one polymorphic modification has been isolated under synthetic conditions.

The proposed synthesis of binimetinib comprises a stepwise reaction sequence of seven process steps The proposed starting material are accepted as suitable starting materials for regulatory purposes as well characterised and relatively simple molecules, which require a number of discrete synthetic steps interspersed with isolated intermediates, to prepare the drug substance. As a result, there is sufficient

opportunity for purging impurities or synthetic by-products. Sufficient data has been presented to support the structural elucidation and characterisation of binimetinib and its specified impurities.The specification proposed for the drug substance manufacturer is generally satisfactory. The primary packaging and retest period are considered to be acceptable.

3.2.2. Finished Medicinal Product

Balimkek 15 mg Film-coated Tablets comprises an immediate-release oral solid dose formulation. Primary packaging consists of a blister pack composed of polyvinyl chloride (250 µm) and polyvinylidene chloride (PVdC) 90 g/m2 with aluminium foil lidding (20 µm). The choice of dosage strength is justified, given that the standard dose (90 mg given as two doses of 45 mg twice daily) may be reduced to 30 mg if necessary. The formulation proposed for commercialisation is typical of solid oral dosage forms and is supported by formulation studies.

Manufacture is conventional, comprising serial dilution / dry blending of drug substance with excipients, followed by compression, film-coating and packaging. Excipient choice is typical of solid oral dosage forms; all are controlled to the relevant Ph. Eur. monographs, with the exception of the proprietary coating solution which is satisfactorily controlled in line with manufacturer's recommendations.

The control strategy at release and over shelf-life is generally acceptable. The proposed primary pack comprises a PVC/PVdC/aluminium push through blister presentation. This is supported by stability data. Based on provision of further stability data, a shelf-life of 36 months under no special temperature storage conditions is considered approvable.

3.2.3. Discussion on chemical, pharmaceutical and biological aspects

The dissolution method proposed for routine QC use is considered to be justified and data have been presented to support method discrimination. A more stringent control limit has been proposed in response to questions from the Rapporteurs.

3.3. Non clinical aspects

3.3.1. Pharmacology

In vitro and in vivo studies were performed to evaluate the ability of binimetinib to affect its intended targets (MEK 1/2) and the pharmacodynamic outcomes.

In biochemical studies, binimetinib has been shown to be a potent and selective inhibitor of MEK1/2 with an enzyme IC50 of 12.1 nM.

In cellular studies *in vitro*, binimetinib potently inhibited MEK-dependent phosphorylation of ERK in human N-Ras-mutant melanoma lines, as well as B-Raf-mutant melanoma cell lines. In these studies, employing large panels of B-Raf-mutant and N-Ras-mutant human melanoma cell lines, binimetinib significantly inhibited proliferation and viability. The results showed that binimetinib was most potent in A375 and UACC-62 cell lines. Binimetinib was also tested in a panel of 5 NRAS-mutant melanoma cell lines for viability. The results showed that binimetinib was most potent in IPC-298 and SK-MEL-30 cell lines. Maximal inhibition was around 100% in all lines. Since preclinical studies indicate that the presence of mutations that activate RAS/RAF/MEK/ERK pathway signaling, typically those occurring in the BRAF, NRAS and KRAS genes, are predictive for response to MEK inhibitors [Barretina 2012], it can be expected that a MEK1/2 inhibitor is active both against NRAS-mutant and BRAF-mutant tumor

xenograft models. This activity of binimetinib has been shown using NRAS-mutant and BRAF-mutant cell lines, both in vitro and in vivo. Therefore binimetinib does not act only on NRAS Q61 mutation but could be used in NRAS-mutant melanoma as well as in BRAF mutant melanoma.

In vivo, binimetinib has been evaluated for its ability to inhibit tumour growth and phosphorylation of ERK in xenograft models in nude mice. Significant tumour growth inhibition and regressions were demonstrated in response to binimetinib treatment in N-Ras-mutant melanoma xenograft models.

In vivo, the effects of binimetinib on ERK phosphorylation in HT-29 human colorectal carcinoma xenograft tumours were evaluated in nude mice. Binimetinib significantly inhibited p-ERK in HT-29 tumours in a dose- and time-dependent manner. Target inhibition of nearly 100% was achieved at all doses of binimetinib, and 50% inhibition was maintained at 24 hours following a single dose of either 10 or 30 mg/kg binimetinib.

The effects of binimetinib on the tumours growth in nude mice of A375 BRAF mutant melanoma, MEL-JUSO NRAS-mutant melanoma and Hs944.T NRAS-mutant melanoma xenografts revealed that binimetinib given as BID oral doses for 14, 21 or 33 days resulted in dose-dependent and marked anti-tumour effects in these 3 models of human melanoma. Significant anti-tumour activity was observed at doses ≥ 3 mg/kg. Tumours regressions were observed at the highest dose tested in the 3 models.

In vivo assessments of potential biomarkers for clinical implementation have shown Dual-specificity phosphatase 6 (DUSP6) and pro-apoptotic BH3-only protein (BMF) as target inhibition and tumours response biomarkers. Results from both the single dose and repeat dose experiments indicated that DUSP6 was a marker of MEK inhibition in tumours, which was inhibited within 1 hour, and behaved in a dose-dependent fashion at later time points when using relatively high doses. BMF was induced after 6-24 h in a dose-dependent fashion in tumours and showed cumulative effects with repeated dosing. The dose-dependent effect on these biomarkers correlated with the dose-related efficacy response.

Binimetinib was tested against a panel of 219 kinases. Other than MEK1, 1 µM binimetinib did not inhibit any of the other kinases by more than 30%. With 10 µM binimetinib, only calcium/calmodulin kinase IV (31%), Fer (fps/fes related) tyrosine kinase (phosphoprotein NCP94) (38%) and MEK1 (92%) were inhibited by more than 30%. Binimetinib demonstrated high selectivity for MEK versus over 200 other kinases. Therefore, off-target kinase activity at relevant free-therapeutic concentrations in vivo is not anticipated.

GLP safety pharmacology studies evaluated the potential effects of binimetinib on the CNS (IRWIN test in rats), the cardiovascular system (hERG assay and *in vivo* monkey telemetry), the respiratory system (plethysmography study in rats), the gastrointestinal system (motility and secretion in rats) and the renal system (*in vivo* study in rats). Rats received single oral doses of 10, 30 or 100 mg/kg and monkeys were given single oral doses of 1, 3 and 10 mg/kg. There were no significant *in vivo* safety findings after single dose administration of binimetinib up to 100 mg/kg in rats and up to 10 mg/kg in monkeys.

In the hERG channel assay evaluating binimetinib, concentrations up to 30 µM were tested and 30% inhibition was seen at the highest concentration. One additional hERG assay was performed with the main metabolite at concentrations up to 100 µM where 11% inhibition was observed. These studies showed minimal to low activity of binimetinib and its primary metabolite and indicated a low potential to induce increased QT segment duration.

Additional non-GLP exploratory safety pharmacology studies demonstrated that binimetinib had no effect on normal wound healing in mice and had a potential beneficial effect (survival protection) on immune modulation in mice.

3.3.2. Pharmacokinetics

The oral bioavailability of binimetinib in the test species (non-fasted mice, rats, and monkeys) was about 50% and was similar to the fraction absorbed (based on radioactivity excreted) suggesting a minimal first pass effect. In Nude mice, the species used in primary pharmacology studies, after oral single administration the mean AUCinf values of binimetinib at 3, 10, and 30 mg/kg were 3,727, 13,672, and 47,256 ng-hr/mL respectively. The mean AUC0 →t values at 122,653 and 252,376 nghr/ mL. These values can be used to compare the pharmacologically effective dose level in mice with the exposure in patients treated with different doses in clinical studies. Absolute oral bioavailability of binimetinib in athymic female nu/nu NCr mice at 3, 10, 30, 100, or 300 mg/kg was approximately 43, 47, 54, 42, and 29%, respectively.

Binimetinib showed a low hepatic extraction, low total systemic plasma clearance and low volume of distribution at steady state after intravenous (IV) administration across the test species. The mean t1/2 calculated after IV administration of binimetinib ranged from 2.4-6.6 hours in rodents, and up to 10 hours in monkeys. In vitro experiments indicated that binimetinib had a moderate to high cell membrane permeability and is a substrate for P glycoprotein (P-gp) and the breast cancer resistance protein (BCRP).

Quantitative whole body autoradiography (QWBA) revealed that [14C]-binimetinib-derived radioactivity was absorbed and extensively distributed to tissues in both pigmented and albino rats following a single oral dose. However, there was no to minimal exposure of binimetinib and/or its metabolites in the brain of either non-pigmented rats (BQL at all time- points) or pigmented rats (minimal in the cerebellum at the 2 h time point). There was no accumulation of radioactivity in various glands (testes, thyroid, pituitary gland, pancreas, harderian gland and adrenal gland). Selective distribution into the pigmented skin was apparent; however, association with melanin could not be confirmed given that selective distribution into the pigmented eye was not observed. Binimetinib was highly bound to plasma proteins across species (97.2% in humans), and preferentially distributed to the plasma. The blood-to-plasma concentration ratios ranged from 0.652 to 0.994 across species (0.718 in humans).
The routes of binimetinib metabolism were generally conserved across non-clinical species, both in vivo and in vitro. In ADME studies with [14C]-binimetinib in rats and monkeys, binimetinib was the major circulating entity. The data in rats and monkeys suggested that binimetinib was metabolized through multiple routes, including both oxidative and conjugative metabolism. The primary metabolites of binimetinib across species, and in vitro systems, occurred through direct glucuronidation, oxidative N-desmethylation, and cleavage of the N-O bond of the alkyl side chain to form an amide. In rats, binimetinib-derived metabolites were not detected in plasma at levels greater than 10% of the total administered dose of [14C]-binimetinib. In monkeys, a direct glucuronide conjugate and the N-desmethyl amide metabolites of [14C]- binimetinib accounted for >20% and 10% of the total circulating radioactivity, respectively. The N-desmethyl metabolite, which is the most prominent oxidative metabolite in humans, was not present at quantities > 10% of the total drug in the non-clinical species. Because the non-clinical development programme for binimetinib was performed in accordance with the ICH S9 guidance, plasma concentrations of M3 were not determined in either the rat or the monkey toxicity studies.

Studies using in vitro model systems also suggested the potential for oxidative and conjugative metabolism of binimetinib. These metabolic routes were largely confirmed in the definitive human ADME study. Based on these analyses, the principle route of binimetinib metabolism in humans was predicted to occur through direct glucuronidation (primarily via UGT1A1), and to a lesser extent by oxidative pathways (primarily via CYP1A2 and CYP2C19). UGT1A1 was the major contributor (90%) to the formation of the direct glucuronide. In human liver microsomes and recombinant CYPs (expressing CYP1A2 and 2C19), the major oxidative metabolite was an N-desmethyl (M3) metabolite. Given that the M3 metabolite retains pharmacological activity against MEK, the plasma concentrations of M3 were monitored in clinical studies.

Following IV dosing of [14C]-binimetinib in the rat, faecal and urinary excretion accounted for 45% and 46% of total radioactivity, respectively. Approximately 15% of binimetinib was excreted unchanged in the urine and 16% in the faeces of rats. Total radioactivity in the excreta of monkey was 99% and 85% following PO and IV dosing, respectively, with an equal contribution for urinary and faecal excretory routes. The most abundant drug-related components in monkey urine included binimetinib and two direct glucuronides. In monkey faeces, binimetinib and the amide metabolite were the most abundant entities.
The pharmacokinetic drug-drug interaction potential of binimetinib was assessed in various in vitro human model systems. Binimetinib inhibited CYP2B6 (IC50 = 6 µM) and was a weak inhibitor of CYP1A2 and CYP2C9.

As per guidance (CPMP/EWP/560/95/2012), the in vitro data for CYP2B6 inhibition was applied to the recommended basic and mechanistic models for CYP2B6 inhibition to assess the potential for binimetinib to cause a clinically significant drug-drug interaction with co-administered drugs metabolized by CYP2B6. Based on basic and mechanistic models for CYP2B6 inhibition, it was concluded that binimetinib is not likely to be an inhibitor of CYP2B6 and an in vivo human study is not needed to assess the interaction potential. Binimetinib was not a time dependent inhibitor of CYP1A2, CYP2C9, CYP2D6, or CYP3A4/5. Binimetinib was determined to be a concentration-dependent inducer of CYP3A in cultured primary human hepatocytes, but CYP3A induction was not observed in a subsequent human drug-drug interaction study. Binimetinib was a substrate of P-gp and BCRP. Binimetinib was an inhibitor of a renal OAT3 xenobiotic transport protein in vitro (IC50 = 1.9 µM).
However, through incorporation of the in vitro data for OAT3 inhibition into the recommended model (CPMP/EWP/560/95/2012) for determining whether an OAT3 inhibitor might cause a drug-drug interaction and warrant a clinic DDI study, it was determined that binimetinib was not expected to cause drug-drug interactions with OAT3 substrates. Overall, the risk for binimetinib to be a victim or a perpetrator of significant drug-drug interactions was predicted to be low.

3.3.3. Toxicology

The toxicological evaluations of binimetinib included single-dose, 28-day and combined 13-week/6-month repeat-dose studies in Sprague Dawley rats, 28-day and combined 13-week/9-month repeat-dose studies in cynomolgus monkeys with toxicokinetic evaluation in each repeat dose study. All studies except exploratory studies were conducted in accordance with GLP.

No significant adverse effects were observed in the acute toxicity study in female rats. In male rats transient decreases in body weight and food consumption occurred in the mid-dose (100 mg/kg) and the high-dose (300 mg/kg) groups. Histopathological findings included mineralization of the glandular stomach in males at ≥100 mg/kg and in females at all doses. Mineralization in the ovaries was seen at all doses. Therefore, based on the histopathological findings, the NOAEL for a single oral dose of binimetinib was 30 mg/kg in male rats (mean Cmax = 10 µg/mL; mean AUCinf = 81 µg.hr/mL); the NOAEL in female rats could not be determined and was <30 mg/kg. In a gastric irritation study, stomach lesions (mucosal lesions, gastric ulcer) were observed in rats after single oral application of 100 mg/kg binimetinib. In the single dose as well as the 1-month repeat-dose toxicity study in rats also doses of up to 100 mg/kg binimetinib were orally applied. No signs of such stomach lesions but only tissue mineralization were reported. The differences in histopathological findings were attributed to differences in experimental conditions. Whereas in the gastric irritation study fasted animals were treated and investigated rapidly after treatment, in the single dose as well as in the 1 month-repeat-dose study non-fasted animal were treated and histopathological examination were performed at a later point in time. This is considered to be a plausible explanation.

In the 28-day repeat-dose toxicity study in the rat in which the dose levels were 10, 30 or 100mg/kg/day, the primary histopathology findings were dose related moderate to severe mineralization of soft tissues including the heart, aorta, lungs and kidneys with partial reversibility of these findings in recovery animals. Based on the histopathological findings of tissue mineralization most prominently in the glandular stomach at all doses and in the recovery groups, the NOEL in the 28-day study could not be established. By contrast, in the 6-month repeat-dose toxicity study in rats in which the dose levels were 1, 3 or 10mg/kg/day the primary findings were skin inflammation with erosions/ulcers/scabbing and hair loss in all groups with reversibility at 1 and 3 mg/kg/day. Soft tissue mineralization was not reported in this study. It should be noted that the systemic exposure (based on Cmax and AUC values in female rats which were 1.3 to 1.7 times greater than in males) was greater in the 28 day study (highest Cmax and AUC 0-24 values of 22.6 µg/ml and 348 µg.h/ml respectively) than in the 6 month study (highest Cmax and AUC 0-24 values of 14.5 µg/ml and 86.7 µg.h/ml respectively). The systemic exposures in the test animals should be compared to the much lower stated clinical systemic exposure at steady state of Cmax and AUC 0-12 values of 0.35µg/ml and 2.1 µg.h/ml respectively. Based on the skin findings, the 3 mg/kg/day and 1 mg/kg/day dose levels are considered to be the NOAEL in males and females, respectively for daily administration of binimetinib to rats for 26 weeks.

Skin toxicity was identified as a major risk in patients treated with binimetinib. Skin toxicity was also observed in rat and monkey studies performed with binimetinib. Adverse effects to the skin are known as a class-specific side effect typically for EGFR inhibitors. Since RAF and MEK are downstream of EGFR signalling, similar skin effects can be expected for MEK and RAF inhibitors. Thus binimetinib modulation of the EGFR signalling pathway probably resulted in cutaneous adverse effects in patients as well as in animals studied.

In the 28-day repeat-dose toxicity study in monkeys conducted at 1, 3 or 10mg/kg/day, the top dose was associated with morbidity in 2 of 10 animals requiring humane sacrifice. In these 2 animals, there were significant changes in BUN, creatinine, phosphorus and hematologic parameters consistent with dehydration and inflammation in the gastrointestinal tract. The primary histopathology findings in this dose group were intestinal inflammation and degeneration of the mucosal epithelium and bone marrow hyper-cellularity. Based on these data, the NOAEL in monkeys was 3 mg/kg/day after 28 days oral dosing of binimetinib. Exposure (mean AUC 0-12) achieved at the NOAEL was 1.48 µg.h/mL on day 28, for male and female monkeys (combined). This exposure is 0.7 fold that achieved in cancer patients receiving the 45 mg BID dose level of binimetinib. In the 9-month repeat-dose toxicity study in the monkey conducted at dose levels of 0.2, 2 or 5 mg/kg/day, the primary findings were gastrointestinal inflammation and intolerance and mucosal epithelial degeneration with associated secondary changes in serum chemistry and haematology values. Based on the slight and reversible histologic findings at 2 mg/kg/day, this is considered to be the NOAEL in this study. Exposure (mean AUC0-24) achieved at this NOAEL was 1.6 µg.h/mL, for male and female monkeys (combined). This exposure is 0.4-fold that achieved in cancer patients receiving the 45 mg BID dose level of binimetinib. Mineralisation of soft tissues was not reported. The gastrointestinal findings observed in rats and monkeys receiving binimetinib are related to the mechanism of action of the drug product, i.e., blockage of the EGFR signal transduction pathway, as for other already marketed EGFR-TKIs. These findings appear to be clinically relevant, with a potential concern of severe gastrointestinal effects due to mucosal lesions. This issue is addressed in the RMP of the product.

In the rat studies, mineralization attributed to binimetinib administration reported in the 28-day study was not seen in the 6- month study. In monkeys, there was no evidence of soft tissue mineralization. The systemic exposure in the monkey studies was lower than in the rat studies. In the 28-day monkey study the highest Cmax and AUC 0-12 values were 0.89 µg/ml and 3.31 µg.h/ml respectively. In the 9-month study the highest Cmax and AUC 0-24 values were 0.58 µg/ml and 4.47 µg.h/ml respectively. In this study, compared to day 1, there was a statistically significant ($p < 0.001$) decrease in mean

Cmax and AUC 0-24 values at 5 mg/kg/day on Day 28. The decrease in AUC 0-24 of about 40% was maintained on subsequent days.

This finding in the rat may be species specific and has been seen with the MAP kinase (MEK) inhibitor PD 0325901 in rats (A.P. Brown, 2005). The finding of soft tissue mineralization, increased phosphorus and decreased calcium in rats has prompted evaluation of calcium and phosphorus in human patients receiving MEK inhibitors. To date, no effects on calcium or phosphorus have been reported in human patients receiving the MEK inhibitor PD 0325901 (P. Lorusso, 2005). The data in the published literature confirm that MEK inhibition causes soft tissue mineralisation in the rat secondary to serum inorganic phosphorus increase, but the molecular mechanisms remain undetermined.

The finding of soft tissue mineralisation was proposed by the applicant to be rat specific. An abstract relating to another MEK-inhibitor, PD325901, that also induced tissue mineralisation in rats was cited (Brown et al. 2005). Tissue mineralisation of PD325901 was preceded by increases in phosphate, vitamin D and protein free calcium resulting in dysregulation of phosphate and calcium homeostasis. In other species, even at higher exposures, tissue mineralisation was not observed. Therefore, mineralisation was concluded for PD325901 to be rat specific. Phosphate, calcium, vitamin D and parathyroid hormone levels were also measured during the repeat-dose toxicity studies performed for binimetinib. However, changes observed for binimetinib do not show a pattern comparable to PD325901 and exposures in the monkey, studied as second animal species in repeat-dose studies, were only marginally above human exposures. The applicant performed a thorough discussion of parameters (calcium, phospporus, parathormon and vitamin D3) measured during the rat studies. Findings were compared to the literature data published for the MEK inhibitor PD325901. Although not all chemistry findings showed an identical level of reduction or increase, a similar pattern can be assumed indicating similar mechanism of tissue mineralization in rats for binimetinib and PD325901.

In the context of an anticancer drug in advanced cancer therapy, fertility and early embryonic development study and pre- and post-natal development study are not warranted according to the guideline ICH S9. No such specific studies were conducted. In repeat-dose toxicity studies conducted for up to 6 months and 9 months in rats and monkeys, respectively, no toxicological concern arose from the histopathological examination of reproductive organs in males and females. However embryo-foetal development was investigated in the rat and rabbit.

In the rat embryo foetal developmental toxicity study (n=24/25 pregnant females/group; 0, 10, 30, 100 mg/kg/day; G6-G17), food consumption was reduced in all dose groups. No binimetinib related mortality was observed during the study. Treatment related clinical signs and reduced gestational body weight were seen at 100 mg/kg/d. Gestation body weight changes and foetal body weights were significantly reduced at ≥ 30 mg/kg/d. On skeletal examination, a significantly increased number of un-ossified sternebrae and hyoid was observed at ≥ 10 mg/kg/d. Based on the skeletal anomalies observed in this study, the binimetinib oral NOAEL with respect to embryofoetal development in rats is 10 mg/kg/d. This dose level corresponds to a plasma exposure (group mean AUC 0-24 value determined in independent TK assessments at day 27 in the 28-day GLP repeat-dose study in female rats) of 56.5 µg.h/mL. This exposure is about 13- fold that achieved in cancer patients receiving the 45 mg BID dose level of binimetinib.

In the rabbit embryo foetal developmental toxicity study (n=22/23 pregnant females/group; 0, 2, 10, 20 mg/kg/d; G6-G18), treatment-related mortality was observed at 10 (3 animals) and 20 (6 animals) mg/kg/d. Treatment related clinical observations (watery stools/diarrhoea/hair loss) and reduced gestational body weight and body weight gain were observed at ≥10 mg/kg/d. Food consumption was significantly reduced at ≥2 mg/kg/d. One animal in each of the 2 higher dose groups aborted. Significant increased number of resorption and percentage of post-implantation loss, significant decreased number of viable foetuses and foetal body weights were observed at ≥ 10

mg/kg/d. Aortic arch malformations with discontinuous interventricular septum and small pulmonary trunk were present at 20 mg/kg/d. Based on the results of this study, the binimetinib oral NOAEL with respect to embryo-fetal development in rabbits was 2 mg/kg/day. This dose level corresponds to an interpolated plasma exposure (group mean AUC 0-12 value determined in the dose-range finding study on GD 18) of 5.90 µg.h/mL, assuming similar exposure to the 3 mg/kg dose group. This exposure is 2.8-fold that achieved in cancer patients receiving the 45 mg BID dose level of binimetinib. Toxicokinetic investigations performed in the course of the DRF embryofetal development study in pregnant rabbits revealed a different metabolic profile when compared to rats, monkeys, and humans, respectively, as the principle metabolite was demonstrated to be an amide metabolite. This amide metabolite has been shown to be inactive in two *in vitro* cell systems.

The embryo-fetal developmental toxicity studies indicate the exclusion of pregnant women and the continued requirement that women of child-bearing potential use appropriate contraception. The SPC (Section 4.6) states that women of childbearing potential should be advised to use effective contraception during treatment with binimetinib and for 2 weeks following the last dose. Furthermore the SPC states that studies in animals have demonstrated reproductive toxicity. Binimetinib may harm the foetus when administered to a pregnant woman. Binimetinib administration is not recommended during pregnancy. The adverse treatment related findings are also described in section 5.3 of the SPC.

In a juvenile Sprague-Dawley rat study, daily oral administration of binimetinib on day 10 up to day 40 post-partum (pp), inclusively, at 1, 3, 10 and 30 mg/kg/d was not tolerated when administered at ≥ 10 mg/kg/d, resulting in mortality after 4 days of dosing at 30 mg/kg/d and after 5 days of dosing at 10 mg/kg/d. There were overt signs of toxicity at ≥ 10 mg/kg/d, decreased body weight and body weight gains at doses ≥ 3 mg/kg/d, a slight decrease in lymphocytes in both sexes at 3 mg/kg/d, clinical chemistry change (minimal increase in phosphorus) at 1 and 3 mg/kg/d and histopathological changes (microscopic mineralization in the heart and stomach) in males at 3 mg/kg/d that may be related to the increase in phosphorus noted. Under the conditions of this study, the NOAEL was 1 mg/kg/d. The plasma exposure (AUC and Cmax) was about 3-fold higher in the younger rats (days 10, 16 and 18 pp) than that observed in the older rats (days 25 and 40 pp) at the 3 mg/kg/d dose level. The rationale for the conduct of juvenile toxicity study at this point in time is not clear. The safety and efficacy of binimetinib in children and adolescents (<18 years) have not yet been established. No data are available.

Binimetinib was not genotoxic in a standard battery of in vitro (Ames and L5178Y mouse lymphoma cell) and in vivo (mouse bone marrow) tests.

No carcinogenicity studies have been conducted. Since this is an anti-cancer drug in advanced cancer therapy, carcinogenicity studies are not warranted according to the guideline ICH S9.

Since binimetinib is an anticancer drug given orally, skin local tolerance studies are not warranted. However, two local tolerance studies were performed, the first one stated to be to evaluate skin irritation for the manufacturers and the second one to evaluate gastric irritation. Skin irritation was performed in rabbits following single topical application for 4 hours under semi-occlusive conditions on intact skin. Under these conditions, binimetinib would not be classified as a skin irritant. Gastric irritation was evaluated in male rats following single administration at the dose levels of 10, 30, 100 mg/kg. The significant finding was increased superficial mucosal lesions and haemorrhagic ulcers in the stomach of all rats at 100 mg/kg (5 mL/kg) of binimetinib.

Two studies were performed to evaluate the phototoxic/photo-irritative potential of binimetinib. While the *in vitro* Balb/c 3T3 fibroblast neutral red uptake assay predicts positive for binimetinib phototoxicity (PIF = 18.8) when tested up to precipitating concentrations, the *in vivo* murine local lymph node assay indicated that there was minimal risk for photosensitization (increased ear weight, transient erythema of the ear, increased lymph node weight and cell count in individual animals) but with no effects at an oral dose of 10 mg/kg/d providing exposures of 16 µg.h/mL in terms of AUC 0-24, which corresponds

to about 3.8-fold than that achieved in humans at the currently recommended 45 mg dose level. The clinical experience with binimetinib indicates that it is not phototoxic under therapeutic conditions of use. In view of the fact that the in vitro Neutral Red Uptake Phototoxicity test is known to over predict phototoxicity and the reassuring clinical data, a warning statement concerning the potential for phototoxicity is not considered necessary. The dose modifications for dermatological events in section 4.2 of the SmPC and management of skin toxicities in section 4.4 of the SmPC are considered to be sufficient to manage phototoxicity reactions.

Binimetinib is intended for treatment of adult advanced cancer (unresectable or metastatic melanoma with NRAS Q61 mutation) as defined in the scope of ICH S9, *Nonclinical Evaluation for Anticancer Pharmaceuticals,* March 2010, and thus is not subject to the exposure limits outlined in ICH M7, *Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*, June 2014. As such, the applicant proposed controlling the drug substance and drug product according to thresholds outlined in ICH Q3A(R2), *Impurities in New Drug Substances*, October 2006, and ICH Q3B(R2), *Impurities in New Drug Products*, July 2006. Limits for related substances in binimetinib drug substance have been established based on principles outlined in ICH Q3A (R2), *Impurities in New Drug Substances*, October 2006. No degradation products were observed during release and stability testing of the drug product.

SPC

Negative findings and information which is not of relevance to the prescriber should be deleted.

The predicted potential for phototoxicity indicates a recommendation that patients receiving binimetinib should avoid excessive direct sun exposure and take appropriate precautions (clothing, sunscreen, etc.) to reduce UV skin penetration.

Conclusion

The main adverse treatment related findings following administration of binimetinib to rats by oral gavage was associated with skin lesions (inflammation/scabbing), microscopic findings of soft tissue mineralization (which occurred in the 28-day but not in the 26-week rat study) and reversible minimal to mild clinical changes. Gastric mucosal lesions were associated with binimetinib administration to rats at 100 mg/kg. In cynomolgus monkeys, administration of binimetinib at doses > 5 mg/kg/day was associated with soft stools, moderate clinical pathology changes in some animals, gastrointestinal intolerance and microscopic findings of gastrointestinal inflammation and mucosal epithelial degeneration, which were reversible during non-dosing recovery periods for the low- and mid-dose level animals but only partially reversible in the high-dose animals. Bone marrow (hypercellularity) findings were completely resolved at recovery.

3.3.4. Ecotoxicity / environmental risk assessment

The highest risk ratio for Binimetinib in the current risk assessment has been found for sediment compartments with 0.068, therefore indicating no risk to the environment.

Based on the available information on partition behaviour and adsorption to sludge and soil, Binimetinib is neither expected to bio-accumulate, nor to show any significant transfer to sludge and soil. A risk assessment for terrestrial compartments or a PBT assessment was therefore not necessary for this active substance.

The present environmental risk assessment shows, that the introduction of Binimetinib on the EU market is not expected to lead to any significant risk to the environment.

3.3.5. Discussion on non-clinical aspects

Binimetinib did not have any adverse effects on cardiovascular (monkey telemetry), gastrointestinal motility and secretion (in rats), neurobehavioral (Irwin rats), renal (rats) or respiratory function (rats) up to the highest single dose tested (100 mg/kg in rats and 10 mg/kg in monkeys). These doses are above the MTDs determined in the repeat dose toxicity studies in rats and monkeys.

In rats, no adverse effect on the main physiological functions were observed up to approximately 65 fold the human exposure at the therapeutic dose level. In monkeys, no cardiovascular effects were noted at about 1.2 to 1.6 fold the human exposure at the therapeutic dose, based on AUC.

In vitro, binimetinib and its active metabolite have no appreciable activity on hERG channel current (IC50 > 30 µM and > 100 µM, respectively).

Repeated administration of binimetinib to rats is associated with abrasion, alopecia and scabbing of the skin, and minimal to mild increases in neutrophils and monocytes, ALT, AST, urea and phosphorus, and decreases in calcium and albumin. Test article related microscopic changes included cutaneous erosion/ulceration and multi-centric vascular and tissue mineralization, which partially reversed after a treatment free period. Skin lesions were dose related in terms of severity and incidence and were partially reversible. Dermatological reactions to the administration of binimetinib are a known clinical finding. The finding of mineralisation of soft tissues in the rat may be species specific and has been seen with another MAP kinase (MEK) inhibitor. The data in the published literature confirm that MEK inhibition caused soft tissue mineralisation in the rat secondary to serum inorganic phosphorus increase, but the molecular mechanisms remain undetermined. Gastric mucosal lesions and haemorrhagic ulcers were also seen in rats at doses that exceeded the MTD. The observations were observed with greater frequency and at lower dose level in females than in males. In cynomolgus monkeys, administration of binimetinib is associated with weight loss, soft stools, moderate decrease in red blood cell mass, increased platelet, monocyte and neutrophil counts, serum globulin, and decreases in serum albumin, and albumin/globulin ratio. All these changes were reversible after a treatment free period. Treatment-related histological findings included minimal to mild degeneration of the luminal epithelium and mixed cell infiltrates in the large intestine, mucosal hyperplasia in the cecum, colon and/or rectum which became more chronic and of reparative nature over time.

Binimetinib was not genotoxic. Carcinogenicity studies are not required for this type of product.

Embryo-foetal development studies conducted in rats and rabbits showed evidence of embryotoxicity (increased post- implantation loss and resorptions) and teratogenicity in rabbits only (ventricular septal defects and pulmonary trunk alterations). In rats the decreased ossification was considered to be secondary to decreased foetal body weight at maternally toxic doses. No teratogenic effects were noted in rats and rabbits up to about 30 and 3 fold, respectively, the human exposure at the therapeutic dose, based on AUC.

Binimetinib was phototoxic in an in vitro assay

3.3.6. Conclusion on non-clinical aspects

There are no major objections and no other concerns.

3.4. Clinical aspects

3.4.1. Pharmacokinetics

Binimetinib has been studied in a number of clinical studies to determine the PK in healthy volunteers and patients. A population PK analysis was also performed to determine important covariates on the PK and to support an analysis of exposure versus efficacy and safety.

Table 1: Overview of Clinical Pharmacology Studies in Healthy Subjects

Study Code	Short Title	Design (n)	Formulation[a]	PK sampling[b]
Drug Metabolism and PK studies				
ARRY-162-0601	Single ascending dose study to assess the safety, tolerability, PK and PD	Double-blind, placebo-controlled, dose-escalation (20)	Aqueous Oral Suspension	Rich
ARRY-162-0602	Multiple ascending dose study to assess the safety, tolerability, PK and PD	Double-blind, placebo-controlled, dose-escalation (38)	Aqueous Oral Suspension, PIC	Rich
CMEK162A2102	Single oral dose of 45 mg [^{14}C]MEK162 study to investigate the ADME	Open label, single dose (6)	Capsule	Rich

Key: ADME: absorption, distribution, metabolism and excretion, MEK162: binimetinib, NCSF: Novartis clinical service formulation, P3-MI: phase 3-market image, PD: pharmacodynamics, PIC: powder in capsule, PK: pharmacokinetics, n: number of subjects, MEK162: binimetinib, NCSF: Novartis clinical service formulation, QS-CSF: QS pharma-clinical service formulation.

[a] For detailed descriptions of clinical formulations and drug product please refer to Module 3.2.P.2.2 Pharmaceutical Development

[b] > 6 samples per 24-hour period = Rich

Table 2: Overview of the Clinical Pharmacology Studies in Cancer Patients

Study Code	Study Title	n	Formulation	PK sampling [a]
ARRAY-162-111	A Phase 1 Dose-Escalation Study of Oral ARRY-438162 in Patients with Advanced Solid Tumors Followed by Expansion Cohorts in Patients with Advanced or Metastatic Biliary Cancer or Metastatic Colorectal Cancer	93	Tablet	Rich/Sparse
CMEK162X1101	A Phase I Study of Oral MEK162 in Japanese Patients with Advanced Solid Tumors (enrollment complete)	21	Tablet	Rich
CMEK162X2201	A Phase II, Open-Label Study to Assess the Safety and Efficacy of Oral MEK162 in Adults with Locally Advanced and Unresectable or Metastatic Malignant Cutaneous Melanoma, Harboring BRAFV600E or NRAS Mutations (enrollment complete)	183	Tablet	Rich
CMEK162A2301	The NEMO trial (NRAS melanoma and MEK inhibitor): A Randomized Phase III, Open Label, Multicenter, Two-Arm Study Comparing the Efficacy of MEK162 Versus Dacarbazine in Patients with Advanced Unresectable or Metastatic NRAS Mutation-Positive Melanoma	402	Tablet	Sparse

Key: BRAF: b-raf proto-oncogene serine/threonine-protein kinase, MEK: mitogen-activated protein kinase kinase, MEK162: binimetinib, n: number of subjects, NEMO: NRAS melanoma and MEK Inhibitor, NRAS: neuroblastoma RAS viral oncogene homolog, PK: pharmacokinetics.

[a] > 6 samples per 24-hour period = Rich.

Binimetinib and its active oxidative metabolite (M3) have been determined in six different methods in plasma, plasma dialysate or urine. It can be concluded that the methods have adequate precision, accuracy and specificity to determine Binimetinib and in real samples. Nevertheless the sensitivity of the methods was not suitable for all clinical studies, so due to limitations of the BA methods with LLOQ of 5ng/ml several PK parameters could not be obtained.

The pharmacokinetic and statistical methods applied during the phase I and II clinical pharmacology programme seem adequate.

Binimetinib shows low solubility at physiological pH but higher at acidic pH. A study with PPIs showed no effect on binimetinib exposure. Due to a lack of intravenous data, the extent of absorption cannot be calculated, but appears to be at least 50%. The plasma protein binding has been measured at a

range of physiologically relevant concentrations and is 97.2%. Vz/F in healthy volunteers is high, 374 litres, which corresponds to a lipophilic drug substance. V/z data from the target population was not yet found in the dossier and should be provided.

The clinical pharmacology programme for binimetinib included clinical studies with overall 7 formulations. The tablet formulation P3-MI (Phase 3-Market Image Tablet) is considered the to-be-marketed (commercial) formulation. 2 relevant BE studies were performed between the formulations: BE was not demonstrated between PIC and QS-CSF for C_{max}; BE was demonstrated between the Saltigo-produced drug substance tablet formulation ACSF and the NOVARTIS produced drug substance tablet formulation NCSF tablet formulations utilised in the study CMEK162X2201. BE was not studied between other clinical formulations, which were used interchangeably in study ARRY-162-111; except for a liquid suspension of the P3-MI tablet which is irrelevant for the underlying application. In view of the formulations differing, even only slightly, in either tablet filler, lubricant content or coating material, evidence was provided with the responses to LOQ that the earlier and the P3-MI formulations are similar.

Both a high and low fat meal have only a small effect on Cmax, therefore binimetinib can be taken without regard for food. T_{max} was reached after approximately 1.5 hours.

Following a dose of 14C-binimetinib, an average of 62.3% of the administered radioactive dose was excreted in the faeces and 31.4% in the urine. In faeces binimetinib was the most abundant radioactive component and accounted for an average value of 29.8% of dose. The most abundant metabolites were M4, an ethane-diol cleavage product, and M15.9, a carboxylic acid formed from amide hydrolysis, accounting for 17.2% and 6.7% of the dose, respectively. All other metabolites were present at ≤ 2.7% of the dose. In urine, binimetinib was the most abundant radioactive component and accounted for 5.3% to 8.1% of the administered radioactive dose, with an average value of 6.5%. The most abundant metabolites were M10.9 (direct glucuronide of binimetinib), M3 (N-demethylated binimetinib), and M10.2 (another direct glucuronide of binimetinib), accounting for 6.2%, 5.1% and 4.2% of the dose, respectively. All other metabolites were present at ≤ 3.2% of the dose. As 30% is eliminated unchanged in faeces, biliary excretion, possibly by Pgp, cannot be discounted. In vitro the major route of metabolism is by UGT1A1 (50.9%). Different common UGT1A1 genotypes do not appear to affect the exposure, however there is limited data. Cytochrome P450 enzymes account for less than 25% of the elimination.

Binimetinib is the main component circulating in plasma and all metabolites are less than 10%. M3 is stated to be equipotent and attributes less than 20% of binimetinib exposure at steady state, the increased free fraction however needs to be considered in this calculation.

Binimetinib appears essentially linear over the dose range of 20 to 100 mg, there is some indication of less than proportional increase at steady state in patients at doses above 30 mg but data is limited. Modest accumulation is seen following multiple dosing, ~1.4-1.5 fold for C_{max} and AUC in patients following 45 mg. This is consistent with the calculated half-life, steady state is reached at approximately day 8.

The population pharmacokinetics of binimetinib was evaluated based on 601 subjects (n=75 healthy volunteers and n=526 cancer patients) entered in 6 clinical studies. Binimetinib pharmacokinetics obeys a two-compartment linear disposition model with first order absorption and a lag-time. Cl/F is influenced by moderate renal impairment, health status, total bilirubin, mild renal impairment, sex, and age. Cl/F in patients with moderate renal impairment is significantly decreased by 34% compared to typical clearance in patients (excluding healthy volunteer effect) V/F was influenced by body weight, age, sex, and albumin. The pharmacokinetics of the metabolite after administration of binimetinib was

described by a one-compartment disposition model, first-order and time dependent formation from parent, and first-order elimination. Mild and moderate renal impairment affected metabolite elimination to an extent similar to that of parent drug. There is a time dependency of formation of the metabolite, where Fmet decreases, which is not explained. The POPPK model generally describes the pharmacokinetics of binimetinib adequately.

The exposure is slightly higher in patients compared to healthy volunteers; clearance in melanoma patients was approximately 20 L/hr and in the model is determined to be 32% greater in healthy volunteers. Japanese patients show a ~2fold higher exposure. Age: 79 versus 59 years, was explored and found not to significantly affect the exposure and a further analysis of age categories: 75- 84 and 85+ years old showed some increase in exposure but not enough to warrant a dose adjustment.

Inter-individual variability (with P3-MI formulation) in melanoma patients was moderate to high and was higher than in HV, with up to 42% for AUC_{ss} and 49% for $C_{max,ss}$ in patients, and 23-34% and 21-48%, respectively, in HV.

A dedicated renal impairment study was completed. It had been pre-specified in the CSP that the groups with mild and moderate impairment groups were only to be enrolled in case of a >50% change in exposure for the severe group. Such a strong increase was not observed. The increase in AUC_{inf} was about 29% and the increase in C_{max} ~21%. Clearance was reduced by ~22%, resulting in longer $t_{1/2}$. It is agreed with the applicant that based on these PK results no dose adjustment for renal impairment is necessary.

A dedicated hepatic impairment study with single-dose binimetinib was completed. While an increase in dose-normalised (total) binimetinib exposure was only slight with mild impairment, both moderate and severe hepatic impairment resulted in an AUC increase of about 2-fold, and clearance reduced to about 50%. In contrast to binimetinib, the plasma concentration of the metabolite decreased with increasing hepatic impairment. More than for total binimetinib, the PK parameters for unbound plasma binimetinib changed. Dose-normalised AUC_{last} increased ~3.5-fold, CL/F decreased to ~28%. The applicant proposes a dose reduction in both patient groups to 30mg BID.

The proposed 30mg BID dose for moderate and severe HI corresponds roughly to a binimetinib exposure of 60mg BID in normal patients. The 60mg BID dose, however, was not developed further during the clinical programme as AEs were observed. Accordingly a 45 mg BID dose is recommended for a population without HI. The applicant did not detail whether and which dose reductions in case of drug-related toxicities in patients with HI should be performed.

The applicant's proposal is deemed insufficiently justified. Dose recommendations for both situations (normal and impaired hepatic conditions) need to be (re-)evaluated by popPK and/or PBPK modelling, this should also include the possibility to e.g. change from a BID to TID dosing, like 3x15mg. The clinical importance of the exposure/clearance changes for the unbound fraction should be explicitly addressed both in model and discussion. Based on an appropriate discussion of clinical safety and efficacy, new dose recommendations should be made for the target population. Furthermore, the applicant is asked collect PK samples from melanoma patients with moderate and severe impairment after repeated dosing, and to set the concentrations in relation to administered dose and AEs observed. This is proposed to enable the applicant to confirm, rather to revise, the currently proposed dose recommendations based on new data addressing also exposure-safety-relationship. The current proposal for section 4.4 ("*use with caution*") for the severe group only is not understood when compared to the warnings/recommendations for the moderate group, for that similar exposure increases were observed, and should be clarified or harmonised.

Binimetinib is not a substrate for hepatic uptake transporters. It is substrate for Pgp and BCRP, this is argued to be not relevant to absorption due to high permeability, this needs to be further supported. There are no clinical studies to investigate the effect of UGT 1A1 inhibitors, or inducers.

Binimetinib does not inhibit cytochrome P450s or UGT 1A1. It is an inducer of CYP 3A4 however a midazolam interaction study, following dosing of binimetinib at 30 mg b.i.d., showed no effect on midazolam exposure. Clarification is required on possible induction of CYP 1A2 and 2B6.

In contrast to what was proposed and supported by the CHMP in the Scientific Advice, other DDI studies were not performed. For atazanavir, instead, the applicant submitted the results of a PBPK model simulation for evaluation of DDI potential at transporter or glucuronidation level which was re-evaluated with additional modelling with raltegravir. This model suggested no clinically relevant drug interaction with regard to UGT1A1 inhibition, however further qualification of the model is still required before this can be accepted.

Smoking is an established UGT1A1 and CYP1A2 inducer, the latter is known to increase the drug clearance, in view of the fact that plasma concentrations in smokers were observed at 50% lower levels than in non-smokers in the pivotal study. It needs to be discussed how relevant this reduction in exposure is for an effective binimetinib therapy and an *in vivo* study may be appropriate for investigation of the DDI potential; alternatively inducers could be not recommended with binimetinib.

Binimetinib is not an inhibitor of Pgp, BCRP, OAT1, OCT1, OCT2, MATE-1, MATE-2k or BSEP. It is a weak inhibitor of OATP1B1 and 1B3, but not at clinically relevant concentrations. Binimetinib does inhibit OAT3 and further investigation is required.

3.4.2. Pharmacodynamics

Binimetinib is an orally bioavailable, selective and potent ATP-uncompetitive mitogen-activated protein (MAP) kinase (MEK) 1 and MEK 2 inhibitor.

In cell-free systems, binimetinib inhibits MEK1/2 with a half maximal Inhibitory Concentration (IC50) of 12 nM. In vitro, binimetinib potently inhibits MEK-dependent pERK in human NRAS and BRAF-mutant melanoma cell lines. In vivo, binimetinib treatment results in dose- and time-dependent inhibition of phosphorylation of ERK in relevant tumour models.

The signalling pathway and MoA was only marginally introduced in the clinical pharmacology dossier. The applicant is asked to provide a scientific discussion of MoA, which includes the justification that the MEK inhibitor binimetinib in monotherapy should be specifically used in the proposed indication limited to NRAS Q61 mutation-positive melanoma independent of tests for activation of the RAS/RAF/MEK pathway (including [recognized] activating BRAF mutations) in general, and as compared to the rationales given in early study reports ARRY-162-0601, -0602, and -111 where this signalling pathway was used as justification for treatment of inflammatory diseases, like rheumatoid arthritis, or biliary cancer and colorectal carcinoma.

Primary pharmacology

The results from early single dose study ARRY-162-0601 in HV showed that only doses of 30 and 40mg lead to slight (10% to 25% relative to placebo) inhibition of ERK phosphorylation by MEK, and this inhibition was transient and returned to baseline after 12 hours. In the multiple dose study ARRY-162-0602 at day 14 at 4 hours postdose and thereafter, in all groups the effect (pERK in % day 1 predose)

was generally similar to placebo. This is, on the one hand, supportive of a more than QD dosing, however, the results might suggest that TID or QID dosing would be even better than BID.

In a mouse CRC tumour model the concentration in tumour (in ng/g) was about 85% lower than in plasma (in ng/ml) and only single oral doses at 10-30mg/kg (with plasma concentrations of 1000-2000 ng/ml) inhibited ERK phosphorylation by MEK. Considering that the proposed human dose is 45mg BID independently of weight, the human dose is calculated with roughly 1-1.5mg/kg. Binimetinib C_{trough} in steady state in melanoma patients is at ~100 ng/ml, Cav of unbound binimetinib of ~6ng/ml and C_{trough} of the active metabolite is ~7-8 ng/ml. The IC_{50} of 12nM for inhibition of *in vitro* ERK-phosphorylation by MEK is ~5.3 ng/ml. This means that the drug concentration is in the steepest part of the dose-response curve and a slight decrease of concentration might presumably lead to strong reduction in effect/efficacy.

Overall, primary pharmacology evaluations are inconclusive, especially from patient studies. With regard to pERK levels no dose-response trend could be established. Overall, this supports the hypothesis that the proposed dose of 45mg BID is not in the saturation part of a dose-efficacy response curve.

PopPK evaluated the most relevant ADRs all-grade retinal events, grade 3/4 CK elevations and ≥ grade 2 LVEF reduction. Incidence of retinal events were found to be directly related to increasing C_{max}, grade 3/4 CK elevations were directly related to C_{max} and AUC; whereas for LVEF reduction no correlations to these PK parameters were found.

In the pivotal study A2301 (sparse sampling) week 4-geometric mean PK in the binimetinib arm was:
30mg BID: $C_{trough,ss}$ was 96 ng/ml and $C_{1.5h,ss}$ 283 ng/ml
45mg BID: $C_{trough,ss}$ was 101 ng/ml and $C_{1.5h,ss}$ 418 ng/ml

In the phase II study X2201 on Cycle 1 day 15:
45mg BID: C_{trough} was 109 ng/mL, C_{max} 439 ng/mL, and AUC_{tau} 2103 ng*h/mL
60mg BID: C_{trough} was 136 ng/mL, C_{max} 531 ng/mL, and AUC_{tau} 2638 ng*h/mL

In view of the very narrow range between the minimal effective dose of 30mg BID binimetinib, the recommended dose of 45mg BID, and the MTD of 60mg BID there is only minimal room for exposure variability with a positive benefit-risk relationship.

Secondary pharmacology

Secondary pharmacology with regard to cardiac safety was assessed by by popPK modelling. No relevant change of QTcF from baseline was found, and this supported also results from the pivotal study.

Regarding pharmacodynamic drug interactions the applicant argued that in the pivotal study no potential interacting drugs were used, but this is considered not a sufficient justification that the potential for such PD interactions is generally low. Referenced non-clinical models should be provided.

Regarding genetic differences in PD response of binimetinib UGT1A1 genotype analysis of binimetinib exposure performed in the pivotal study did not establish meaningful changes of predose concentrations between genotypes. Presumably, for a similar concentration safety and efficacy effects could be expected comparable.

The interpretation of analysis for a relationship of PFS to exposure from the pivotal study is difficult, but is suggestive of a positive relationship for C_{min}.

3.4.3. Discussion on clinical pharmacology

The pharmacokinetics of binimetinib are generally well presented however there are a number of omissions in the reporting of data. In particular, the human ADME is not reported adequately to allow the conclusions to be endorsed. There are also a number of points for clarification on interactions and some clinical studies may be required.

A POPK analysis was used to investigate the effect of covariates and for concentration effect modelling. There are some aspects of the model that require discussion and further data is required to support dosing in all sub-populations.

The pharmacodynamic aspects of binimetinib are considered not sufficiently elaborated. Several aspects are open and need to be adequately addressed in the response to LoQ.

3.4.4. Clinical efficacy

Study CMEK162A2301 provides the primary data for clinical efficacy claims for binimetinib in the treatment of unresectable or metastatic NRAS mutation-positive melanoma. Supportive efficacy data for the proposed indication are derived from study CMEK162X2201.

The studies supporting efficacy are listed in the table 3 below. Efficacy data are presented separately by study, with no pooled analyses performed.

Table 3: Overview of Efficacy Studies and Sources of Data

Study	Study Design, Objectives and Population	No. Of Patients	Treatment Groups and Dose Regimen (patients- n)	Efficacy Endpoints	Status
CMEK 162A2301	Phase 3 randomized, open-label, multicentre two-arm study comparing the efficacy and safety of binimetinib versus dacarbazine in patients with advanced unresectable or metastatic NRAS mutation-positive melanoma	Planned: 393 Randomised: 402 Patients treated: 383	Binimetinib 45 mg BID continuous dosing (n=269) Dacarbazine 1000 mg/m2 q3w (n=114)	Primary: PFS Key secondary: OS Other secondary: ORR, TTR, DOR, DCR	Ongoing at data cut-off date of 24 August 2015 42 patients with ongoing treatment, 32 in the binimetinib arm and 10 in the dacarbazine arm.
CMEK162X 2201	Phase 2 open-label, multicentre, three-group study to assess the safety and efficacy of binimetinib in patients with advanced unresectable or metastatic BRAF or NRAS mutation-positive melanoma	Planned: 156 Actual: 183 NRAS melanoma: 117	Binimetinib 45 mg BID (NRAS group, n=117) Binimetinib 45 mg BID (BRAF group, n=41)	Primary: ORR Key Secondary: PFS Other Secondary: OS, SOR, TTR	Ongoing at data cut-off date of 7th January 2014 15 patients with ongoing treatment, 13 in the NRAS group and 2 in the BRAF 60 mg group

			Binimetinib 60 mg BID (BRAF group, n=25)		

Dose-response studies

The dose recommended for binimetinib and the administration schedule for patients with *NRAS* mutation-positive melanoma is 45 mg BID. This corresponds to 0.35 µg/mL and 2.1 µg.hr/mL in terms of Cmax and AUC0-12h at steady state in humans.

Non-clinical data with MEK inhibitors of this class support a continuous dosing schedule to inhibit MEK consistently. In the PK studies in healthy subjects (Studies ARRY-162-0601 and ARRY-162-0602), binimetinib exposure was dose proportional with a reproducible time to maximum plasma concentration (Tmax) of 1 to 2 hours, t1/2 of approximately 8 hours and minimal drug present by 12 hours. Such PK characteristics suggest that BID dosing of binimetinib is most appropriate for maintaining sufficient plasma concentrations over the dosing interval to inhibit MEK consistently.

In vitro and *in vivo* studies confirm the ability of binimetinib to affect its intended target (MEK 1/2) and produce beneficial pharmacodynamic/ efficacy outcomes at well tolerated doses *in vivo*. In biochemical studies, binimetinib was a potent and selective inhibitor of MEK with an enzyme IC50 of 12 nM. In cellular studies *in vitro*, binimetinib potently inhibited MEK-dependent phosphorylation of ERK in human NRAS-mutant melanoma lines, as well as BRAF-mutant melanoma cell lines. In these studies employing large panels of BRAF-mutant and NRAS-mutant human melanoma cell lines, binimetinib significantly inhibited proliferation and viability. *In vivo*, binimetinib was evaluated for its ability to inhibit tumour growth and phosphorylation of ERK in xenograft models in nude mice. In particular, significant tumour growth inhibition and regressions were demonstrated in response to binimetinib treatment in NRAS-mutant melanoma xenograft models. Additionally, binimetinib had potent anti-tumour activity in numerous BRAF-mutant xenograft models, including melanoma and colorectal carcinoma.

The recommended single-agent dose and administration schedule for patients with *NRAS* mutation-positive melanoma was selected based on **the Phase 1 Study ARRAY-162-111**, which established 45 mg BID as the recommended Phase 2 dose (RP2D), and the **Phase 2 Study CMEK162X2201**, which demonstrated preliminary signs of antitumor activity and confirmed the RP2D as a generally well-tolerated dose with an acceptable safety profile in patients with *NRAS* mutation-positive advanced cutaneous melanoma. Clinical studies relevant in the determination of binimetinib dose selection are presented in the table 4, below.

Table 4: Clinical Studies Relevant in Determination of Binimetinib Dose Selection

Study No.	Study Objective, Population	No. of Patients Receiving Binimetinib	Binimetinib Dose	Efficacy Endpoint
ARRY-162-0601	Single ascending dose in healthy subjects	Planned: 20 Actual: 20	5, 10, 20, 30 and 40 mg	None
ARRY-162-0602	Multiple ascending dose in healthy subjects	Planned: 46 Actual: 38	5, 10, 20, 40 and 60 mg QD, 20 mg BID and 80 mg single dose	None
ARRAY-162-111	MTD/RP2D-finding study in patients with advanced solid tumors	Planned: 95 (30 dose escalation, 65 expansion) Actual: 93 (19 dose escalation, 74 expansion)	30, 45, 60, 80 mg BID	Objective response rate
CMEK162X2201	Efficacy/safety in BRAF or NRAS mutation-positive cutaneous melanoma	Planned: 156 (100 NRAS, 56 BRAF) Actual: 183 (117 NRAS, 66 BRAF)	45, 60 mg BID	Objective response rate

Sources: Synopses of Individual Studies, Tabular Listing of All Clinical Studies

Key: BID: twice daily, BRAF: b-raf proto-oncogene serine/threonine-protein kinase, MTD: maximum tolerated dose, No.: number, NRAS: neuroblastoma ras viral oncogene homolog, QD: once daily, RP2D: recommended phase 2 dose.

In study ARRY-162-0601, healthy subjects received single, escalating doses of 5, 10, 20, 30 and 40 mg binimetinib or matching placebo. Twenty subjects (4 subjects per dose level) received treatment with binimetinib and 1 subject per dose level received placebo. Headache was the most common adverse in this study. Clinical laboratory results, vital signs, electrocardiograms and physical examinations indicated no safety concern of a single dose of binimetinib ranging from 5 mg to 40 mg.

In study ARRY-162-0602, healthy subjects received escalating doses of 5, 10, or 20 mg Once Daily (QD) binimetinib, 20 mg BID binimetinib, 40 or 60 mg QD binimetinib for 14 days, a single dose of 80 mg binimetinib or matching placebo. A total of 50 subjects were enrolled and 44 completed the study. The most commonly reported adverse events were diarrhoea, headache, rash and acne. There was no evidence that diarrhoea or headache was dose-related and none of these events led to discontinuation of study drug. Adverse events in the Skin and Subcutaneous Tissue Disorders system organ class occurred with the greatest incidence in the 20 mg BID, 40 mg QD, and 60 mg QD binimetinib groups.

Study ARRAY-162-111 was a Phase 1 dose-escalation study in patients with solid tumours followed by expansion cohorts in patients with advanced or metastatic biliary cancer or metastatic Colorectal Cancer (CRC). The primary objectives were to determine the Maximum Tolerated Dose (MTD) following 30, 45, 60 and 80 mg binimetinib BID and to characterize the safety and PK of binimetinib. Nineteen patients with advanced solid tumours received binimetinib in the Dose-escalation Phase. Four dose levels were evaluated: 30 mg BID, 45 mg BID, 60 mg BID and 80 mg BID. Two of 4 patients receiving 80 mg BID experienced Dose Limiting Toxicities (DLTs), thus the 80 mg BID dose was declared non tolerable. Seven patients were enrolled at 60 mg BID and no DLTs were observed; therefore, 60 mg BID was declared the MTD. Following completion of the Dose-escalation Phase, 74 patients were enrolled in the Expansion Phase, including 28 patients in the biliary cancer cohort at 60 mg BID dose, 31 patients in *KRAS*-mutant CRC cohort with 6 patients at 60 mg BID and 25 at 45 mg BID dose, and 15 patients in the BRAF-mutant CRC cohort at 45 mg BID dose. The incidence of adverse events

resulting in reduction of binimetinib dose were reported at a 3-fold higher incidence in patients in the 60 mg BID dose group compared with the 45 mg BID dose group, and resulted in the decision to discontinue evaluation of the 60 mg BID dose in this study, thus 45 mg BID was determined to be the RP2D.

Efficacy dose-finding studies were not performed. However, analyses exploring the relationship between exposure and efficacy in Study CMEK162A2301, in which binimetinib were administered at 45 mg BID, suggest that efficacy was observed across the range of observed exposures with a trend towards greater efficacy both in terms of PFS and ORR with higher exposures. This supports the conclusion that binimetinib 45 mg BID, the maximum dose that is well tolerated based on dose-ranging studies for safety, maximizes the potential for benefit while providing a tolerated dose.

Main clinical study: CMEK162A2301- The NEMO Trial

The NEMO trial (NRAS melanoma and MEK inhibitor) is an ongoing randomized Phase III, open label, multicentre, two-arm study comparing the efficacy of MEK162 (binimetinib) versus dacarbazine in patients with advanced unresectable or metastatic NRAS mutation-positive melanoma.

The study was initiated on the 12th of July 2013 (date of the first informed consent) and is currently still ongoing though enrolment has been completed. **The data presented here is from the primary analysis cut-off date of the 24th of August 2015.** This includes the results of the primary analysis for primary endpoint-PFS, as well as the planned interim analyses for overall survival and other efficacy and safety variables. As of the cut-off date, 42 patients (10.4%) were still on treatment, 18 patients (4.5%) had discontinued treatment but were still being evaluated in the post-treatment follow-up phase and a total of 125 patients (31.1%) were still in follow-up for survival. **An updated main OS analysis has also been conducted, with a cut-off date of the 18th of March 2016** (provided as a CSR addendum). **In response to requests for updated analyses, the applicant subsequently also presented updated PFS and ORR results from this (but not later) date.**

Data collected past the data cut-off date of 24-Aug-2015 is planned to be further summarized in 2 subsequent reports, unless the study is stopped at an earlier point in time: one at the time of the final hypothesis testing time point of the OS end point, and one at the time of the final OS analysis (end of study).

Eligible patients were male or female ≥ 18 years of age with histologically confirmed diagnosis of locally advanced, unresectable or metastatic cutaneous or unknown primary melanoma AJCC Stage IIIC or IV who were previously untreated or who progressed on or after prior treatment with any number of lines of immunotherapy for unresectable or metastatic disease.

All patients were required to have documented presence of NRAS Q61 mutation in tumour tissue (archival or fresh biopsy fixed in formalin) prior to randomization, as determined by a Novartis designated central laboratory. NRAS mutation status was determined using an NRAS Q61 clinical trial assay that is Investigational Device Exempt (IDE; G130073). Presence/absence of other activating mutations such as BRAF V600 was not an inclusion/exclusion criterion and not tested during the molecular screening phase of the trial. The applicant provided meanwhile subgroup analysis of post hoc BRAF testing (of stored tissue) of this trial.

Of note, inclusion criterion of the original protocol was "*Naïve untreated patients*", a criterion which was expanded to "*Naïve untreated patients or patients who have progressed on or after prior treatment with any number of lines of immunotherapy for unresectable or metastatic melanoma*" in 2 subsequent protocol amendments.

Patients were assigned to one of the following 2 treatment arms in a ratio of 2:1 in favour of the investigational treatment.

Patients who were randomized to the binimetinib arm received binimetinib 45 mg orally bid. Patients could continue treatment with the study drug until locally assessed PD was confirmed by the BIRC, unacceptable toxicity, death, physician decision, study termination or discontinuation from study treatment for any other reason (e.g., withdrawal of consent, lost to follow-up, start of a new anticancer therapy).

Patients who were randomized to the dacarbazine arm received 1000 mg/m2 dacarbazine for i.v. administration, once every 3 weeks, administered by authorized site personnel.

The **primary efficacy endpoint** of the study was PFS, defined as the time from the date of randomization to the date of the first documented progression or death due to any cause, whichever occurred first. If a patient did not have an event at the time of the analysis cut-off or at the start of any new antineoplastic therapy, PFS was censored at the date of last adequate tumour assessment.

The **key secondary** objective of the study was to compare OS between treatment arms. Overall survival was defined as the time from the date of randomization to the date of death due to any cause. If a death had not been observed by the date of analysis cut-off, OS was censored at the date of last contact.

Other secondary endpoints

The BIRC assessments were used for the main analyses of ORR, TTR, DOR and DCR.

Best overall response was derived as per RECIST version 1.1, Novartis Guideline version 3.1. Overall response rate was defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR). Two sets of ORR were considered, one for confirmed and one for unconfirmed responses. ORR was presented by treatment arm along with exact 95% CI. The Cochran-Mantel Haenszel chi-square test at the two-sided significance level of 0.05, stratified by randomization strata, was used to compare the treatment arms.

Time to overall response was the time between date of randomization until first documented response of CR or PR.

Duration of overall response was calculated as the time from the date of first documented response (CR or PR) to the first documented progression or death due to underlying cancer.

Disease control rate was calculated as the proportion of patients with a BOR of CR, PR, stable disease (SD) or non-CR/non-PD per RECIST version 1.1, Novartis Guideline version 3.1.

Other secondary efficacy objectives were:

- To assess the safety and tolerability of MEK162 in this patient population using NCI CTCAE v4.03
- To characterize the pharmacokinetics of MEK162 in this population
- To compare the global health status between the treatment arms using the EORTC Quality of Life Questionnaire Core 30 and the EuroQoL-5D (EQ-5D-5L)
- To compare the ECOG PS between the treatment arms
- To assess the concordance between the NRAS mutation status obtained using the registrational clinical trial assay and the companion diagnostic assay which will be submitted for PMA

Summary of main efficacy results

The following table summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 5: Summary of efficacy for trial **CMEK162A2301**

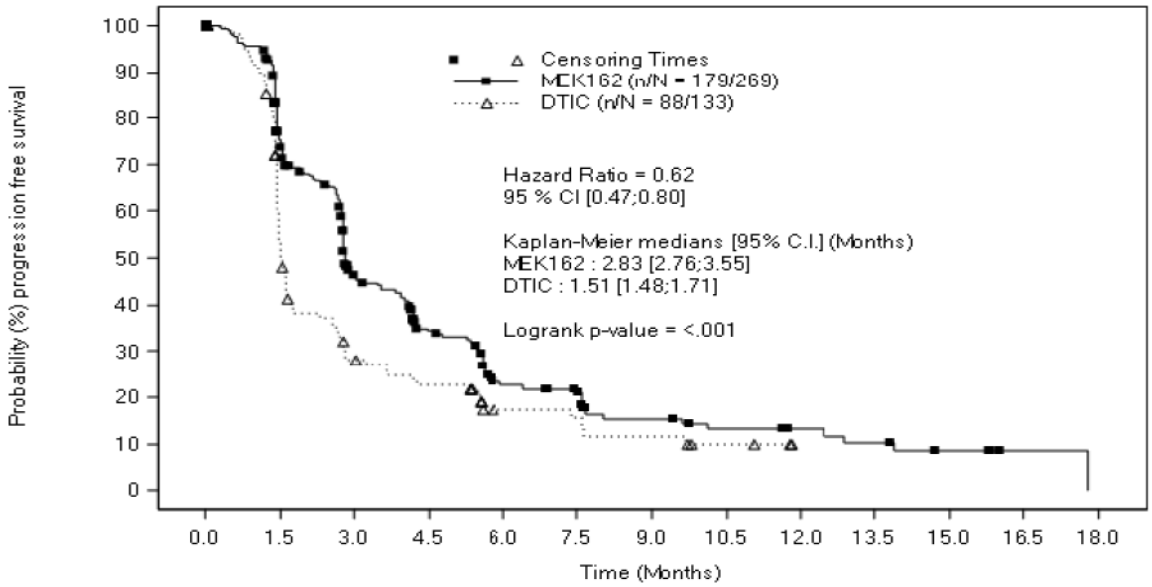
Title: The NEMO trial (NRAS melanoma and MEK inhibitor): A randomized Phase III, open label, multi-centre, two-arm study comparing the efficacy of MEK162 versus dacarbazine in patients with advanced unresectable or metastatic NRAS mutation-positive melanoma.			
Study identifier	CMEK162A2301, EudraCT no 2012-003593-51		
Design	Two-arm, randomized, parallel group, open-label, multicentre, Phase III study		
	Study initiation: Duration of Run-in phase: Duration of Extension phase:		12th July 2013 not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Test Product		Binimetinib 45 mg orally bid, continued till progression, death or unacceptable toxicity, 269 patients randomized.
	Reference Therapy		Dacarbazine 1000mg/m2 IV every 3 weeks, 133 patients randomized.
Endpoints and definitions	**Primary endpoint**	**Progression free Survival (PFS)**	The time from the date of randomization to the date of the first documented progression or death due to any cause, whichever occurred first. If a patient did not have an event at the time of the analysis cut-off or at the start of any new antineoplastic therapy, PFS was censored at the date of last adequate tumour assessment.
	Secondary endpoint	**Overall Survival (OS)**	Overall survival was defined as the time from the date of randomization to the date of death due to any cause. If a death had not been observed by the date of analysis cut-off, OS was censored at the date of last contact.
	Secondary endpoint	**Overall Response rate (ORR)**	Overall response rate was defined as the proportion of patients with best overall response (BOR) of complete response (CR) or partial response (PR).
Primary Analysis Cut-off	24th August 2015		
Other Cut-off dates	18th March 2016 for main OS analysis		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full Analysis Set (as per Central review)		
Descriptive statistics and estimate variability	Treatment group	Binimetinib arm	Dacarbazine arm

	Number of subject	269	133
	Primary endpoint **(Median PFS-months)**	2.83	1.51
	95% CI	(2.76, 3.55)	(1.48, 1.71)
	Secondary endpoint **(Main Overall Survival (analysis at cut-off date 18/03/16); months)**	10.97	10.09
	95% CI	(8.28, 13.60)	(7.03, 16.46)
	Secondary endpoint **(Overall Response Rate-%)**	15.2	6.8
	95% CI	11.2, 20.1	3.1, 12.5

Effect estimate per comparison	**Primary endpoint: Progression free survival**	**Binimetinib vs Dacarbazine**	**Binimetinib 45 mg BID daily vs. Dacarbazine IV 3 weekly.**
		Hazard ratio (stratified unadjusted Cox model)	0.62
		95% CI	0.47, 0.80
		P-value (one sided stratified log rank test)	<0.001
	Secondary endpoint: Overall survival (Main OS analysis)	**Binimetinib vs Dacarbazine**	**Binimetinib 45 mg BID daily vs. Dacarbazine IV 3 weekly.**
		Hazard ratio (stratified unadjusted Cox model)	1.00
		95% CI	0.75; 1.33
		P-value (one sided stratified log rank test)	0.499
	Secondary endpoint: Overall Response Rates	**Binimetinib vs Dacarbazine**	**Binimetinib 45 mg BID daily vs. Dacarbazine IV 3 weekly.**
		ORR	Effect estimate not presented
		variability statistic	Not given
		P-value	Not given
Notes	<free text>		

Further details of the efficacy results from the NEMO trial, including survival curves are presented below. Further details of sub-group analyses and other secondary endpoints are highlighted below.

Figure 01a: Kaplan-Meier plot of PFS based on central review (Full Analysis Set)- Data cut-off 24th August 2015



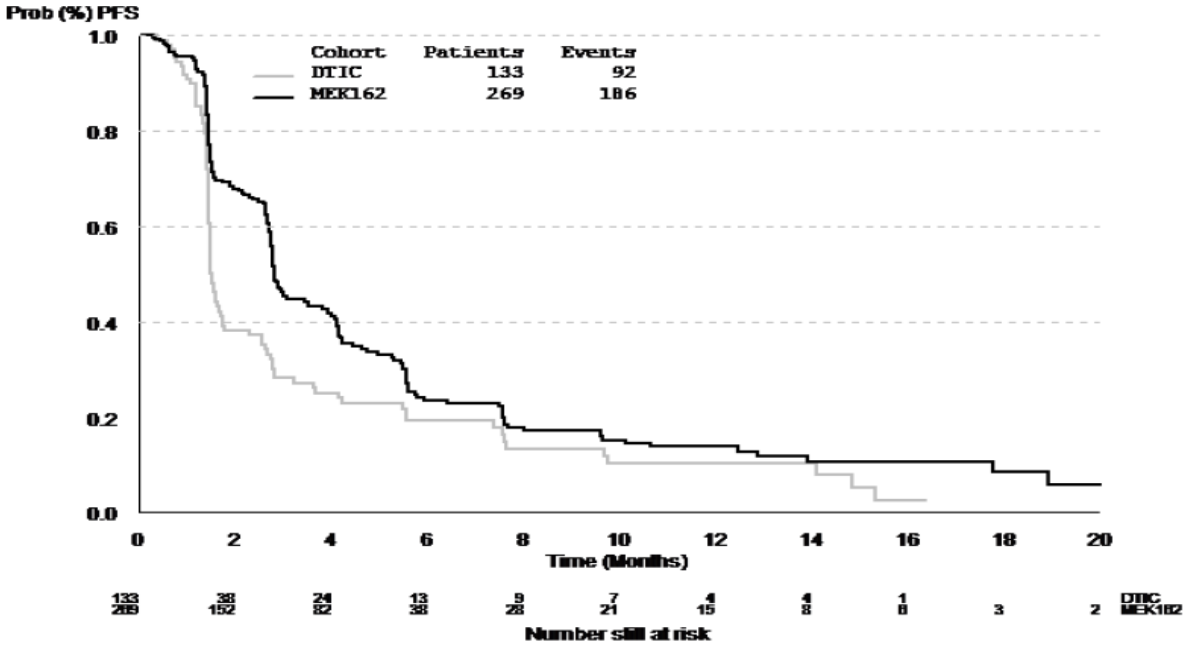
Number of patients still at risk

Time (Months)	0	1.5	3	4.5	6	7.5	9	10.5	12	13.5	15	16.5	18
MEK162	269	175	90	56	30	25	15	11	9	7	4	1	0
DTIC	133	56	27	21	9	8	6	3	0	0	0	0	0

AJCC = American Joint Committee on Cancer; CI = confidence interval; DTIC = dacarbazine; ECOG = Eastern Cooperative Oncology Group; MEK162 = binimetinib; PFS = progression-free survival
Stratified log-rank test and stratified Cox model using strata defined by AJCC stage, prior line immunotherapy and ECOG performance status.

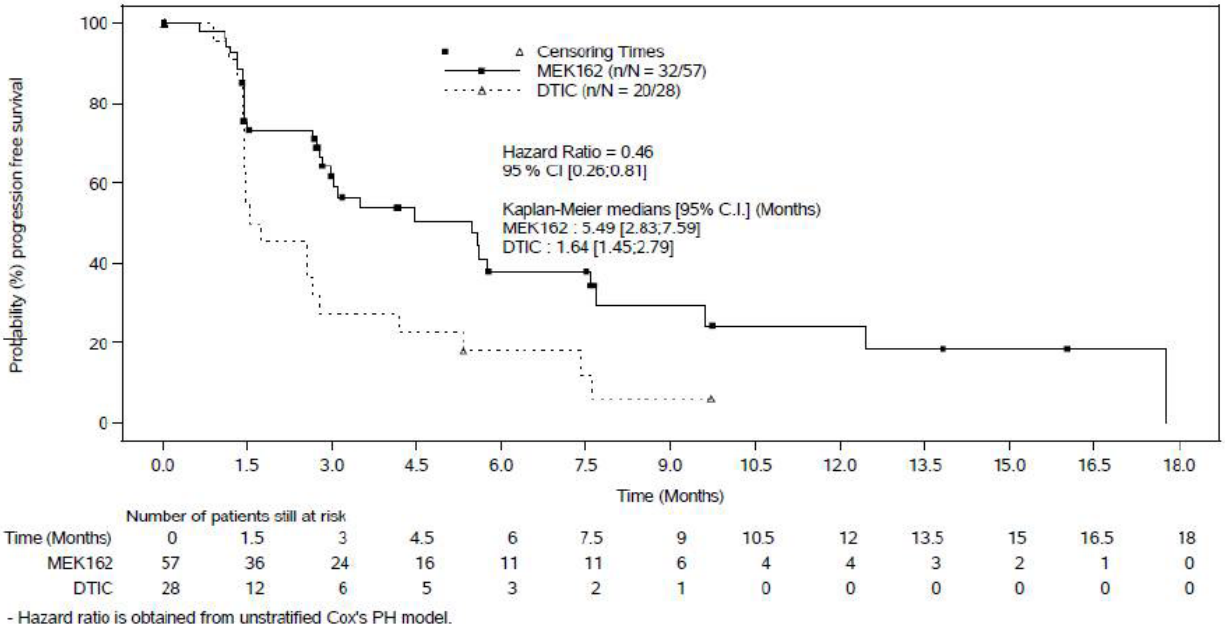
An updated analysis of the PFS was provided at the data cut-off date of 18th March 2016. With an additional 11 events included in the analysis (7 and 4 in the binimetinib and dacarbazine arms, respectively), the median PFS remained unchanged. Median (95% CI) PFS values of 2.83 months (2.76, 3.55) and 1.51 months (1.48, 1.74) were observed in the binimetinib and dacarbazine arms, respectively. An estimated 37% risk reduction in disease progression or death (PFS) was observed for patients treated with binimetinib compared to those treated with dacarbazine (HR 0.63, 95% CI 0.48, 0.82). Slightly more patients were still alive and progression-free at 12 and 15 months in the binimetinib arm compared to the dacarbazine arm (13.76 versus 10.36 at 12 months; 10.62 versus 5.18 at 15 months).

Figure 01b: Kaplan-Meier plot of PFS based on central review (FAS)- Data cut-off 16th March 2016



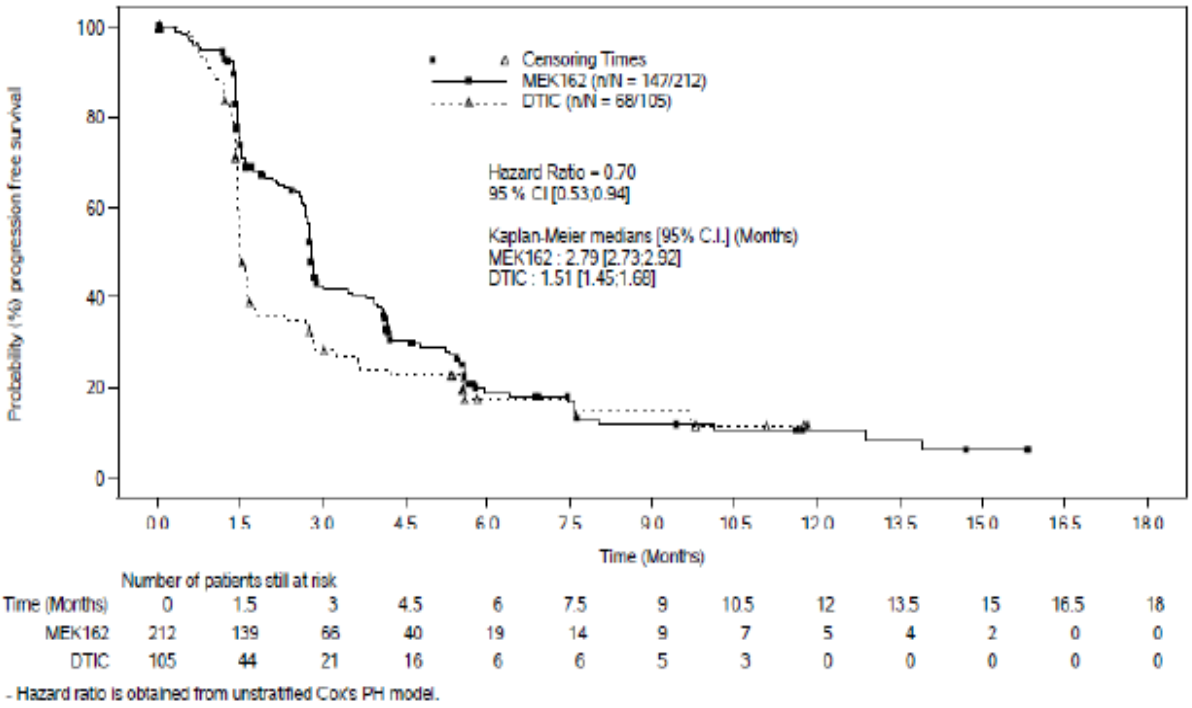
Sub-group analyses were provided for the PFS results based on whether the patients had received prior immunotherapy or not. The graphs in figure 2a and 2b highlight the results.

Figure 02a: Kaplan-Meier plot of PFS based on central review: Prior Immunotherapy Stratum



CI = confidence interval; DTIC = dacarbazine; MEK162 = binimetinib; PFS = progression-free survival

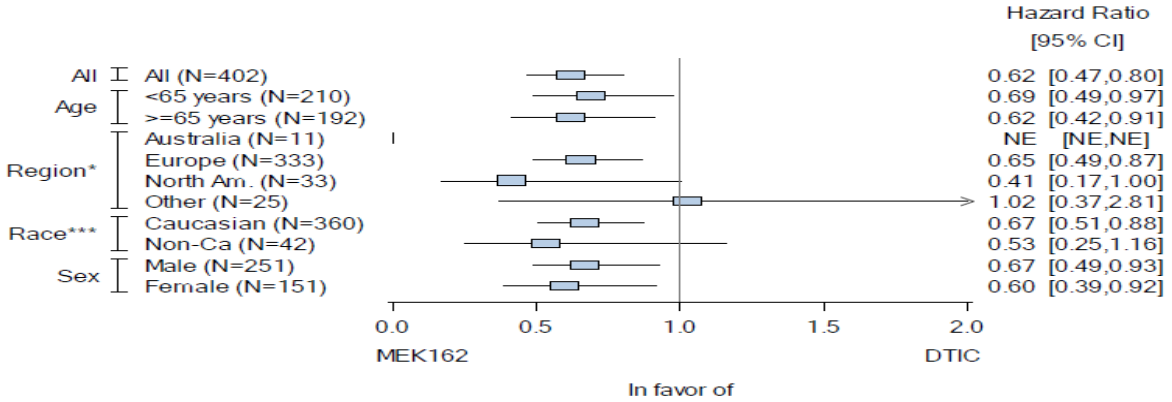
Figure 02b: Kaplan-Meier plot of PFS based on central review: No Prior Immunotherapy Stratum



Eighty-five patients were in the subgroup of patients receiving prior immunotherapy for unresectable or metastatic disease (per stratification factor), 57 in the binimetinib arm and 28 in the dacarbazine arm. Within this subgroup, an estimated 54% risk reduction in PFS was observed for patients treated with binimetinib compared to those treated with dacarbazine (HR 0.46, 95% CI 0.26, 0.81). Median (95% CI) PFS values of 5.49 months (2.83, 7.59) and 1.64 months (1.45, 2.79) were observed in the binimetinib and dacarbazine arms, respectively.

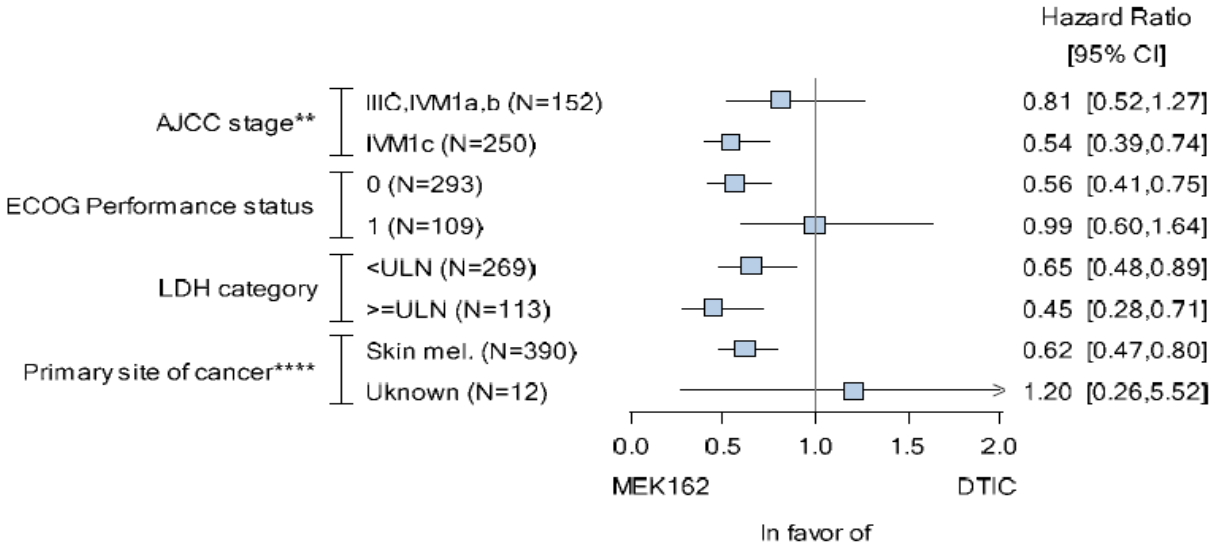
Figure 03-06: Forest plot of PFS based on central review

03: (Full Analysis Set)-Demographics and region



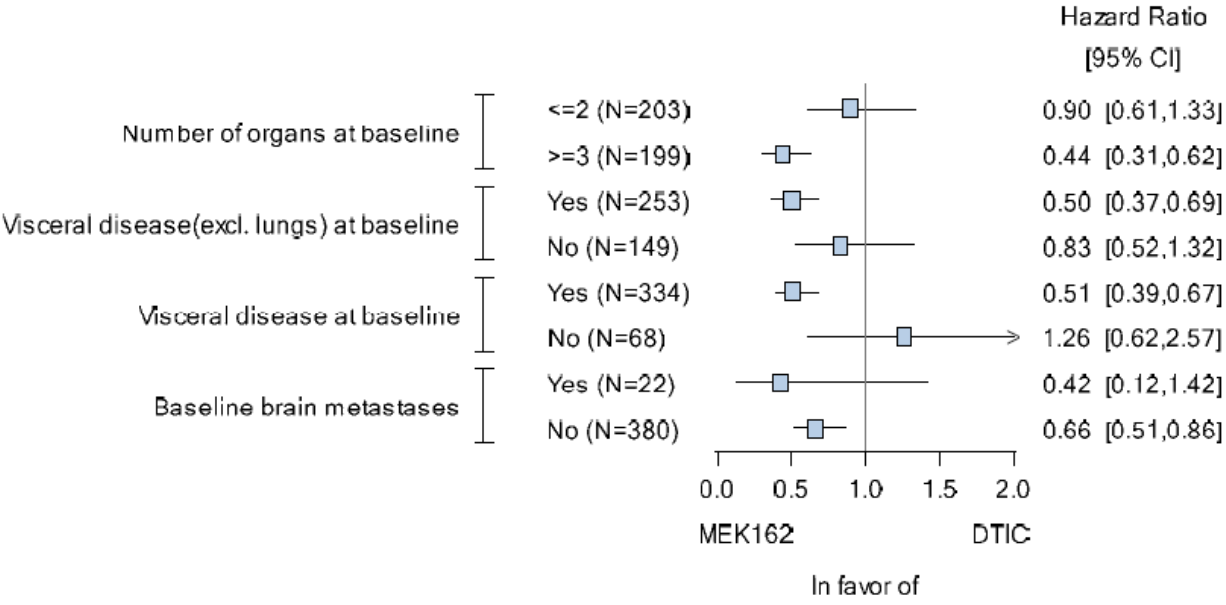
Source: Figure 14.2-1.6
-Hazard ratio for subgroups is obtained from unstratified proportional hazard model.
* North Am. : North America.
** IIIC,IVM1a,b : IIIC, IVM1a, OR IVM1b
*** Non-Ca : Non-Caucasian .
****Skin mel. = Skin melanoma.

04: AJCC stage, ECOG PS, LDH and primary site of cancer



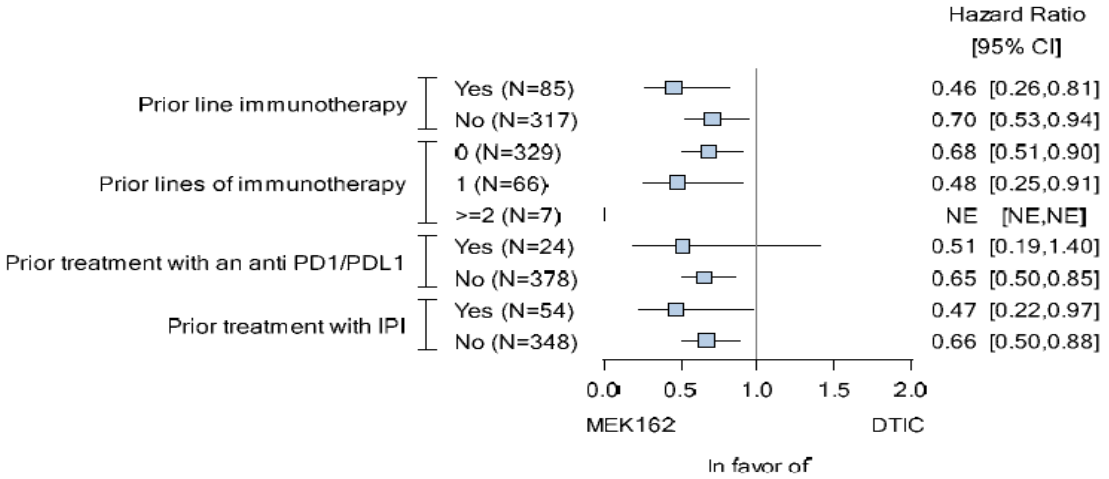
Source: Figure 14.2-1.6
-Hazard ratio for subgroups is obtained from unstratified proportional hazard model.
* North Am. : North America.
** IIIC,IVM1a,b : IIIC, IVM1a, OR IVM1b
*** Non-Ca : Non-Caucasian .
****Skin mel. = Skin melanoma.

05: Baseline disease characteristics



Source: Figure 14.2-1.6
-Hazard ratio for subgroups is obtained from unstratified proportional hazard model.
* North Am. : North America.
** IIIC,IVM1a,b : IIIC, IVM1a, OR IVM1b
*** Non-Ca : Non-Caucasian .
****Skin mel. = Skin melanoma.

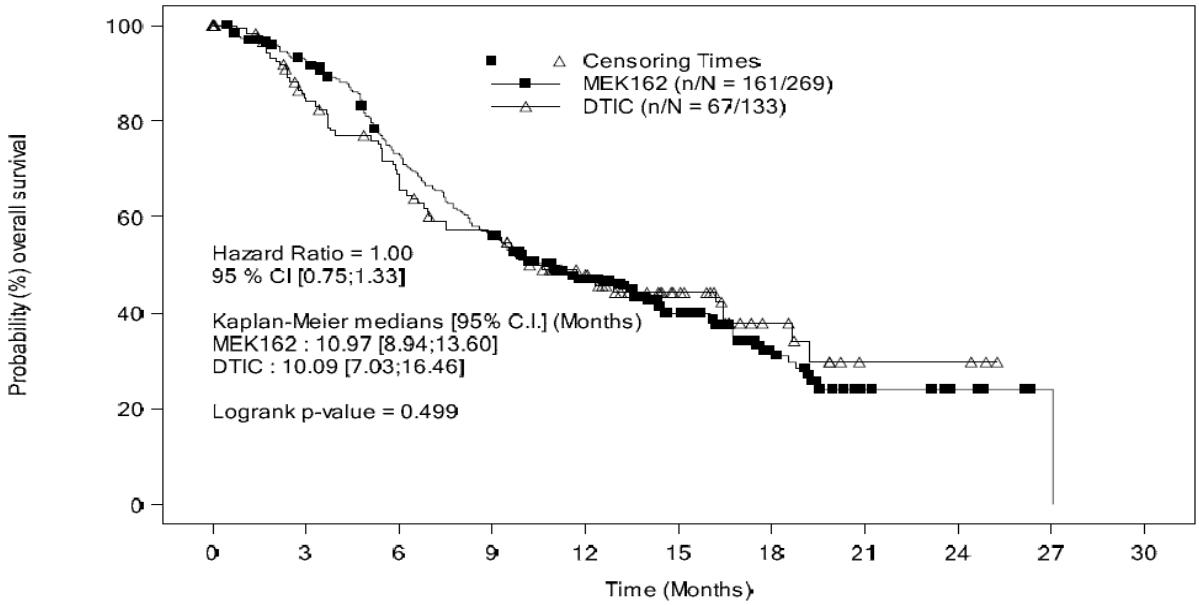
06: Prior immunotherapy



Source: Figure 14.2-1.6
-Hazard ratio for subgroups is obtained from unstratified proportional hazard model.
* North Am. : North America.
** IIIC,IVM1a,b : IIIC, IVM1a, OR IVM1b
*** Non-Ca : Non-Caucasian .
****Skin mel. = Skin melanoma.

DTIC = dacarbazine; eCRF = electronic case report form; IPI = ipilimumab; IRT = Interactive Response Technology; MEK162 = binimetinib; NE = not estimable; ULN = upper limit of normal
Prior line of immunotherapy is per stratification factor (prior immunotherapy yes/no) from the IRT.
Prior lines of immunotherapy and treatment information in the therapeutic/metastatic setting is taken from the eCRF.

Figure 07: Kaplan-Meier plot of overall survival (Main OS Analysis)- Data cut-off date: 18-Mar-2016)



Number of patients still at risk

Time (Months)	0	3	6	9	12	15	18	21	24	27	30
MEK162	269	240	185	141	96	58	26	9	5	1	0
DTIC	133	98	76	62	44	26	11	3	3	0	0

AJCC = American Joint Committee on Cancer; CI = confidence interval; DTIC = dacarbazine; ECOG = Eastern Cooperative Oncology Group; MEK162 = binimetinib
Stratified log-rank test and stratified Cox model using strata defined by AJCC stage, prior line immunotherapy and ECOG performance status.

The planned overall survival, for the event when 80% OS events will have been observed, is still not available and therefore not submitted. Considering the additional 46 OS events that occurred in between 18-Mar-2016 and 20-June-2017, the 320th event is expected to occur at the date 17-Oct-2019. The CHMP raised major objections, allowing two options to the applicant, aware that at day 120 of this procedure 80% of OS events had not occurred. It is unclear as to how many of the above additional 46 OS events occurred in the binimetinib, and how many in the dacarbazine, arm, respectively, in this open label trial. The applicant has not submitted a more mature OS analysis based on either 274 (228 + 46; **68.2%**) or 320 (**80%**) OS events, as of 20-June-2017 or as of the future date 17-Oct-2019, respectively.

The second option offered to the applicant was in the request to actively collect additional information on survival status of patients not older than 14 days before the data cut-off 18 March 2016 for patients that were censored in the OS analysis. However, the applicant seemed unable to collect this information for some patients and has instead presented sensitivity analyses assuming a variety of different outcomes for these 'lost to follow up' patients.

The results are presented in table 4 of the response:

Table 4: Sensitivity Analyses of OS Related to LTFU; Data Cutoff: 18-Mar-2016

	Median (95% CI)	HR (95% CI)[a]	P-value[b]	Additional OS Events Resulting from Analysis
Primary OS analysis				
Binimetinib	**10.97 (8.94, 13.60)**	**1.00 (0.75, 1.33)**	**0.499**	
Dacarbazine	**10.09 (7.03, 16.46)**			
Assume patients LTFU died at date of last contact				
Binimetinib	9.49 (8.21, 11.76)	0.85 (0.66, 1.10)	0.109	38
Dacarbazine	6.97 (5.95, 10.09)			
Assume patients LTFU with prior evidence of PD per BIRC died at date of last contact				
Binimetinib	10.12 (8.61, 13.50)	0.98 (0.74, 1.29)	0.429	12
Dacarbazine	9.72 (6.77, 16.20)			
Assume patients LTFU with at least one valid post-baseline tumor assessment died at date of last contact				
Binimetinib	9.92 (8.31, 12.88)	0.95 (0.73, 1.25)	0.359	21
Dacarbazine	9.30 (6.51, 12.91)			
Assume patients LTFU were alive at data cutoff date				
Binimetinib	12.48 (9.46, 14.55)	1.19 (0.90, 1.59)	0.885	0
Dacarbazine	16.43 (9.72, NE)			

Assuming that all patients LTFU died on the date of last contact would result in a prolonged survival for binimetinib (9.5 vs. 7.0 months), assuming that all patients LTFU were alive at the date of cut-off

would result in a prolonged survival for dacarbazine (16.4 vs. 12.5 months), however, each of the differences not reaching statistical significance. This result shows three things: First, the proportion of patients LTFU is unevenly distributed in both arms (more patients LTFU in the dacarbazine arm), and this causes a major uncertainty as to the overall result, i.e. a HR of 1.0 in the currently most mature primary (or main, see figure 07 above) OS analysis (see results **in bold** as of table 4). Second, the numerical differences of 7.0 and 16.4 months for the median OSs in the dacarbazine arm, depending on the assumption on which the sensitivity analyses were performed, gives a good feeling, or estimate, for the size of the time-span in-between last contact, and data cut-off date, for patients assessed as censored (and LTFU) in the primary OS analysis. Lastly, the way these 'currently censored' subjects are handled in the analysis has an important effect on the results which range from favouring binimetinib to favouring dacarbazine depending on the assumptions made. Therefore, it is very difficult to make firm conclusions on OS as the follow up of patients is not adequate to assess this endpoint.

Reasons for being cautious in the interpretation of the quality of life data have been discussed and mainly include poorer compliance to the EORTC QLQ-C30 by patients on the dacarbazine arm.

Comparison of **ECOG performance status** between the two arms was, following the protocol, also one of the (efficacy) objectives of the pivotal study. ECOG PS was used to assess the physical health of patients, and ranges from 0 (most active) to 5 (dead). Results on ECOG PS, however, were reported in section safety of the CSR:

Frequency counts and percentages of patients in each score category were provided by treatment arm and time window. In addition, the time to definitive deterioration of the ECOG PS was analyzed and compared between treatment arms. The time to definitive deterioration was defined as the time from the date of first dose to the date of event, which was defined as death due to any cause or a decrease in ECOG PS by at least one category from the baseline score. Deterioration was considered definitive if no improvement in the ECOG PS status was observed at a subsequent time of measurement following the time point where the deterioration was observed. The proportion of patients with a definitive 1-point deterioration in ECOG PS was higher in the binimetinib arm compared with the dacarbazine arm (30.9% vs. 11.4%). The median time to definitive 1-point deterioration was not estimable in either group (see figure 14.3-6.1 below).

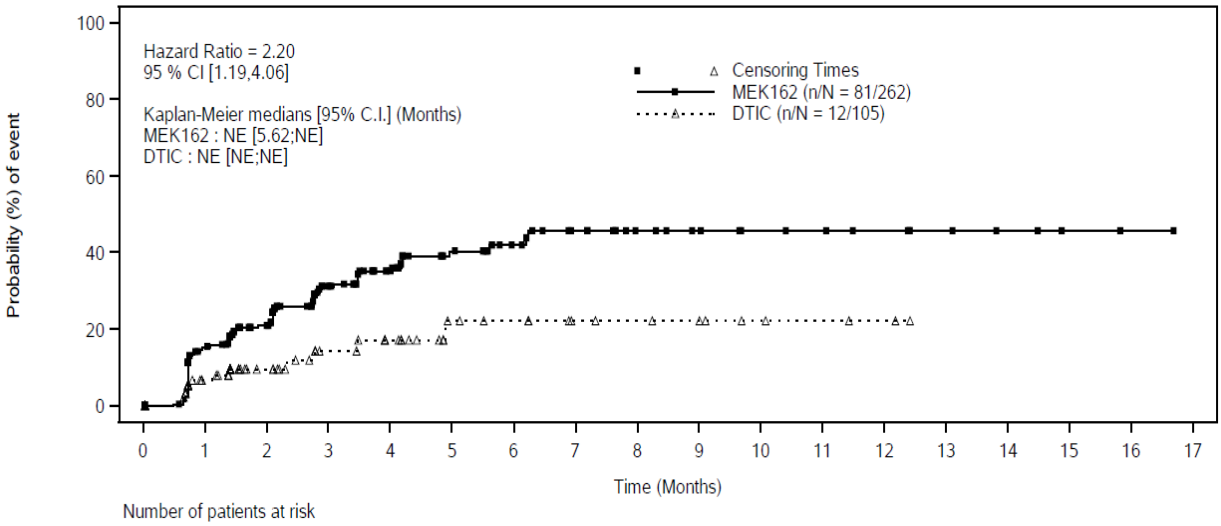
The applicant has explored and discussed several points to discuss reasons for the general health deterioration. Several of these were already known and discussed in the d80 and d120 reports and therefore is not new data.

In most of cases the reasons for physical health deterioration assessed as an SAE, or assessed as a safety endpoint, in the binimetinib arm was due to disease progression rather than due to adverse events/toxicity of the treatment. While this argument can be accepted to clarify that toxicity from study treatment was not the cause for physical health deterioration assessing as a SAE, the fact that a higher proportion of patients on the binimetinib arm experienced physical health deterioration as an SAE because of disease progression is a major concern. This is even more important to consider when the demonstrated difference is 1.3-month in terms of PFS compared to dacarbazine, i.e. progression (or death) as an event occurred earlier in the dacarbazine arm. The overall effect of earlier progressions and toxicity on the health of patients, thus, is discussed subsequently with the more sensitive (efficacy) endpoint **ECOG PS deterioration**.

The ECOG PS data (presented in the protocol as efficacy endpoint and reported in the CSR of the pivotal study in section safety) demonstrate early separation of the two treatment arms, favouring dacarbazine.

Figure 09: ECOG PS deterioration (other secondary endpoint, data cut-off date: 24-Aug-2015)

Figure 14.3-6.1 (Page 1 of 1)
Kaplan-Meier plot of time to definitive deterioration of the ECOG PS by treatment
Safety set



Number of patients at risk

Time (Months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
MEK162	262	199	162	94	72	48	33	25	18	15	12	11	9	6	4	2	1	0
DTIC	105	67	44	31	25	15	13	9	8	7	4	3	2	0	0	0	0	0

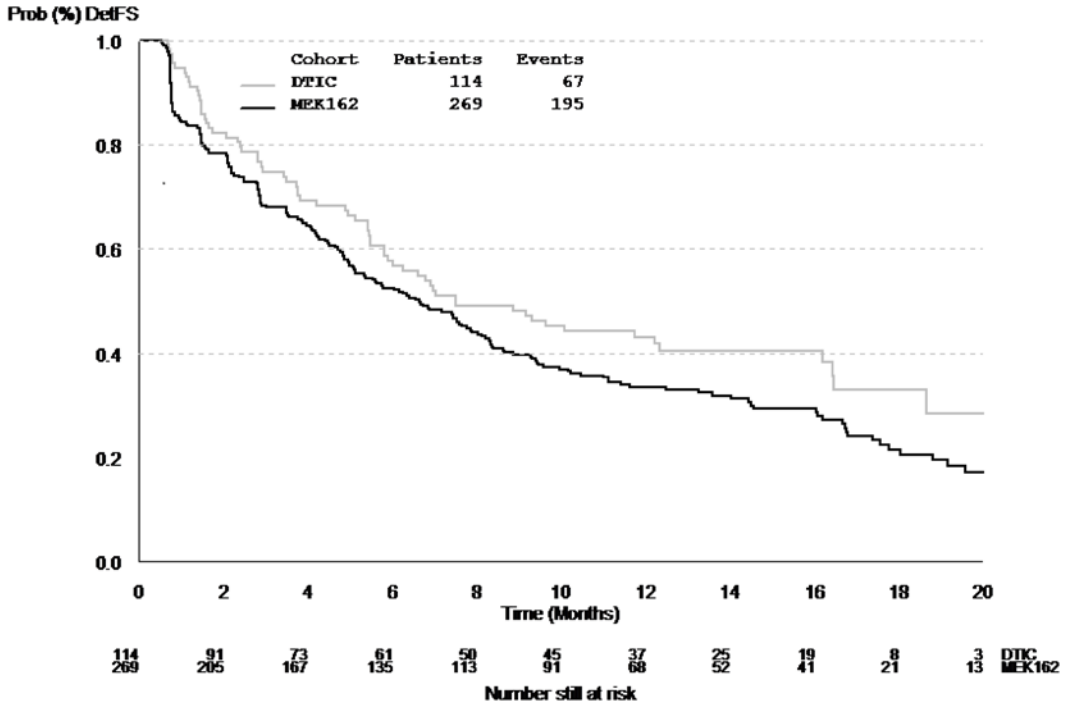
- Stratified Logrank test and stratified Cox model using strata defined by AJCC stage, prior line immunotherapy and ECOG performance status.
- Definitive deterioration is defined as on treatment death due to any cause or decrease in ECOG PS by at least one category from baseline score.
N: Number of patients at risk, i.e., with non-missing values at baseline and post-baseline.
n: Number of patients that meet the criteria.
Assessments occurred up to 3 days after last study treatment date are considered.

Stratified log-rank test and Cox regression model for time to definitive deterioration of the ECOG PS: Safety set

			Log-rank Test	Cox Model	
	Event/N (%)	Median time (95% CI) (months) (1)	p-value (3)	Hazard ratio (2)	95% CI (4)
DTIC	12/ 105(11.4)	NE (NE , NE)	0.995	2.20	(1.19, 4.06)
MEK162	81/ 262(30.9)	NE (5.62 , NE)			

Since death was not analysed as a “definitive deterioration of ECOG PS”, and accordingly median was not reached, the applicant was requested to provide an analysis of the median deterioration free survival (DFS). The median DFS itself is slightly longer (i.e. about 0.9 months) for dacarbazine (7.5 months) than for binimetinib (6.6 months)[HR 1.26 (95% CI: 0.96, 1.67; p-value 0.051]. There is at least a trend for binimetinib **shortening** DFS compared to dacarbazine, deterioration comprising death as an ECOG PS of 5.

Figure 18: Kaplan-Meier plot of Deterioration-free Survival (FAS); Data cutoff: 18-Mar-2016



Source: Data Supporting Response to Q104 [Efficacy Appendix], provided with these Responses to Questions.
FAS=Full Analysis Set

Clinical studies in special populations

N/A

Analysis performed across trials (pooled analyses AND meta-analysis)

N/A

Supportive study- MEK162X2201

This was a Phase II, open-label study conducted to assess the safety and efficacy of oral MEK162 in adults with locally advanced and unresectable or metastatic malignant cutaneous melanoma, harbouring BRAFV600 or NRAS mutations.

The first patient was recruited into the study on the 24th of March 2011. The study is still ongoing and the data presented is from the primary analysis cut-off date of 7th January 2014. A total of 183 patients were enrolled at 13 centres across 5 countries.

The **Primary Objective** was to estimate the objective response rate (ORR) of binimetinib when administered orally at a dose of 45 mg bid to adult patients with advanced, unresectable cutaneous melanoma; i) harbouring BRAFV600 or ii) harbouring NRAS mutations and iii) when administered orally as 60 mg bid to adult patients with advanced, unresectable cutaneous melanoma, harbouring BRAFV600 mutations.

Secondary Objectives

- Key secondary objective was to assess the effect of oral binimetinib on time-related efficacy parameter (progression free survival; PFS).
- To further assess the effect of oral binimetinib on other time-related efficacy parameters including overall survival (OS), duration of response (DOR) and time to response (TTR).
- To characterize the safety and tolerability of oral binimetinib.

Other secondary objectives were

- To assess the effects of binimetinib on MEK/MAPK signalling (pharmacodynamics: PD) changes of molecular status of pERK, and DUSP6) in pre- vs. post-dose tumour biopsies.
- To measure plasma concentrations of binimetinib and the pharmacologically active metabolite.

Exploratory objectives were

- To explore a possible difference in the ORRs of binimetinib when administered orally as 45 mg bid and 60 mg bid to adult patients with advanced, unresectable cutaneous melanoma harbouring BRAFV600 mutations.
- To explore a possible difference in the ORRs of binimetinib in patients with tumours harbouring NRAS Q61 vs G12/13 mutations.
- To investigate the potential correlation between additional markers in tumour tissue relevant to drug mechanism of action/resistance and/or melanoma, and clinical outcomes.
- To identify possible pharmacokinetic (PK)/PD or PK/efficacy and safety correlations, as appropriate.
- To assess the baseline molecular status of the tumour and explore other potential predictive biomarkers of response.

Patients were divided into three treatment groups. All patients in Group 1 (BRAF mutation) and Group 2 (NRAS mutation) received binimetinib 45 mg bid throughout the study. An additional 25 patients with BRAF mutations were treated with binimetinib 60 mg bid (Group 3) as described in Amendment 2 of the protocol.

The three groups are labelled as follows:

- Group 1: Binimetinib 45 mg BRAF
- Group 2: Binimetinib 45 mg NRAS
- Group 3: Binimetinib 60 mg BRAF

Binimetinib 60 mg bid was previously established as the maximum tolerated in a Phase I dose-escalation study in patients with advanced solid tumours (Clinical Study ARRAY-162- 111). However, based on the observed incidence of reversible retinal events during dose expansion at 60 mg bid, binimetinib dose was reduced to 45 mg bid and this dose level was chosen for initial use in this study.

Based on the good safety profile of binimetinib 45 mg bid in the first two groups, the protocol was amended to enrol a third group in order to establish the safety and efficacy profiles of binimetinib 60 mg bid in patients with BRAF-mutations (protocol Amendment 2).

Based on two serious adverse events (SAE) (one patient had an acute hepatic failure with fatal outcome (patient X2201-1003-00202) and another patient experienced reduced ejection fraction, heart failure, myocarditis and tachycardia (patient X2201-1301-00204) in patients treated with 60 mg bid,

the binimetinib dosage received by patients in group 3 was reduced to 45 mg bid (protocol Amendment 3) as an urgent safety measure.

Of the total 183 patients enrolled, all were included in the FAS and the safety set. A subset of 162 (88.5%) patients from the FAS who were sufficiently compliant with the requirements of clinical study protocol was included in the PPS. Safety analyses were based on the safety set.

Analysis of efficacy to support an indication in patients with NRAS-mutated melanoma was focused on the subset of 117 patients with unresectable or metastatic NRAS mutation-positive melanoma who received binimetinib 45 mg BID.

At the time of data cut-off i.e., 07 January 2014, the median duration of exposure to binimetinib was 15.9 weeks (range, 0.3 to 87.9 weeks). Based on Investigator assessment, the **confirmed ORR** was 14.5% (95% CI 8.7, 22.2). The **median PFS** was 3.6 months (95% CI 2.6, 3.8). The **median OS** was not reached at the time of data cut-off. Survival estimates at 4 and 18 months were 82.4% and 58.7% respectively. Median TTR was 1.9 months (95% CI 1.8 to 3.7) for patients with a Complete Response (CR) or Partial Response (PR). In 28 patients who received prior ipilimumab, the ORR was 14.3% and the median PFS was 3.7 months.

Table 6: Summary of best overall response as per Investigator assessment by treatment group (FAS)

	Binimetinib 45 mg BRAF	**Binimetinib 45 mg NRAS**	**Binimetinib 60 mg BRAF**
	N=41	**N=117**	**N=25**
	n (%)	**n (%)**	**n (%)**
Best overall response			
Complete Response (CR)	0	1 (0.9)	0
Partial Response (PR)	2 (4.9)	16 (13.7)	3 (12.0)
Stable Disease (SD)	19 (46.3)	49 (41.9)	7 (28.0)
Progressive Disease	14 (34.1)	39 (33.3)	13 (52.0)
Unknown	6* (14.6)	12** (10.3)	2*** (8.0)
Overall response rate (ORR) (CR or PR)	2 (4.9)	17 (14.5)	3 (12.0)
95% CI	(0.6; 16.5)	(8.7; 22.2)	(2.5; 31.2)
Disease control rate (DCR) (CR or PR or SD)	21 (51.2)	66 (56.4)	10 (40.0)
95% CI	(35.1; 67.1)	(46.9; 65.6)	(21.1; 61.3)

Table 7: Analysis of progression-free survival (PFS) as per Investigator assessment using Kaplan-Meier method by treatment group (FAS)

	Binimetinib 45 mg BRAF N=41	Binimetinib 45 mg NRAS N=117	Binimetinib 60 mg BRAF N=25
No. of PFS events	31 (75.6%)	88 (75.2%)	20 (80.0%)
Progression	28 (68.3%)	84 (71.8%)	16 (64.0%)
Death	3 (7.3%)	4 (3.4%)	4 (16.0%)
No. of censored	10 (24.4%)	29 (24.8%)	5 (20.0%)
Kaplan-Meier estimates (%) PFS rate (95% CI) at:			
4 months	33.0 (16.6, 49.3)	40.5 (31.1, 50.0)	28.1 (9.5, 46.6)
6 months	4.6 (0.0, 13.1)	27.6 (18.8, 36.4)	18.7 (2.4, 35.0)
8 months	0.0 (0.0,0.0)	16.9 (9.0, 24.9)	18.7 (2.4, 35.0)
12 months	0.0 (0.0,0.0)	6.9 (0.0, 14.2)	12.5 (0.0, 27.2)
Median PFS (95% CI) (months)	3.5 (1.9,3.8)	3.6 (2.6,3.8)	1.8 (1.5,3.7)
25th percentile for PFS (95% CI) (months)	1.8 (1.6,2.2)	1.9 (1.8,2.0)	1.4 (1.1,1.8)
75th percentile for PFS (95% CI) (months)	4.4 (3.7,5.5)	7.3 (5.5,7.7)	5.4 (1.9,NE)

Table 8: Analysis of Overall Survival (OS) as per Investigator assessment using Kaplan-Meier method (FAS)

	Binimetinib 45 mg BRAF N=41	Binimetinib 45 mg NRAS N=117	Binimetinib 60 mg BRAF N=25
No of deaths n (%)	5 (12.2%)	34 (29.1%)	9 (36.0%)
No of censored	36 (87.8%)	83 (70.9%)	16 (64.0%)
Kaplan-Meir estimates (%) OS rate (95% CI) at:			
4 months	85.7 (73.9, 97.6)	82.4 (75.0, 89.9)	78.1 (57.9, 98.2)
6 months	85.7 (73.9, 97.6)	73.9 (65.0, 82.9)	60.7 (34.4, 87.1)
8 months	NE	63.6 (53.0, 74.1)	60.7 (34.4, 87.1)
12 months	NE	58.7 (46.9, 70.4)	50.6 (22.1, 79.1)
18 months	NE	58.7(46.9, 70.4)	40.5 (11.6, 69.3)
Median OS (95% CI) (months)	NE	NE	16.6 (4.9,NE)
25th percentile for OS (95% CI) (months)	NE	5.9 (3.8, 7.9)	4.9 (2.9,16.6)
75th percentile for OS (95% CI) (months)	NE	NE	22.3 (11.0,NE)

NE: Not Estimable

Time to response: Of the 17 responding patients (either with a CR or PR) in the NRAS-mutant group, the median TTR was 1.9 months (95% CI: 1.8 to 3.7 months).

Duration of response: The estimated median DOR was 4.0 months (95% CI: 3.7 – NE) for the 17 patients with a response in the NRAS-mutant group.

3.4.5. Discussion on clinical efficacy

Design and conduct of clinical studies

The pivotal study supporting the proposed indication is a phase III study CMEK162A2301, with some supportive data from the phase II study MEK162X2201.

The phase III study was a two-arm, randomized, parallel group, open-label, multicentre study was designed to compare the efficacy and safety of binimetinib vs. dacarbazine in adult patients with advanced unresectable or metastatic *NRAS* mutation-positive cutaneous melanoma, or unknown primary melanoma, who were previously untreated or who had progressed on or after prior treatment with immunotherapy for unresectable or metastatic disease. The phase II, open-label study was designed to assess the safety and efficacy of oral MEK162 in adults with locally advanced and unresectable or metastatic malignant cutaneous melanoma, harbouring BRAFV600 or NRAS mutations.

The design of pivotal study was discussed in the CHMP Scientific advice. The Company at the time discussed that there was no published data to identify the median PFS in NRAS mutated melanoma. At the time PFS data in BRAF-mutation positive patients were quoted, from published literature, as 1.6 months to 2.7 months. Based on other quoted literature data, stating that NRAS mutation represented a poorer prognostic factor than other mutation, a PFS shorter than 1.6 months was predicted. Therefore a doubling of PFS was discussed by the Company as evidence of significant benefit. In addition the Company also quoted other trials where PFS benefit translated into an OS benefit. As agreed in the CHMP scientific advice the primary endpoint was PFS and OS was a key secondary endpoint. These are considered acceptable. In the scientific advice the CHMP did question whether only an improvement in PFS would outweigh the risks.

In addition the use of dacarbazine was discussed and agreed as an acceptable comparator in the CHMP scientific advice. The comparator is at present also considered acceptable, on the bases of its use in other recent trials as well as the availability of approved agents at the time of the initiation of the NEMO trial. The scientific advice discussion did highlight ipilimumab, which at the time was not approved and therefore not feasible to be used as a comparator. The CHMP advice agreed that use of ipilimumab was not feasible at the time, but did highlight that it might be more informative if the study were feasible, referring to the lack of available survival data in NRAS mutation positive melanoma.

The NEMO trial started as a trial investigating first-line treatment in patients with NRAS q61 mutation positive melanoma where no specific agent has been licensed for its treatment. Protocol amendments later allowed patients (stratified) failing any line of prior immunotherapy to be recruited.

The study randomized 402 patients in the FAS (269 binimetinib, 133 dacarbazine). All patients randomized to binimetinib received study drug. Nineteen patients randomized to the dacarbazine arm withdrew from the study prior to receiving dacarbazine. At the time of the data cut-off 42 patients were ongoing in the treatment period of the study (32 patients in the binimetinib arm and 10 patients in the dacarbazine arm). The use of dacarbazine as reference treatment is/once was accepted as there is/once was no product approved for the specific treatment of NRAS mutation positive melanoma.

This sub-group of patients is currently treated as BRAF wild type sub-group of melanomas.

Since the start of the pivotal trial there are other agents that have been approved for the treatment of melanoma in general and for the BRAF wild type sub-group.

All patients that entered into the studies are accounted for.

There are a frequent number of protocol deviations (more than 70% of patients had protocol violations).

Efficacy data and additional analyses

The result was a median PFS of **2.83** (2.76, 3.55) and **1.51** (1.48, 1.71) months in the binimetinib and dacarbazine arm respectively, the difference of the effect (Δ=1.32 month) with a HR of 0.62 (0.47, 0.80) being statistically significant (p< 0.001, one-sided). These results for the primary analysis of PFS

are supported by the ancillary, sensitivity and sub-group analyses. Further updated analyses from the cut-off date of the 16th of March 2016 show similar medians, HRs, and differences in PFS, favouring binimetinib.

The PFS improvement does not, however, translate into an overall survival benefit. The main OS analysis was conducted at the data cut-off date of 18 March 2016, when 228 OS events were observed with 161 deaths [59.9%] in the binimetinib arm and 67 deaths [50.4%] in the dacarbazine arm (not statistically significantly different; p=0.499, one-sided). Median (95% CI) OS was 10.97 months (8.9, 13.6) and 10.0 months (7.0, 16.5) in the binimetinib and dacarbazine arms, respectively [HR: 1.00 (95% CI 0.75, 1.33)]. It is also noted that the median overall survival in the dacarbazine arm is 10.09 months which is higher than that expected with dacarbazine treatment provided it would be such a poor prognostic patient population, as originally supposed by the applicant (especially taking into consideration the discussion once made about NRAS mutation representing an aggressive form of the disease, an aggressiveness now no longer claimed by the applicant). It also noted from the K-M curves of the main OS analyses (18th March 2016) that the lines crossover after about 12 months suggesting a late detrimental effect of the initial treatment ("as randomized").

The quality of life (QoL) results are difficult to interpret for methodological reasons. If interpreted, the QoL data would show that treatment with binimetinib may have a negative impact on QoL. Using such an interpretation for a decision would be unfair but the result is mentioned here for the similar trend of QoL and ECOG PS data, the latter discussed here in more detail:

In addition, from the data presented under safety, the proportion of patients with definitive 1-point deterioration in ECOG PS (an efficacy endpoint similar to QoL according to the protocol) was higher in the binimetinib arm compared to the dacarbazine arm (30.9% vs. 11.4%). Since median for a definitive 1-point deterioration in ECOG PS was not reached (but the median of OS in both arms), and death constitutes an ECOG PS of 5, additional analysis of deterioration free survival (DFS; same definition as a definitive 1-point deterioration in ECOG PS but this time death also counted as a definitive event) was requested by CHMP. Accordingly, patients in the **dacarbazine** arm have a by 0.9 months **prolonged DFS (**HR and its 95% CI of 1.26 (0.96, 1.67), the CI comprising barely 1 with a p value of 0.051). There are good reasons, deriving from the inadequate OS assessment, assuming that with more information and less censored OS events the result will be statistically significant.

Thus, a (statistically significantly) prolonged PFS is accompanied by (nearly statistically significantly) shortened DFS in the binimetinib arm compared with dacarbazine.

Therefore, even though the difference in PFS is statistically significant, the observed magnitude of improvement in PFS is considered clinically not relevant.

In line with the CHMP scientific advice dacarbazine was used as the comparator. However, other agents including such as PD-1 inhibitors are approved for use in the treatment of melanoma.

The results of the phase II study show evidence of activity for binimetinib in the NRAS and BRAF V600 mutation positive melanomas and is considered supportive of the phase III study results.

3.4.6. Conclusions on clinical efficacy

Overall the results presented show evidence of activity and a small prolongation in progression free survival in patients with the NRAS mutation positive melanoma. A benefit is not seen for overall survival or the QoL results. Rather, with a HR of 1.00 but more OS events in the binimetinib arm than the dacarbazine arm, there are concerns that in a more mature OS analyses the HR could become larger than 1.00.

Patients in the open label dacarbazine arm were less compliant to report on patient-reported outcomes and therefore the QoL data may be confounded and difficult to interpret. However, treatment with binimetinib has early and dramatic negative effects on ECOG PS. Comparing tumour performance (in terms of progression pattern) and clinical performance of patients, this is an effect contributable to the safety profile of the substance not counterbalanced by its anti-tumour activity.

The clinical benefit of a 1.3-month improvement in PFS alone, with binimetinib compared to dacarbazine, is therefore considered clinically not relevant. The lack of a clear benefit in OS and moreover a possible detrimental effect remains a concern. The lack of mature OS data makes the assessment of benefit difficult.

The availability of other agents including immunotherapy, check point inhibitors (and their combination) offers more effective treatment options in the proposed patient population. Therefore, an unmet medical need does not exist, nor is it clear that NRAS mutation positive tumours represent a poor prognostic entity which can specifically benefit from treatment with binimetinib monotherapy.

3.4.7. Clinical safety

Binimetinib has been evaluated in 566 patients with cancer, including 427 patients with metastatic melanoma treated at the recommended dose of 45 mg Twice Daily (BID). In the pool of patients with metastatic melanoma, 97 patients (23%) were exposed for at least ≥ 24 weeks and 15 (4%) were exposed for at least ≥ 48 weeks.

This summary of safety provides a review of the safety data from six clinical trials conducted to date with binimetinib. These studies are as follows:

Table 9: Clinical Trials Conducted with Binimetinib (Safety Data)

Study ID	Phase	Status	Study Report
ARRAY-162-111	Phase 1	Completed	Yes (final CSR)
CMEK162X1101	Phase 1	Ongoing	interim analysis report available
CMEK162AUS11	Phase 2	Ongoing	interim analysis report available
CMEK162X2201	Phase 2	Ongoing	interim analysis report available
ARRAY-162-311	Phase 3	Ongoing	Study closed; interim analysis report available
CMEK162A2301	Phase 3	Ongoing	interim analysis report available

Key: CSR: clinical study report

Binimetinib is an orally bioavailable, selective and potent MEK1/2 inhibitor. Considering the vital role of MEK in RAS-mediated carcinogenesis, other highly specific and potent MEK1/2 inhibitors have been evaluated over the last 15 years. Trametinib and cobimetinib are the only MEK inhibitors that have been approved as single agent and/or in combination with a BRAF inhibitor for the treatment of advanced metastatic melanoma (Mekinist® [trametinib] Summary of Product Characteristics (SmPC); Cotellic® [cobimetinib] SmPC).

The development of these agents and their introduction into common clinical use has revealed several AEs that are believed to be class effects of MEK inhibitors. These include ocular events, elevations of CK, left ventricular dysfunction, dermatological events including rash and acneiform dermatitis, hypertension, thromboembolic events, diarrhoea, oedema and haemorrhage. Most of these AEs are reversible with discontinuation of treatment (Zhao and Adjei 2014).

Ocular events associated with MEK inhibition include RVO and a characteristic exudative retinal detachment at the retinal pigment epithelium layer that has been variably classified as retinal detachment, central serous retinopathy, chorioretinopathy or detachment of the retinal pigment epithelium (i.e., Retinal Pigment Epithelial Detachment [RPED]) (McCannel et al 2014; Urner-Bloch et

al 2014). While RVO is less frequently reported than RPED lesions, it is potentially sight threatening. In contrast, RPED is more common and is most often asymptomatic or mildly symptomatic and generally completely reversible (Urner-Bloch et al 2014). As cited in the literature, MEK-associated serous retinopathy is often time-dependent and reversible despite continuation of the study medication. Monitoring for signs and symptoms of RPED events in patients treated with MEK inhibitors is recommended, but discontinuation of administration generally does not seem necessary because of the relatively low visual impact and transient nature of the associated serous retinopathy (van Dijk et al 2015; Niro et al 2015). Optical Coherence Tomography (OCT) is a non-invasive test that allows cross-sectional imaging of the retina and is a highly sensitive test for detecting RPED. With the recognition of this class-related effect, the more recent studies with binimetinib have included extensive monitoring, including OCT, to fully evaluate the retinal effects in order to better define the overall frequency. Thus, the rate of RPED, not associated with visual impairments, may have been underestimated in programs that did not include regular monitoring with OCT.

Elevation of CK is also a very common event of MEK inhibitors. It is generally not associated with symptoms or clinical consequences, although it can be associated with the development of muscle symptoms and rarely with frank rhabdomyolysis. Dropped head syndrome, a rare but distinctive myopathy that has been described with MEK inhibition, presents with weakness of the neck extensor muscles causing a dropped head appearance. It is fully reversible with discontinuation of the MEK inhibitor (Chen et al 2012).

Clinical programs for MEK inhibitors have all included monitoring of left ventricular function with Multigated Acquisition (MUGA) or Echocardiography (Patients with a history of clinically significant cardiovascular disease were excluded). Left ventricular dysfunction is generally fully reversible with discontinuation of MEK inhibition or with dose reduction when the dysfunction is not severe or symptomatic (Flaherty et al 2012).

Several potential AEs requiring close follow-up were identified as a result of signals observed from other drugs within the class of MEK inhibitors as described above. For each category, selected AEs similar in nature were identified and grouped as Adverse Events of Special Interest (AESIs). AESIs were identified based on the known class effects of MEK inhibitors as well as emerging safety signals from the clinical program and health authority interactions and analysed extensively to fully understand the nature, severity and clinical course of these events.

The list of AESIs was updated during the course of the program based on accumulating safety data. Protocol amendments were implemented across studies as required to refine eligibility criteria as data emerged as well as to increase or add evaluations for safety monitoring for AESIs. Across studies, patients with risk factors for or a history of RVO were excluded from trials and patients were monitored regularly for ocular toxicities with ophthalmological exams and OCT. Patients with known left ventricular dysfunction were excluded from trials, and LVEF was regularly monitored and serum CK was monitored routinely. In addition to routine monitoring of AEs, laboratory evaluations, Electrocardiograms (ECGs) and vital signs, specific monitoring protocols for ocular toxicity (including monitoring by OCT at each visit), were instituted across the clinical program. Studies also included frequent monitoring of liver function and specific protocols for monitoring hypertension. Clinical trials also provided guidance for management of known toxicities including hypertension, skin reactions, liver function abnormalities and diarrhoea.

The non-clinical evaluation of binimetinib showed soft tissue mineralization, a finding common to other MEK inhibitors that appears most prominent in rodents. Because of this finding, early clinical studies evaluated changes in calcium and phosphorous metabolism and found no changes in these parameters. Other non-clinical findings included gastrointestinal changes with soft stools, moderate clinical

pathology changes in some animals and reversible histopathological changes in the gastrointestinal tract.

Re-administration of MEK162 to rats is associated with (among other findings) minimal to mild increases in Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT). Liver function abnormalities, mainly AST and ALT elevations, can occur with binimetinib. Liver laboratory tests should be monitored before initiation of binimetinib and monthly during treatment, or more frequently as clinically indicated. Grade 3 and 4 liver laboratory abnormalities should be managed with dose interruption, reduction, or discontinuation of binimetinib.

Embryo-foetal development studies showed evidence of teratogenicity in rabbits (ventricular septal defects and pulmonary trunk alteration) and decreased ossification in rats that was considered to be secondary to decreased foetal body weight at maternally toxic doses. However, no teratogenic effects were noted in rats and rabbits up to about 13- and 3-fold, respectively, of the human exposure at the therapeutic dose, based on Area Under the Curve (AUC).

Overall, apart from routine exclusion of pregnant women and mandating contraception for women of childbearing potential, the non-clinical studies did not impact safety monitoring in the clinical program.

With multiple routes of metabolism, binimetinib is metabolized primarily by glucuronidation pathways (mainly via Uridine 5'-Diphospho-Glucuronosyltransferase [UGT] 1A1, 1A3 and 1A9) and to a lesser extent by oxidation pathways (mainly via Cytochrome P450 [CYP] 1A2 and 2C19). UGT1A1 was shown to be the major contributor (90%) to the formation of the direct glucuronide. Because of this, patients with a history of Gilbert's syndrome were excluded from Study CMEK162A2301. Other concomitant medication restrictions were included in clinical trials based on potential drug interactions.

Safety data from 4 clinical studies are pooled (studies CMEK162A2301, CMEK162X2201, CMEK162X1101, ARRAY-162-111), and 1 clinical study is presented separately (CMEK162AUS11). For 1 ongoing study (ARRAY-162-311), only SAE data are presented.

The safety data presented in this Application are presented in three groups:

- The **Restricted Safety Set** (also referred to as the "all melanoma [binimetinib 45 mg]" group) includes pooled data from 427 patients with metastatic melanoma treated with single-agent binimetinib 45 mg BID, the proposed marketed dose, in 2 clinical studies (CMEK162A2301 and CMEK162X2201).
- The **Broad Safety Set** (also referred to as the "all cancers [binimetinib any dose]" group) includes pooled data from 566 patients with advanced cancers in 4 clinical studies (CMEK162A2301, CMEK162X2201, CMEK162X1101, ARRAY-162-111).
- **Pivotal Phase 3, (CMEK162A2301)** including 269 patients treated with single-agent binimetinib 45 mg BID and 114 patients receiving dacarbazine).

As only data from the pivotal trial CMEK162A2301 allows a comparison to standard treatment findings from this trial is most informative. Moreover, as differences in mode of safety assessment in the broad safety population has to be taken into account. The pivotal trial data is deemed most valid.

Additionally, overall differences regarding AE between the safety populations are small and almost consistent with the findings in the pivotal trial. At the end, the main value of the broad safety population is regarding rare adverse events and particularly with respect to SAEs and deaths.

Clinical safety data for binimetinib was collected to include standard reporting of AEs, SAEs, vital signs, ECGs and other laboratory data. Additional monitoring for specific AEs of interest, including monitoring

of left ventricular function with MUGA or cardiac echocardiography and complete ophthalmological assessments, including regular OCT, were also conducted. Thus, the overall approach for assessing safety especially in the pivotal trial is acceptable and raises no specific concern.

Whether the pivotal study population is large enough to conclude adequately may be challenged. It is stated in the relevant guideline ICH Topic E 1 [Population Exposure: The Extent of Population Exposure to Assess Clinical Safety (CPMP/ICH/375/95)] that when the benefit from a drug is small or surrogate endpoints are involved "a larger safety population is needed to evaluate the benefit-risk balance".

Patient exposure

Currently, a total of 2555 healthy subjects and patients have received at least 1 dose of binimetinib including 220 healthy subjects, 164 patients with rheumatoid arthritis, 12 patients with hepatic dysfunction and 2159 patients with advanced cancer either as a single-agent (884 patients) or in combination with other agents (1275 patients).

A total of 566 patients in the Broad Safety Set, from 4 clinical studies are included in this evaluation of the safety of binimetinib. Among these 566 patients, 332 were < 65 years of age, 350 were male and 504 were Caucasian. Among all patients in the Broad Safety Set, the mean and median duration of exposure were 16.1 weeks and 12 weeks, respectively. There were 120 patients with exposure of 24 weeks or more and a total exposure of 2091 patient-months. The majority of patients (427) were treated at the intended starting dose of 45 mg BID. The remaining patients (139) were treated at starting dose ranging from 30 mg BID to 80 mg BID.

Table 10: Patient exposure

	All cancers	All melanoma	Study CMEK162A2301	
	Binimetinib any dose	Binimetinib 45 mg	Binimetinib 45 mg	DTIC
Exposure variable	N=566	N=427	N=269	N=114
Actual dose intensity (mg/day)/(mg/m^2/21 days)				
Mean (SD)	76.42 (18.807)	74.08 (16.452)	72.85 (16.666)	907.87 (159.887)
Median	81.80	78.86	75.41	981.29
Min-Max	15.0-124.6	28.9-90.0	28.9-90.0	1.0-1052.0
Relative dose intensity (%) – n (%)				
< 50	32 (5.7)	19 (4.4)	16 (5.9)	4 (3.5)
50 - < 80	201 (35.5)	164 (38.4)	107 (39.8)[a]	16 (14.0)
80 - < 100	176 (31.1)	107 (25.1)	76 (28.3)	59 (51.8)
≥ 100	157 (27.7)	137 (32.1)	70 (26.0)	33 (28.9)
Missing	0	0	0	2 (1.8)
Relative dose intensity (%)				
Mean (SD)	82.11 (18.622)	82.31 (18.280)	80.94 (18.518)	90.79 (15.989)
Median	87.50	87.63	83.78	98.13
Min-Max	13.9-100.0	32.1-100.0	32.1-100.0	0.1-105.2

Source: ISS Table 1.2-3
Key: DTIC: dacarbazine, min: minimum, max: maximum, N: total number of patients, n: number of patients, SD: standard deviation.
[a] In Study CMEK162A2301, of these 107 patients, 40 (37.4%) patients achieved a relative dose intensity of 70-79.9% (CMEK162A2301 CSR Listing 16.2.5-1.3).
Note: Actual dose intensity = Cumulative dose /Duration of exposure. Relative dose intensity = 100*[(Cumulative dose /Duration of exposure)/(Total planned dose/planned duration of exposure)].

Table 11: Duration of Exposure to Study Drug

	All cancers	All melanoma	Study CMEK162A2301	
	Binimetinib any dose	Binimetinib 45 mg	Binimetinib 45 mg	DTIC
Exposure variable	N=566	N=427	N=269	N=114

Duration of exposure (weeks)				
Mean (SD)	16.1 (14.74)	16.7 (13.14)	16.4 (13.22)	13.8 (12.17)
Median	12.0	12.7	12.6	9.0
Min-Max	0-102	0-88	0-73	3-57
Duration of exposure category (weeks) – n (%)				
< 3	42 (7.4)	22 (5.2)	18 (6.7)	0
≥ 3 - < 6	68 (12.0)	43 (10.1)	28 (10.4)	23 (20.2)
≥ 6 - < 9	112 (19.8)	71 (16.6)	35 (13.0)	27 (23.7)
≥ 9 - < 12	57 (10.1)	50 (11.7)	30 (11.2)	18 (15.8)
≥ 12 - < 18	117 (20.7)	101 (23.7)	70 (26.0)	14 (12.3)
≥ 18 - < 24	50 (8.8)	43 (10.1)	31 (11.5)	13 (11.4)
≥ 24 - < 30	45 (8.0)	37 (8.7)	23 (8.6)	6 (5.3)
≥ 30 - < 36	25 (4.4)	23 (5.4)	13 (4.8)	5 (4.4)
≥ 36 - < 42	20 (3.5)	18 (4.2)	7 (2.6)	1 (0.9)
≥ 42 - < 48	6 (1.1)	4 (0.9)	2 (0.7)	4 (3.5)
≥ 48	24 (4.2)	15 (3.5)	12 (4.5)	3 (2.6)
Patient-months	2091.0	1639.0	1014.8	362.8

Source: ISS Table 1.2-1

Key: DTIC: dacarbazine, min: minimum, max: maximum, N: total number of patients, n: number of patients, SD: standard deviation.

In applied target population of melanoma patients treated at the recommended dose of 45 mg (N = 427), 200 patients (46.8%) were aged 65 years and above, 272 (63.7%) were male and 399 (93.4%) were Caucasian. Because of the known demographics and epidemiology of melanoma, other races were, as expected, underrepresented in the data set. Sources of safety data for this analysis of safety included 1 randomized (2:1) trial, CMEK162A2301, with an active control that included 269 patients treated with binimetinib and 114 patients treated with dacarbazine. Specific exclusion criteria in clinical trials, may limit the evaluation of safety in some groups of patients in this analysis.

In Study CMEK162A2301, the median duration of exposure to binimetinib (12.6 weeks) was longer than the median duration of exposure to dacarbazine (9.0 weeks). Whether this finding is reasoned by the fact that progressive disease more often leads to study discontinuation in the DTIC arm needs to be further substantiated.

Study drug exposure was similar across all binimetinib-treated populations, with a median duration of exposure of 12.7 weeks in the all melanoma (binimetinib 45 mg) population and 12.0 weeks in the all cancers (binimetinib any dose) population. In the all melanoma (binimetinib 45 mg) population, 97 (22.7%) were exposed for ≥ 24 weeks and 15 (3.5%) were exposed for ≥ 48 weeks.

The median relative dose intensity in Study CMEK162A2301 was 83.8% in the binimetinib arm and 98.1% in the dacarbazine arm. This difference can be attributed to dose reductions/interruptions due to AEs but also missed doses of self-administered oral dosing of binimetinib BID compared to IV-administered dacarbazine once every 3 weeks. No patients on the binimetinib arm received more than the recommended total daily dose of 90 mg and there were no AEs of overdose reported.

Considering the exposure in 566 patients, AEs with a true frequency of 1% or greater, have a probability of 0.3% of not being represented in the safety data.

In Study CMEK162A2301, the median duration of exposure to binimetinib was short (12.6 weeks); however, longer than in the median duration of exposure to dacarbazine (9.0 weeks). Study drug exposure was similar across all binimetinib-treated populations, with a median duration of exposure of 12.7 weeks in the all melanoma (binimetinib 45 mg) population and 12.0 weeks in the all cancers (binimetinib any dose) population. In the all melanoma (binimetinib 45 mg) population, 97 (22.7%) were exposed for ≥ 24 weeks and 15 (3.5%) were exposed for ≥ 48 weeks. Insofar, the long-term safety data is restricted and it needs to be clarified why the median duration of exposure in the pivotal trial was only 12.6 weeks.

However additionally presented data shows an even higher incidence of nearly all AESI groupings in the subgroup with > 24 weeks' exposure particular for grade ≥3 adverse events. The comparison of potential pre-existing risks overall and between patients who tolerated longer and shorter durations of exposure did not identify any markers that could explain the occurrence of AESIs in these populations.

Adverse events

An overview of safety is provided for the different safety populations (Broad, Restricted and Pivotal Trial safety set) in Table 12, including separate columns for data from the "all cancers (binimetinib any dose)", "all melanoma (binimetinib 45 mg)" and "Study CMEK162A2301" populations.

Table 12: Death and Overall Summary of Adverse Events by Treatment

Broad Safety Set								
			Restricted Safety set					
					Study CMEK162A2301			
	All cancers Binimetinib any dose N=566		All melanoma Binimetinib 45 mg N=427		Binimetinib 45 mg N=269		DTIC N=114	
Category	**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 deaths [a]	240 (42.2)	-	159 (37.2)	-	120 (44.6)	-	50 (43.9)	-
On-treatment deaths [b]	65 (11.5)	-	46 (10.8)	-	23 (8.6)	-	3 (2.6)	-
AEs	566 (100.0)	370 (65.4)	427 (100.0)	283 (66.3)	269 (100.0)	183 (68.0)	104 (91.2)	52 (45.6)
SAEs	184 (32.5)	151 (26.7)	137 (32.1)	111 (26.0)	91 (33.8)	74 (27.5)	25 (21.9)	18 (15.8)
AEs leading to discontinuation	126 (22.3)	84 (14.8)	94 (22.0)	66 (15.5)	66 (24.5)	45 (16.7)	9 (7.9)	6 (5.3)
AEs requiring dose interruption and or change	379 (67.0)	224 (39.6)	283 (66.3)	176 (41.2)	187 (69.5)	116 (43.1)	41 (36.0)	23 (20.2
AEs requiring additional therapy[c]	218 (92.8)	218 (38.5)	393 (92.0)	160 (37.5)	255 (94.8)	112 (41.6)	73 (64.0)	29 (25.4)

Source: ISS Table 2.2-1
Key: AE: adverse event, DTIC: dacarbazine, N: total number of patients, n: number of patients, SAE: serious adverse event.
a All deaths including those > 30 days after end of treatment.
b Deaths occurring > 30 days after end of treatment are not included.

c Additional therapy includes all non-drug therapy and concomitant medications.
Note: Categories are not mutually exclusive. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

In Study CMEK162A2301, a higher percentage of patients in the binimetinib than dacarbazine arm experienced at least 1 AE (100.0% binimetinib vs. 91.2% dacarbazine), SAE (33.8% vs 21.9%), AE leading to treatment discontinuation (24.5% vs. 7.9%), AE requiring dose reduction or study drug interruption (69.5% vs. 36.0%), and AE requiring additional therapy (94.8% vs. 64.0%).

The incidences reported for these safety categories were similar for the all melanoma (binimetinib 45 mg) and the all cancers (binimetinib any dose) populations. In the all melanoma (binimetinib 45 mg) and all cancers (binimetinib any dose) populations, all patients experienced at least 1 AE, with approximate incidence rates of 32% of patients with SAEs, 22% of patients with AEs leading to discontinuation, 67% of patients with AEs requiring dose reduction or study drug interruption, and 92% of patients with AEs requiring additional therapy.

A similar percentage of patients died during Study CMEK162A2301 (44.6% binimetinib vs. 43.9% dacarbazine) and in the all melanoma (binimetinib 45 mg) and all cancers (binimetinib any dose) populations (37.2% and 42.4% of patients, respectively), most of whom died during the posttreatment follow-up period. The incidence of deaths occurring during treatment or within 30 days of the last dose (within 28 days for CMEK162X1101) was similar among the 3 binimetinib-treated populations (range 8.6% to 11.5%) and all were higher than the incidence of on-treatment deaths in the dacarbazine arm of Study CMEK162A2301 (2.6%). Most on-treatment deaths were attributed to disease progression.

Adverse Events by System Organ Class (SOC)

Table 13 presents a summary of adverse events (AEs), regardless of relationship to study drug by SOC (overall and maximum grade 3/4) for the Broad Safety Set, including separate columns for data from the “all cancers (binimetinib any dose)”, “all melanoma (binimetinib 45 mg)” and “Study CMEK162A2301”populations.

In the binimetinib arm of Study CMEK162A2301, AEs were reported most frequently (> 50.0% of patients) under the SOCs of skin and subcutaneous tissue disorders (88.1%), general disorders and administration site conditions (73.6%), gastrointestinal disorders (70.6%), investigations (61.7%) and eye disorders (57.2%). These same SOCs, as well as the SOCs of infections and infestations, musculoskeletal and connective tissue disorders, nervous system disorders and vascular disorders, were reported at an incidence of ≥10.0% more in the binimetinib arm as compared to the dacarbazine arm. AEs were reported most frequently (> 10.0% of patients) as grade 3/4 in severity in the binimetinib arm under the SOCs of investigations (29.7%) and vascular disorders (10.4%).

In the dacarbazine arm of Study CMEK162A2301, AEs were reported most frequently (> 50.0% of patients) under the SOCs of general disorders and administration site conditions (57.9%) and gastrointestinal disorders (50.9%). The SOCs reported at an incidence of ≥ 10.0% more patients in the dacarbazine arm as compared to the binimetinib arm included the blood and lymphatic system disorders SOC. AEs were reported most frequently (> 10.0% of patients) as grade 3/4 in severity in the dacarbazine arm under the SOCs of blood and lymphatic system disorders (17.5%) and investigations (12.3%).

There is generally little difference observed across the 3 binimetinib-treated populations for the rate of AEs by SOC. The incidences of grade 3/4 AEs within each SOC were also comparable across all binimetinib-treated patients.

Table 13: Adverse Events, Regardless of Study Drug Relationship, by Primary System Organ Class by Treatment – Overall and Maximum Grade 3 or 4 (Broad Safety Set)

	All cancers		All melanoma		Study CMEK162A2301			
	Binimetinib any dose N=566		Binimetinib 45 mg N=427		Binimetinib 45 mg N=269		DTIC N=114	
Primary system organ class	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	**566 (100.0)**	**370 (65.4)**	**427 (100.0)**	**283 (66.3)**	**269 (100.0)**	**183 (68.0)**	**104 (91.2)**	**52 (45.6)**
Skin and subcutaneous tissue disorders	490 (86.6)	42 (7.4)	376 (88.1)	37 (8.7)	237 (88.1)	27 (10.0)	21 (18.4)	0
General disorders and administration site conditions	430 (76.0)	58 (10.2)	316 (74.0)	45 (10.5)	198 (73.6)	26 (9.7)	66 (57.9)	8 (7.0)
Gastrointestinal disorders	429 (75.8)	58 (10.2)	303 (71.0)	38 (8.9)	190 (70.6)	24 (8.9)	58 (50.9)	4 (3.5)
Investigations	338 (59.7)	174 (30.7)	263 (61.6)	129 (30.2)	166 (61.7)	80 (29.7)	36 (31.6)	14 (12.3)
Eye disorders	308 (54.4)	17 (3.0)	232 (54.3)	15 (3.5)	154 (57.2)	10 (3.7)	9 (7.9)	0
Infections and infestations	223 (39.4)	37 (6.5)	169 (39.6)	29 (6.8)	111 (41.3)	23 (8.6)	21 (18.4)	3 (2.6)
Musculoskeletal and connective tissue disorders	209 (36.9)	23 (4.1)	157 (36.8)	19 (4.4)	94 (34.9)	13 (4.8)	22 (19.3)	4 (3.5)
Nervous system disorders	181 (32.0)	26 (4.6)	127 (29.7)	16 (3.7)	85 (31.6)	10 (3.7)	24 (21.1)	5 (4.4)
Respiratory, thoracic and mediastinal disorders	166 (29.3)	29 (5.1)	116 (27.2)	20 (4.7)	73 (27.1)	12 (4.5)	22 (19.3)	3 (2.6)
Vascular disorders	126 (22.3)	52 (9.2)	95 (22.2)	42 (9.8)	58 (21.6)	28 (10.4)	13 (11.4)	2 (1.8)
Metabolism and nutrition disorders	150 (26.5)	39 (6.9)	87 (20.4)	20 (4.7)	55 (20.4)	10 (3.7)	23 (20.2)	6 (5.3)
Psychiatric disorders	63 (11.1)	3 (0.5)	44 (10.3)	3 (0.7)	32 (11.9)	3 (1.1)	14 (12.3)	0
Blood and lymphatic system disorders	103 (18.2)	41 (7.2)	60 (14.1)	20 (4.7)	31 (11.5)	12 (4.5)	36 (31.6)	20 (17.5)
Cardiac disorders	58 (10.2)	11 (1.9)	49 (11.5)	10 (2.3)	30 (11.2)	7 (2.6)	8 (7.0)	1 (0.9)
Injury, poisoning and procedural complications	45 (8.0)	6 (1.1)	28 (6.6)	4 (0.9)	19 (7.1)	3 (1.1)	2 (1.8)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	28 (4.9)	8 (1.4)	21 (4.9)	5 (1.2)	16 (5.9)	5 (1.9)	12 (10.5)	2 (1.8)
Renal and urinary disorders	48 (8.5)	8 (1.4)	30 (7.0)	3 (0.7)	16 (5.9)	2 (0.7)	6 (5.3)	0
Ear and labyrinth disorders	17 (3.0)	0	13 (3.0)	0	9 (3.3)	0	2 (1.8)	0
Hepatobiliary disorders	20 (3.5)	13 (2.3)	10 (2.3)	6 (1.4)	8 (3.0)	4 (1.5)	4 (3.5)	2 (1.8)
Reproductive system and breast disorders	14 (2.5)	1 (0.2)	11 (2.6)	1 (0.2)	6 (2.2)	0	1 (0.9)	0
Congenital, familial and genetic disorders	9 (1.6)	0	6 (1.4)	0	1 (0.4)	0	0	0
Endocrine disorders	4 (0.7)	0	2 (0.5)	0	1 (0.4)	0	0	0
Immune system disorders	5 (0.9)	0	3 (0.7)	0	1 (0.4)	0	0	0
Pregnancy, puerperium and perinatal conditions	1 (0.2)	0	1 (0.2)	0	0	0	0	0
Surgical and medical procedures	3 (0.5)	1 (0.2)	1 (0.2)	0	0	0	0	0

Source: ISS Table 2.2-2

Key: DTIC: dacarbazine, N: total number of patients, n: number of patients.

Note: A patient with multiple Adverse Events (AEs) within a primary system organ class is counted only once in the total row.

A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment at the maximum severity grade.

Primary system organ classes are sorted in descending frequency of the all grades CMEK162A2301 binimetinib column.

MedDRA Version 18.1 has been used for the reporting of AEs.

Adverse Events by Preferred Term

Table 14 presents a summary of AEs, regardless of relationship to study drug, that were reported for >10.0% of patients in the binimetinib arm of Study CMEK162A2301 by preferred term (overall and maximum grade 3/4) for the Broad Safety Set, including separate columns for data from the "all cancers (binimetinib any dose)", "all melanoma (binimetinib 45 mg)" and "Study CMEK162A2301"populations.

In the binimetinib arm of Study CMEK162A2301, AEs were reported most frequently (>20.0% of patients) under the preferred terms of blood CK increased (42.0%), diarrhoea (40.1%), rash (36.4%), oedema peripheral (36.1%), dermatitis acneiform (35.3%), nausea (29.4%), fatigue (22.3%) and vomiting (21.2%). PTs that were reported at an incidence of ≥ 10% in binimetinib arm and with an incidence of ≥ 5% more patients in the binimetinib arm as compared to the dacarbazine arm were blood CK increased, rash, dermatitis acneiform, oedema peripheral, diarrhoea, retinal detachment, skin fissures, hypertension, pruritus, vomiting, AST increase, ejection fraction decrease and dyspnoea.

The only AEs reported most frequently (>10.0% of patients) as grade 3/4 in severity in the binimetinib arm were under PT of blood CK increased (19.3%).

In the dacarbazine arm of Study CMEK162A2301, AEs were reported most frequently (>20.0% of patients) under the PTs of nausea (32.5%) and fatigue (31.6%). Other AEs reported in the dacarbazine arm reported in more than 10% of patients were constipation (18.4%), neutropenia (18.4%), asthenia (16.7%), decreased appetite (15.8%), pyrexia (14.9%), thrombocytopenia (14.9%), vomiting (12.3%) and diarrhoea (11.4%). No preferred terms were reported as grade 3/4 in severity in the dacarbazine arm for >10.0% of patients.

There is generally little difference observed across the 3 binimetinib-treated populations for the rate of AEs by preferred term. The incidences of grade 3/4 AEs by preferred term were also comparable across all binimetinib treated patients.

Table 14: Adverse Events, Regardless of Study Drug Relationship, by Preferred Term and Treatment - Overall and Maximum Grade 3 or 4 (> 10.0% in CMEK162A2301 Binimetinib) (Broad Safety Set)

	All cancers		All melanoma		Study CMEK162A2301			
	Binimetinib any dose N=566		Binimetinib 45 mg N=427		Binimetinib 45 mg N=269		DTIC N=114	
Preferred term	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	**566 (100.0)**	**370 (65.4)**	**427 (100.0)**	**283 (66.3)**	**269 (100.0)**	**183 (68.0)**	**104 (91.2)**	**52 (45.6)**
Blood creatine phosphokinase increased	228 (40.3)	107 (18.9)	185 (43.3)	90 (21.1)	113 (42.0)	52 (19.3)	3 (2.6)	0
Diarrhea	253 (44.7)	8 (1.4)	182 (42.6)	8 (1.9)	108 (40.1)	4 (1.5)	13 (11.4)	1 (0.9)
Rash	207 (36.6)	14 (2.5)	140 (32.8)	12 (2.8)	98 (36.4)	11 (4.1)	1 (0.9)	0
Edema peripheral	233 (41.2)	5 (0.9)	171 (40.0)	3 (0.7)	97 (36.1)	1 (0.4)	3 (2.6)	0
Dermatitis acneiform	205 (36.2)	13 (2.3)	173 (40.5)	11 (2.6)	95 (35.3)	7 (2.6)	1 (0.9)	0
Nausea	194 (34.3)	9 (1.6)	126 (29.5)	5 (1.2)	79 (29.4)	4 (1.5)	37 (32.5)	1 (0.9)
Fatigue	170 (30.0)	19 (3.4)	111 (26.0)	14 (3.3)	60 (22.3)	6 (2.2)	36 (31.6)	3 (2.6)
Vomiting	143 (25.3)	11 (1.9)	83 (19.4)	8 (1.9)	57 (21.2)	6 (2.2)	14 (12.3)	0
Asthenia	68 (12.0)	8 (1.4)	60 (14.1)	8 (1.9)	48 (17.8)	8 (3.0)	19 (16.7)	5 (4.4)
Retinal detachment	56 (9.9)	0	44 (10.3)	0	39 (14.5)	0	0	0
Constipation	90 (15.9)	4 (0.7)	63 (14.8)	2 (0.5)	37 (13.8)	2 (0.7)	21 (18.4)	0
Hypertension	76 (13.4)	37 (6.5)	63 (14.8)	32 (7.5)	37 (13.8)	20 (7.4)	4 (3.5)	2 (1.8)
Aspartate aminotransferase increased	84 (14.8)	17 (3.0)	58 (13.6)	9 (2.1)	35 (13.0)	6 (2.2)	4 (3.5)	0
Pruritus	78 (13.8)	4 (0.7)	58 (13.6)	4 (0.9)	32 (11.9)	2 (0.7)	2 (1.8)	0
Decreased appetite	88 (15.5)	3 (0.5)	54 (12.6)	2 (0.5)	31 (11.5)	2 (0.7)	18 (15.8)	1 (0.9)
Ejection fraction decreased	45 (8.0)	16 (2.8)	40 (9.4)	15 (3.5)	30 (11.2)	10 (3.7)	2 (1.8)	1 (0.9)
Dyspnea	63 (11.1)	11 (1.9)	43 (10.1)	6 (1.4)	29 (10.8)	3 (1.1)	6 (5.3)	2 (1.8)
Pyrexia	78 (13.8)	1 (0.2)	50 (11.7)	0	28 (10.4)	0	17 (14.9)	0
Skin fissures	33 (5.8)	0	31 (7.3)	0	28 (10.4)	0	0	0

Source: ISS Table 2.2-3
Key: DTIC: dacarbazine, N: total number of patients, n: number of patients.
Note: A patient with multiple occurrences of an Adverse Event (AE) under one treatment is counted only once in the AE category for that treatment at the maximum severity grade.
Preferred terms are sorted in descending frequency of the all grades CMEK162A2301 binimetinib column.
Medical Dictionary for Regulatory Activities (MedDRA) Version 18.1 has been used for the reporting of AE.

Potential Relationship of Adverse Events to Study Treatment

ADRs were identified using a number of different methods. Common ADRs were identified mainly through analysis of AE data from study CMEK162A2301. As this study was a randomized trial against a comparator, it provides the only comparative data set for assessment of whether AEs are related to treatment with binimetinib. Although dacarbazine, the comparator in the study, has its own set of AEs, there was little expected overlap between the AE profiles of binimetinib and dacarbazine and events seen significantly more frequently with binimetinib treatment were reasonably likely to be related to treatment with binimetinib. In comparing the relative rates of various events in the binimetinib and dacarbazine arms of study CMEK162A2301, the longer duration of exposure in the binimetinib arm as well as the overall number of patients in each treatment group was considered.

All AEs occurring more frequently in patients receiving binimetinib than in patients receiving dacarbazine were reviewed.

In addition, safety data for the Broad Safety Set, (i.e., all cancers [binimetinib any dose] population), as well as other sources of safety data including ongoing trials and publications were reviewed, particularly to identify uncommon, typical drug reactions (e.g., Stevens-Johnson Syndrome [SJS]). Among these events, groupings of PTs were created to define similar clinicopathological entities. To determine whether a particular PT was to be included, a number of factors were considered including the specificity of the term, the verbatim terms used by Investigators that mapped to the PT, its overall frequency and its relative frequency to the comparator arm. Also considered were potential relationships between AEs either as manifestations of the same event or as secondary events (e.g., dyspnoea and left ventricular dysfunction or rash and skin infections). For retinal events, the objective findings on Optical Coherence Tomography (OCT) were correlated with preferred terms to determine whether a given term described unique or distinct findings. Some preferred terms were not grouped as they represented a single clinical entity without other similar terms in the data set.

ADRs were finally defined based on non-clinical binimetinib data, on a clinical review of the data considering known class effects, observed differences between binimetinib and dacarbazine in severity as well as AEs associated with SAEs, deaths and discontinuations from therapy.

The Investigator assessment of causality was not a primary consideration for determining ADRs.

Based on the investigator assessment only, in the binimetinib arm of Study CMEK162A2301, AEs were considered to be related to study treatment most frequently (> 10.0% of patients) under the PTs of blood CK increased (38.3%), rash (35.7%), dermatitis acneiform (34.9%), diarrhoea (31.6%), oedema peripheral (28.3%) , nausea (20.8%; 28.1% in dacarbazine arm), fatigue (14.1%; 21.9% in dacarbazine arm), vomiting (14.1%), retinal detachment (13.8%), asthenia (13.4%; 14.0% in dacarbazine arm), AST increased (11.2%), ejection fraction decreased (11.2%) and pruritus (10.4%).

Treatment-related AEs that were reported at an incidence of ≥10% in binimetinib arm and with ≥5% more patients in the binimetinib arm as compared to the dacarbazine arm, by preferred term were, blood CK increased, rash, dermatitis acneiform, diarrhoea, oedema peripheral, retinal detachment, AST increased, ejection fraction decreased and pruritus. Treatment-related AEs reported most frequently (> 10.0% of patients) as grade 3/4 in severity in the binimetinib arm were of blood CK increase (17.8%).

In the dacarbazine arm of Study CMEK162A2301, treatment-related AEs were reported most frequently (>10.0% of patients) under the preferred terms of nausea (28.1%), fatigue (21.9%), neutropenia (16.7%), asthenia (14.0%), thrombocytopenia (13.2%), vomiting (10.5%). No treatment-related AEs were reported as grade 3/4 in severity in the dacarbazine arm for > 10.0% of patients.

There is generally little difference observed across the 3 binimetinib-treated populations for the rate of Investigator-assessed treatment-related AEs by PT. The incidences of Investigator-assessed grade 3/4 treatment-related AEs by PT were also comparable across all binimetinib-treated patients.

Common Adverse Drug Reactions

The frequencies of ADRs in the proposed EU SmPC (see table 15) were calculated based on the restricted safety set. The following convention has been utilized for the classification of frequency:

• Very common ≥ 1/10

• Common ≥ 1/100 to < 1/10

• Uncommon ≥ 1/1,000 to < 1/100

Table 15: Adverse Reactions Occurring in Metastatic Melanoma Patients Receiving Binimetinib at the Recommended Dose (Restricted Safety Set; n=427)*

System Organ Class	Adverse reaction	Frequency (All grades)	Grade3/4 (%)
Infections and infestations	Skin infection [a]	Very common	4
Nervous system disorders	Dropped head syndrome [b]	Uncommon	0
Eye disorder	RPED [c]	Very common	1
	Visual impairment		Below 1
	Increased intraocular pressure including glaucoma	Common	0
	Retinal vein occlusion		1
Cardiac disorders	Left ventricular dysfunction [d]	Very common	4
	Bradycardia	Common	0
Vascular disorders	Hypertension	Very common	8
	Venous thromboembolism [e]	Common	2
	Haemorrhage [f]		2
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Very common	2
	Pneumonitis	Common	Below 1
Gastrointestinal disorders	Diarrhoea	Very common	2
	Vomiting		2
	Nausea		1
	Dry mouth	Common	0
	Stomatitis [g]		2
Skin and subcutaneous tissue disorders	Rash [h]	Very common	4
	Acneiform dermatitis		3
	Pruritus		1
	Dry skin		0
	Alopecia	Common	0
	Skin fissures		0
Musculoskeletal and connective tissue disorders	Myopathy [i]	Very common	2
	Rhabdomyolysis	Uncommon	Below 1
Renal and urinary disorders	Renal failure	Common	Below 1
General disorders and administration site conditions	Peripheral oedema [j]	Very common	Below 1
	Periorbital oedema, eye oedema, eyelid oedema		Below 1
	Face oedema	Common	Below 1
Investigations	Blood creatine phosphokinase increased	Very common	21
	Aspartate aminotransferase increased		2
	Alanine aminotransferase increased	Common	2
	Hypokalaemia		2
	Hypoalbuminaemia		Below 1
	Blood creatinine increased		0

Adverse events of special interest

Adverse events of special interest (AESI) were identified based on the known class effects of MEK inhibitors as well as emerging safety signals from the clinical program and health authority interactions and were analysed extensively to fully understand the nature, severity and clinical course of these events.

Gastrointestinal events occurred in 64.3% of patients in the binimetinib arm and 50.9% of patients in the dacarbazine arm of the pivotal study. The very common ADRs in this category include: diarrhea,

nausea, and vomiting; stomatitis and dry mouth were reported as common in the all melanoma group. The relative high frequency and the difference not in favor for binimetinib with respect to gastrointestinal events indicate a relevant burden due to these AEs for the patient. However, it is noted that grade 3 events occurred not very frequent.

The very common ADRs in the category **ophthalmic events** include retinal pigment epithelium detachment (RPED) and visual impairment. RPED occurred in 33.1%, visual impairment in 14.5% of patients in the binimetinib arm of the pivotal trial. In the dacarbazine arm no ophthalmic events were seen. It is noted that grade 3 events occurred not very frequent and most of the events were transient, self-limiting and reversible. However, the fact that 33.2 % of the binimetinib patients had retinal pigment epithelium detachment (RPED) (and 13.8 % grade 2 as well as 1.1% grade 3 events) all associated with visual impairment is disturbing. It indicates a clinical relevant high risk for blinding, although current data failed to demonstrate persistent blinding. In addition vascular events (RVO as a potentially sight-threatening event) were observed in 2.2% of the patients in the binimetinib arm.

Dermatologic events were captured under the two separate groupings of rash and skin except rash (i.e., non-rash) events. Rash events (e.g. rash, acneiform dermatitis) occurred in 81.4% of patients in the binemtinib arm and in 3.5% in the dacarbazine arm. Non-rash events (pruritus, skin fissures, dry skin, alopecia, and erythema) occurred in 42.4% of patients in the binimetinib arm and 8.8% of patients in the dacarbazine arm. It is noted that grade 3 events occurred not very frequent but 2/3 of all events needed additional therapy and thus indicates a relevant burden to the patient. In addition, approx. 25% of the patients showed - often secondary to other dermatologic events- a skin infection; 3.3% of these events were resulting in hospitalization. Regarding this issue the applicant was requested to provide an analysis regarding the impact of dermatological infections and particular concomitant treatment of dermatological adverse event with corticosteroids on the occurrence of systemic infections/sepsis in patients who died on-treatment. In the responses provided, the applicant concludes that there is no evidence of a link between the concomitant treatment of dermatological events with corticosteroids and the occurrence of sepsis, both non-fatal and fatal. To the Rapporteur the presented data seems to be contradictory. The applicant's conclusion is not agreed with either. Furthermore, it should be considered to reflect this point more adequately in the product information. Photosensitivity reactions occurred in 1.5 % of the patients and were identified also as a relevant toxicity of binimetinib in the non-clinical trials. The potential concern of phototoxicity/photosensitization was not supported by clinical data. In pivotal Study CMEK162A2301, mild to moderate photosensitivity reaction was reported in the binimetinib arm (1.5% of patients, no Grade 3/4 events) and at a higher frequency in the dacarbazine arm (3.5% of patients). AEs of photosensitivity reaction were reported in 5 (0.9%) patients in the all cancers (binimetinib any dose) population, and 4 (0.9%) patients in the all melanoma (binimetinib 45 mg) population; with no Grade 3/4 events reported. Dose modifications for dermatological events in Section 4.2 of the SmPC and management of skin toxicities in Section 4.4 of the SmPC are sufficient to manage phototoxicity reactions.

In the pivotal trial CMEK162A2301, **cardiac events** are reported in 13.0% of patients in the binimetinib arm and 1.8% of patients in the dacarbazine arm nearly all relevant events were due to deterioration of LVEF. These events are a significant safety concern. In particular, as these events occure early during the treatment as indicated by a median time to a decrease in LVEF to < 50% was 1.4 months and recovery is not assessable form the analysis provided. As decrease in LVEF has a significant impact on mortality, but may be clinically only apparent in a general physical health deterioration (which was clearly more frequently reported from the binimetinib arm), cardiac events

may have contributed more to the mortality than currently presumed. Further data regarding the reversibility of the cardiac adverse events were requested. In the responses provided the applicant concludes that after dose adjustment of binimetinib, cardiac events also generally resolved, with resolution generally occurring within 30 days (range: 11 to 57 days), and the overall interpretation of LVEF values were generally 'normal' or 'clinically insignificant abnormality' within this time. These assumptions are not shared by the Rapporteurs as the applicant in some cases did not present any further data (LVEF) after the dose reduction. Further, with regards to warnings/ recommendations in the product information, it is strongly recommended to add a contraindication for binimetinib in patients with a reduced LVEF under 50% or the institutional LLN.

In the pivotal trial CMEK162A2301 binimetinib treated patients had a significant higher degree of **hypertension** than those treated with DTIC (B: 15.2% versus DTIC: 3.5%) and especially more severe events as indicated by the difference not in favor for binimetinib regarding the grade ≥ 3 events (B: 8.6% versus DTIC: 1.8%). The significantly higher frequency for increases of creatinine indicating a decrease in renal function may explain at least partially this finding. It seems very likely that the increase in cardiac events was also affected by hypertension results. To adequately manage the risk of severe hypertension, the Applicant proposes to amend the warning regarding hypertension in Section 4.4 of the SmPC (see above). The amendments proposed for section 4.4. of the SmPC seem to be acceptable. However, recommendations for dose modification (SmPC section 4.2.) should be more precise.

Binimetinib is associated very frequently with a **myopathy**, as indicated by **CK increases**. Nearly every other patient developed this complication and grade 3 and higher events were observed in about every fifth patient. Whether this adverse event can be really tolerated may be challenged. Taking into account the high rate of discontinuation and dose–interruptions necessary to manage this adverse event and the complications due to persistent myoglobinemia for the renal function, this is challenged. The applicant's statement that although CK elevations occurred frequently (B: 42.0% versus DTIC: 2.6%) and were consistently reported from all studies of binimetinib, notable clinical consequences were rare, is not very helpful and in consequence not shared. Renal complications and clinical symptoms of myopathy are often clinically not very impressive, but their impact on overall morbidity and mortality should not be underestimated. Instructions have been provided, regarding monitoring, dose modification and clinical handling of the adverse event in case of myopathy or rhabdomyolyis, in the product information.

Liver events occurred in 18.6% of patients in the binimetinib arm and 10.5% of patients in the dacarbazine arm. In both arms, the most frequently reported liver events were AST increased and ALT increased. This indicates a significantly increased hepatotoxicity which is clinical relevant as illustrated by the case of fatal liver failure in a patient during the development program and probably occurrence of so called Hy's law cases in the binimetinib population. Further clarification provided by the applicant on the issue regarding possible Hy's law in 3 subjects. The clarifications provided by the applicant and the liver function test values described for the three patients do not show clear criteria for Hy's law for the two of the subjects. The events in one subject (6051-004) with a raised AST of 241 U/L, requiring binimetinib dose to be discontinued is concerning. The patient was subsequently described as having ascites due peritoneal deposits but not cytology is available. The patient died later due to embolism. This event is worrying regarding the effect of binimetinib on the liver, especially in patients with prior hepatic impairment. With respect to overall tolerability hepatotoxicity observed indicate a critical safety issue which needed to be balanced by a clear benefit. Amendments in section 4.2 regarding the criteria for adverse reactions involving hepatic laboratory abnormalities and hepatotoxicity, with accompanying

recommendations for dose modifications are acceptable. The dose recommendations in patients with HI however, should be further discussed / revision.

Although **hemorrhage** is classified as an AESI an occurred in 11.2% of patients in the binimetinib arm of the pivotal trial it seems that clinical relevant hemorrhage event beside epistaxis were not observed. The INR increases reported were also classified in this category, but no clear reason for these elevations were found beside concomitant treatment with anticoagulants from the analyses. The PTs reported failed to indicate a clear signal for systemic impairment of hemostasis system or thrombocytes, although at the time being it cannot be completely excluded. The retinal hemorrhage (2.2% in the binimetinib arm) seems to reflect more a symptom of the retinal toxicity than really a bleeding disorder. Additionally, hematuria (0.4% in the binimetinib arm) in the absence of a hemostatic impairment is often symptom of a urogenital infection like acute cystitis. In summary, the data presented seemed not to indicate a significantly increase bleeding risk during binimetinib treatment.

Pneumonitis is as well a known class effect of MEK inhibitors. In the pivotal trial CMEK162A2301 pneumonitis events occurred in 1.9% of patients in the binimetinib arm and 0% of patients in the dacarbazine arm. Events >grade 2 occurred relatively late in comparison with other AESIs, but lead to discontinuation and require additional steroid treatment. The underlying mechanism behind pulmonary toxicities, considered as being MEK inhibitor class effects, is not yet known. It has been hypothesized that the blockage of epidermal growth factor receptor (EGFR)-dependent epithelial proliferation by EGFR tyrosine kinase inhibitors augments pulmonary fibrosis (Min et al, 2011, Suzuki et al, 2003). However, it is notable that MEK inhibition may not have the same effect. For example, an in vivo study in mice demonstrated that the MEK inhibitor, selumetinib (ARRY-142886), prevented the progression of established pulmonary fibrosis associated with EGFR activation (Madala et al 2012).

According the non-clinical data binimetinib has no **electrophysiological effects in the heart** and lack of effects on cardiac waveform and intervals (including QTc) at doses as high as 10 mg/kg (mean Maximum Concentration [Cmax] 2.7 µM, range 1.04 to 7.05 µM) in monkeys. Insofar, QT prolongation was routinely monitored and classified as an AESI. This is confirmed by the clinical data in the different safety sets (restricted and broad). In the pivotal trial QTc prolongation events occurred with similar frequency in patients in both arms (binimetinib: 3.3% versus DTIC: 3.5%). All events were asymptomatic and none of the patients had presyncope, syncope or loss of consciousness associated with the QT prolongation, potentially indicating dangerous arrhythmias (e.g. “torsade de pointes”).

Edema events occurred very frequent in trial CMEK162A2301 nearly exclusively in the binimetinib arm. The most frequently reported edema events by PT were edema peripheral, eyelid edema and periorbital edema. As reflected by the difference observed (B: 43.5% versus DTIC: 2.6%) this AESI seems to be clearly caused by binimetinib. The applicant showed that the incidence of retinal events was broadly similar between patients who did and did not experience face/eyelid oedema. Thus, although retinal events often appeared to occur simultaneously with face/eyelid oedema, their incidence did not appear to be increased as a result of concomitant face/eyelid oedema. Specifically, the incidence of retinal detachment did not appear to be increased as a result of concomitant face/eyelid oedema.

Fatigue as well as asthenia events were the only AESI which were reported more frequent in the DTIC than in the binimetinib arm. Fatigue was reported in 31.6% of the dacarbazine patients compared to the 22.3% in the binimetinib arm.

Venous thromboembolic events including pulmonary embolism occurred more frequent in 5.6% of patients receiving binimetinib than in of patients receiving dacarbazine 1.8 %. However, the cancer

disease itself is also associated with higher thromboembolic event rates. Whether the difference observed allows concluding that binimetinib is really associated with a higher risk for such events can be challenged due to the small number of patients in the trial as well as the 2:1 randomization.

Severity of Adverse Events

In the binimetinib arm of Study CMEK162A2301, the maximum reported severity of AEs was grade 1 for 4.5% of patients, grade 2 for 27.5% of patients, grade 3 for 53.9% of patients and grade 4 for 14.1% of patients. Grade 4 AEs reported for >1 patient in the binimetinib arm included blood CK increase (7.1% of patients), and general physical health deterioration, renal failure, RVO and sepsis (0.7% of patients each).

In the dacarbazine arm of Study CMEK162A2301, the maximum reported severity of AEs was grade 1 for 21.9% of patients, grade 2 for 23.7% of patients, grade 3 for 37.7% of patients and grade 4 for 7.9% of patients (ISS Table 2.2-9). Grade 4 AEs reported for > 1 patient in the dacarbazine arm by preferred term included neutropenia (4.4% of patients), and thrombocytopenia (1.8% of patients).

Maximum AE severity in the all melanoma (binimetinib 45 mg) population was similar to that observed in the binimetinib arm of Study CMEK162A2301, with maximum reported AE severity of grade 1 for 6.3% of patients, grade 2 for 27.4% of patients, grade 3 for 53.2% of patients and grade 4 for 13.1% of patients. In the all cancers (binimetinib any dose) population, AE severity was consistent with both the all melanoma (binimetinib 45 mg) population and Study CMEK162A2301, with maximum reported AE severity of grade 1 for 5.5% of patients, grade 2 for 29.2% of patients, grade 3 for 52.8% of patients and grade 4 for 12.5% of patients.

In Study CMEK162A2301, using the Kaplan-Meier (KM) method, the probability of a patient in the binimetinib arm experiencing a grade 3/4 AE on or before 1, 2 and 3 months on treatment was 32.4%, 48.1% and 60.9%, respectively, while the probability of a patient in the dacarbazine arm experiencing a grade 3/4 AE at these same time points was 29.4%, 38.9% and 47.8%, respectively. In the binimetinib arm, the probability of the risk increased slightly over the next 5 months and plateaued at 80.9% at Month 8, and in the dacarbazine arm, the probability of the risk increased slightly over the next 6 months and plateaued at 65.2% at Month 9; however, the number of patients at risk was much smaller at these time points.

Grade 3/4 blood CK increased was reported in 19.3% of binimetinib-treated patients in Study CMEK162A2301 and was the single most frequent AE reported in the binimetinib arm. Grade 3/4 elevations of CK; however, were often not associated any symptoms and were often benign. A time-to-event KM analysis of grade 3/4 AEs excluding AEs of isolated grade 3/4 blood CK increased was performed and indicated that the incidence of grade ¾ events in the binimetinib arm more closely resembled that of the dacarbazine arm (57.6% in the binimetinib arm vs. 45.6% in the dacarbazine arm). In addition, the probability of a patient in the binimetinib arm experiencing a grade 3/4 AE on or before 1, 2, 3 and 6 months on treatment was 25.3%, 37.1%, 48.6% and 66.3%, respectively, while the probability of a patient in the dacarbazine arm experiencing a grade 3/4 AE at these same time points was 29.4%, 38.9%, 47.8% and 53.6%, respectively.

Adverse Events by Time of Onset

Time to onset for SAEs and AEs leading to discontinuation was analysed in Study CMEK162A2301. The time to onset of the first SAE was similar between the 2 treatment arms in Study CMEK162A2301. Using the KM method, the probability of a patient in the binimetinib arm experiencing an SAE on or

before 1, 2 and 3 months on treatment was 13.4%, 22.3% and 27.2%, respectively, while patients in the dacarbazine arm had a probability at these same time points of 14.2%, 20.2% and 26.0%, respectively. The probability of the risk increased slightly over the next 7 months in the binimetinib arm and plateaued at 49.6% at Month 10; however, the number of patients at risk was much smaller at these time points. In the dacarbazine arm, the risk plateaued at Month 3 at 26.0%.

The time to onset of treatment discontinuation due to an AE assessed using the KM method showed the probability of a patient in the binimetinib arm discontinuing treatment due to an AE on or before 1, 2 and 3 months was 1.5%, 7.4% and 14.9%, respectively, while patients on the dacarbazine arm showed a probability at these same time points of 0.9%, 6.1% and 6.1%, respectively. The probability of the risk increased slightly over the next 9 months in the binimetinib arm and plateaued at 50.6% at Month 12; however, the number of patients at risk was much smaller at these time points. In the dacarbazine arm, the risk plateaued at Month 5 at 14.5%.

Serious adverse events and deaths

Deaths

Deaths in Broad Safety Set

On-treatment deaths for all studies included in the Broad Safety Set were collected while patients were on treatment or within 30 days of the last dose of study drug, with the exception of Study CMEK162X1101, in which deaths were collected within 28 days of the last dose of study drug.

Table 16 presents a summary of on-treatment deaths by SOC and PT for the Broad Safety Set, and Table 17 presents these data adjusted for patient-month exposure.

Table 16: On-treatment Deaths by Primary System Organ Class, Preferred Term and Treatment (Broad Safety Set)

	All cancers	All melanoma	Study CMEK162A2301	
	Binimetinib any dose	Binimetinib 45 mg	Binimetinib 45 mg	DTIC
Primary system organ class Principal cause of death	N=566 n (%)	N=427 n (%)	N=269 n (%)	N=114 n (%)
Total	**65 (11.5)**	**46 (10.8)**	**23 (8.6)**	**3 (2.6)**
Gastrointestinal disorders	1 (0.2)	0	0	0
Large intestinal hemorrhage	1 (0.2)	0	0	0
General disorders and administration site conditions	15 (2.7)	2 (0.5)	1 (0.4)	0
Multi-organ failure	1 (0.2)	1 (0.2)	1 (0.4)	0
Disease progression	12 (2.1)	0	0	0
Euthanasia	1 (0.2)	1 (0.2)	0	0
Ill-defined disorder	1 (0.2)	0	0	0
Hepatobiliary disorders	1 (0.2)	0	0	0
Hepatic failure	1 (0.2)	0	0	0
Infections and infestations	2 (0.4)	2 (0.5)	2 (0.7)	0
Sepsis	2 (0.4)	2 (0.5)	2 (0.7)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	44 (7.8)	40 (9.4)	19 (7.1)	3 (2.6)
Malignant melanoma	42 (7.4)	40 (9.4)	19 (7.1)	3 (2.6)
CRC metastatic	1 (0.2)	0	0	0
Neoplasm malignant	1 (0.2)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.2)	1 (0.2)	0	0
Dyspnea	1 (0.2)	1 (0.2)	0	0
Vascular disorders	1 (0.2)	1 (0.2)	1 (0.4)	0
Embolism	1 (0.2)	1 (0.2)	1 (0.4)	0

Table 17: On-treatment Deaths Adjusted by Patient-Month Exposure by Primary System Organ Class, Preferred Term and Treatment (Broad Safety Set)

Primary system organ class Principal cause of death	All cancers Binimetinib any dose N=566 n (Adj Rate)	All melanoma Binimetinib 45 mg N=427 n (Adj Rate)	Study CMEK162A2301 Binimetinib 45 mg N=269 n (Adj Rate)	Study CMEK162A2301 DTIC N=114 n (Adj Rate)
Patient-month exposure	**2091.0**	**1639.0**	**1014.8**	**362.8**
Total	**65 (3.1)**	**46 (2.8)**	**23 (2.3)**	**3 (0.8)**
Gastrointestinal disorders	1 (0.0)	0	0	0
Large intestinal hemorrhage	1 (0.0)	0	0	0
General disorders and administration site conditions	15 (0.7)	2 (0.1)	1 (0.1)	0
Multi-organ failure	1 (0.0)	1 (0.1)	1 (0.1)	0
Disease progression [a]	12 (0.6)	0	0	0
Euthanasia	1 (0.0)	1 (0.1)	0	0
Ill-defined disorder	1 (0.0)	0	0	0
Hepatobiliary disorders	1 (0.0)	0	0	0
Hepatic failure	1 (0.0)	0	0	0
Infections and infestations	2 (0.1)	2 (0.1)	2 (0.2)	0
Sepsis	2 (0.1)	2 (0.1)	2 (0.2)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	44 (2.1)	40 (2.4)	19 (1.9)	3 (0.8)
Malignant melanoma [a]	42 (2.0)	40 (2.4)	19 (1.9)	3 (0.8)
CRC metastatic	1 (0.0)	0	0	0
Neoplasm malignant [a]	1 (0.0)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.0)	1 (0.1)	0	0
Dyspnea	1 (0.0)	1 (0.1)	0	0
Vascular disorders	1 (0.0)	1 (0.1)	1 (0.1)	0
Embolism	1 (0.0)	1 (0.1)	1 (0.1)	0

The incidence of on-treatment deaths in Study CMEK162A2301 was higher in the binimetinib arm compared to the dacarbazine arm (8.6% binimetinib vs 2.6% dacarbazine). Most on-treatment deaths in the binimetinib arm (7.1%) and all in the dacarbazine arm were due to progression of metastatic melanoma. AEs resulting in death for patients in the binimetinib arm of Study CMEK162A2301 included sepsis (0.7%) and multi-organ failure and embolism (0.4% each). Death rates adjusted for patient-month exposure were 2.3% in the binimetinib arm and 0.8% in the dacarbazine arm.

With Sponsor approval in Study CMEK162A2301, patients were allowed to continue on study drug treatment post disease progression. Of the 23 on-treatment deaths in the binimetinib arm, 11 patients received treatment post-progression. Of these 11 patients, 5 patients received <2 weeks of treatment beyond progression after BIRC-confirmed disease progression (likely due to the interval between the assessment of progression and the treatment visit where the patient would have been taken off study), 2 patients received treatment beyond progression between 14 to 30 days after BIRC-confirmed disease progression and 4 patients received treatment beyond progression >30 days after BIRC-confirmed disease progression. One of 3 patients on the dacarbazine arm who died on treatment received 2 cycles of treatment post-progression.

Compared to the binimetinib arm of Study CMEK162A2301, on-treatment deaths occurred in a similar proportion of patients in the all melanoma (binimetinib 45 mg) population (10.8% of patients) and in the all cancers (binimetinib any dose) population (11.5% of patients). Similar to Study CMEK162A2301, the majority of on-treatment deaths in these binimetinib-treated populations were attributable to disease progression, with sepsis as the only AE resulting in death for >1 patient in either population.

Deaths in Other Ongoing Studies

The by-patient listing of SAEs in ARRAY-162-311 indicated a total of 14 deaths (11 binimetinib arm, 3 control arm) in the on-going Study ARRAY-162-311 as of 20 January 2016. Of these, 9 of 11 deaths in the binimetinib arm were considered on-treatment deaths (occurring during treatment or within 30

days of the last dose); 4 were considered due to PD and 5 were considered due to AEs. Additionally, 3 patients also had events reported as grade 3 SAEs and died within 30 days of last dose.

A by-patient listing of SAEs, including those with a fatal outcome, reported for patients in the Compassionate Use Protocols and Investigator-sponsored trials includes data collected in the Safety database through 20 January 2016. Of the 20 patients treated in Compassionate Use Protocols and Investigator-sponsored trials with single-agent binimetinib in the relevant NRAS/BRAF-mutant metastatic melanoma population, 6 patients had SAEs with a fatal outcome. Of these 6 patients, 3 fatal outcomes were due to PD, 1 was due to an SAE of pneumonia and sepsis, and 2 others provided no further information other than patient death.

Serious Adverse Events in Completed Studies

Table 18 presents a summary of SAEs, regardless of relationship to study drug, that were reported for >1.0% of patients in the binimetinib arm of Study CMEK162A2301 by PT (overall and maximum grade 3/4) for the Broad Safety Set, including separate columns for data from the "all cancers (binimetinib any dose)", "all melanoma (binimetinib 45 mg)" and "Study CMEK162A2301" populations. Treatment-related SAEs are summarized by SOC and PT (overall and maximum grade 3/4) in ISS Table 2.2-14 and by PT (overall and maximum grade 3/4) in ISS Table 2.2-15, and ISS Listing 2.1-3 presents a by-patient listing of all SAEs for the Broad Safety Set.

In Study CMEK162A2301, the incidence of patients with SAEs was higher in the binimetinib arm than in the dacarbazine arm (33.8% binimetinib vs. 21.9% dacarbazine). SAEs were reported most frequently (> 5.0% of patients in either treatment arm) under the SOCs of infections and infestations (6.3% binimetinib vs. 4.4% dacarbazine), general disorders and administration site conditions (5.6% vs. 3.5%) and gastrointestinal disorders (6.7% vs. 0.9%; ISS Table 2.2-12). The SOCs in which SAEs were reported for ≥ 2.0% more patients in the binimetinib than dacarbazine arm were gastrointestinal disorders (6.7% binimetinib vs. 0.9% dacarbazine), investigations (2.6% vs. 0%), respiratory, thoracic and mediastinal disorders (4.8% vs. 2.6%), eye disorders and vascular disorders (each 2.2% vs. 0%) and general disorders and administration site conditions (5.6% vs. 3.5%). A ≥ 2.0% higher incidence of SAEs was reported in the dacarbazine than binimetinib arm under the SOC of blood and lymphatic system disorders (1.5% binimetinib vs. 3.5% dacarbazine). The PT that was reported most frequently (> 2.0% of patients) as an SAE in the binimetinib arm of Study CMEK162A2301 was general physical health deterioration (4.5%). No PTs were reported for > 2.0% of patients in the dacarbazine arm (see Section 2.7.4.2.2.1.4 for an analysis of time to onset of first SAE).

Compared to the binimetinib arm of Study CMEK162A2301, a similar proportion of patients in the all melanoma (binimetinib 45 mg) and the all cancers (binimetinib any dose) populations experienced SAEs (32.1% and 32.5% of patients, respectively). In both populations, the SAE incidences for all SOCs were within 1.0% of the equivalent SOC incidences in the binimetinib arm of Study CMEK162A2301, with the exception of gastrointestinal disorders, which was reported in 1.1% more patients in the all cancers (binimetinib any dose) population compared with the binimetinib arm of Study CMEK162A2301 (ISS Table 2.2-12). Other than the PT of general physical health deterioration, no PTs were reported for > 2.0% of patients in either of these binimetinib-treated populations. Of the 17 patients treated with binimetinib arm that had an SAE under the PT of general physical health deterioration, 11 patients experienced this SAE within days of declaration of PD and 2 patients died within days of this event.

In Study CMEK162AUS11, 45.5% of patients experienced at least 1 SAE while on study, which was higher than in the 3 binimetinib-treated populations. The most frequently reported SAE was dyspnoea (10.9% of patients), followed by abdominal pain, dehydration and small intestinal obstruction (3.6% of

patients each). One potentially relevant consideration in evaluating these events as compared to the 3 binimetinib-treated populations included in the pooled safety data sets is that the population of patients enrolled in CMEK162AUS11 was a heterogeneous mixture of heavily pretreated patients with late-stage solid tumours and hematologic malignancies (most frequent being non-small cell lung cancer, ovarian and uterine cancer).

Table 18: Serious Adverse Events, Regardless of Study Drug Relationship, by Preferred Term and Treatment - Overall and Maximum Grade 3 or 4 (> 1.0% in CMEK162A2301 Binimetinib) (Broad Safety Set)

	All cancers		All melanoma		Study CMEK162A2301			
	Binimetinib any dose N=566		Binimetinib 45 mg N=427		Binimetinib 45 mg N=269		DTIC N=114	
Preferred term	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	**184 (32.5)**	**151 (26.7)**	**137 (32.1)**	**111 (26.0)**	**91 (33.8)**	**74 (27.5)**	**25 (21.9)**	**18 (15.8)**
General physical health deterioration	17 (3.0)	16 (2.8)	16 (3.7)	15 (3.5)	12 (4.5)	11 (4.1)	0	0
Retinal vein occlusion	6 (1.1)	5 (0.9)	6 (1.4)	5 (1.2)	5 (1.9)	4 (1.5)	0	0
Pulmonary embolism	5 (0.9)	4 (0.7)	4 (0.9)	3 (0.7)	4 (1.5)	3 (1.1)	0	0
Anaemia	7 (1.2)	7 (1.2)	3 (0.7)	3 (0.7)	3 (1.1)	3 (1.1)	0	0
Blood creatine phosphokinase increased	6 (1.1)	5 (0.9)	5 (1.2)	4 (0.9)	3 (1.1)	2 (0.7)	0	0
Dyspnea	5 (0.9)	5 (0.9)	5 (1.2)	5 (1.2)	3 (1.1)	3 (1.1)	2 (1.8)	2 (1.8)
Sepsis	3 (0.5)	3 (0.5)	3 (0.7)	3 (0.7)	3 (1.1)	3 (1.1)	2 (1.8)	2 (1.8)
Skin infection	4 (0.7)	4 (0.7)	4 (0.9)	4 (0.9)	3 (1.1)	3 (1.1)	0	0
Vomiting	7 (1.2)	5 (0.9)	5 (1.2)	4 (0.9)	3 (1.1)	2 (0.7)	0	0

It seems that the multiplicity of toxicities of binimetinib nevertheless caused a significant deterioration of the patient's ECOG PS. Due to inherent methodological problems in the collection of data, results of the quality of life data should either not be regarded or only with caution Laboratory findings

Table 19 summarizes laboratory values that met predefined quantitative criteria in data from Study CMEK162A2301 of ≥ 5% increased frequency in binimetinib-treated patients over patients treated with dacarbazine or ≥ 2% increased frequency of grade 3 or 4 abnormalities. The table includes all abnormal values that represent a change from baseline grade.

Table 19: Laboratory Abnormalities Occurring at a Higher Incidence in Patients Treated with Binimetinib in Study CMEK162A2301 (Between-arm Difference of ≥ 5% [All Grades] or ≥ 2% [Grades 3 or 4])

Test Parameter	Study CMEK162A2301			
	Binimetinib 45mg BID N=269		Dacarbazine N=114	
	All Grades n (%)	Grade 3/4 n (%)	All Grades n (%)	Grade 3/4 n (%)
Hematology				
Increased lymphocyte count	20 (7.4)	1 (0.4)	0	0
Increased Prothrombin INR	19 (7.1)	3 (1.1)	1 (0.9)	0
Chemistry				
Increased creatine kinase	205 (76.2)	56 (20.8)	4 (3.5)	0
Increased aspartate aminotransferase	194 (72.1)	9 (3.3)	25 (21.9)	0
Increased creatinine	192 (71.4)	4 (1.5)	66 (57.9)	0
Increased alanine aminotransferase	113 (42.0)	10 (3.7)	24 (21.1)	2 (1.8)
Hypoalbuminemia	87 (32.3)	6 (2.2)	9 (7.9)	1 (0.9)
Hypernatremia	72 (26.8)	3 (1.1)	15 (13.2)	1 (0.9)
Increased alkaline phosphatase	63 (23.4)	6 (2.2)	17 (14.9)	1 (0.9)
Hypocalcemia	63 (23.4)	1 (0.4)	10 (8.8)	0
Hyperkalemia	41 (15.2)	7 (2.6)	14 (12.3)	0
Hypokalemia	14 (5.2)	7 (2.6)	1 (0.9)	0

Key: BID: twice daily, INR: international normalized ratio, N or n: number.
Patients are counted only for the worst grade observed at post-baseline.
Baseline is defined as the last non-missing value prior to the first dose.

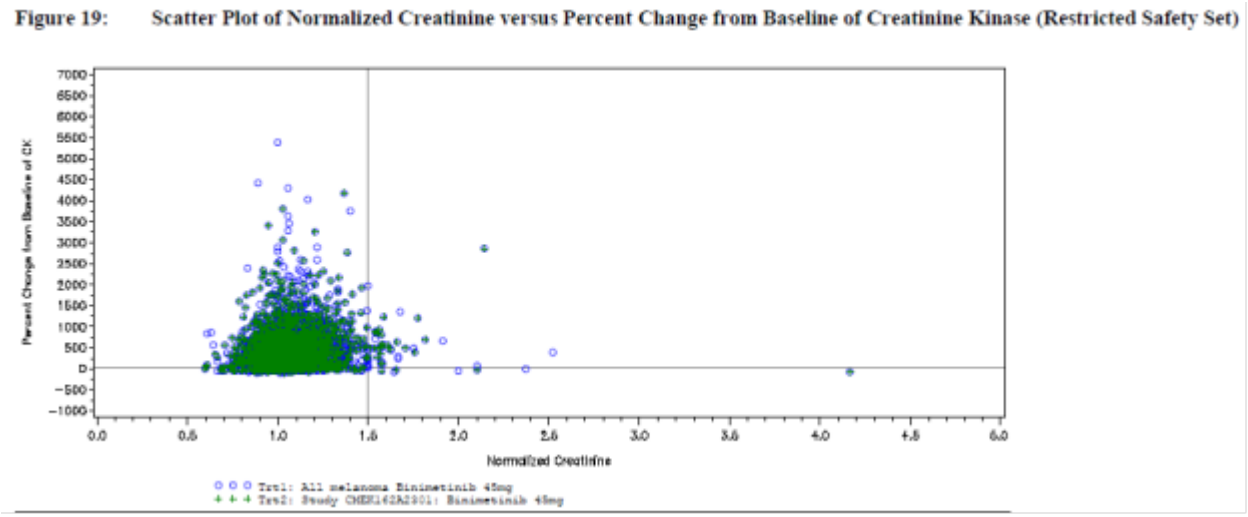
As already discussed in the AESI section increases of CK, ALT/AST and Creatinine, all reflecting rhabdomyolysis as well as hepatotoxicity, were reported as very common biochemistry abnormalities in the binimetinib arm of Study CMEK162A2301 and in the other safety populations defined. Moreover, decreases of albumin probably indicating clinical relevant impairment of liver function and consecutive relative hypocalcemia are very common.

Elevation of blood CK is a frequently observed laboratory finding associated with the administration of MEK inhibitors and clinically associated sometimes with concomitant muscular symptoms. Although grade 1 and grade 2 CK events occurred frequently as usual, it is important to note that with respect to CK grade 3 and grade 4 values were reported. In particular, the occurrence of grade 3 and 4 increases of CK in 13.2% and 8.6% of patients is a significant concern, as clinical consequences for renal function are obvious. As Grade 3 and 4 increases in creatinine were observed only in the binimetinib arm these events, the impact of CK increases on deterioration of renal function needs further discussion during this procedure.

Increases of CK are not specific for skeletal muscles, but may also reflect heart muscle cell damage. As already mentioned above in the pivotal trial, cardiac events occurred in 13.0% of patients in the binimetinib arm and in 1.8% of patients in the dacarbazine arm. As a concerning deterioration of left ventricular function was observed and heart muscle cell damage may be masked by the increases of CK due to rhabdomyolysis, the applicant was requested to provide the analysis of the CK isoenzymes and troponin results. A total of 101 (39.6%) patients in the binimetinib arm and no patients in the dacarbazine arm had post-baseline CK laboratory values of $\geq 3 \times$ ULN. Of these patients, high CK-MB and troponin I values were measured in 17 (16.8%) patients and 12 (11.9%) patients, respectively, with 4 (4.0%) of these patients having high values for both CK-MB and troponin I. Of the patients with CK laboratory values of $\geq 3 \times$ ULN who also had high CK-MB and/or troponin I values, 3 patients had LVEF abnormalities, all of which were Common Terminology Criteria (CTC) Grade 2 reductions. Regarding this issue the applicant is asked to further discuss the cardiac toxicity.

Increases in creatinine were also very commonly reported in the binimetinib populations. In both arms of Study CMEK162A2301, the majority of increases in creatinine were grade 1 in severity In order to understand better the impact of increases of CK on renal function the applicant is requested to provide an analysis of CK and myoglobin in patients with an increase in creatinine. The correlation between increases in CK and creatinine in both arms was analysed. The applicant has further presented data to correlating CK levels and creatinine to explore the effect on renal function. The presented data show no relationship between CK elevation and creatinine in patients in Study CMEK162A2301 and the all melanoma (binimetinib 45 mg) population.

Figure 19: Scatter Plot of Normalized Creatinine versus Percent Change from Baseline of Creatinine Kinase (Restricted Safety Set)



Moreover, a clinical relevant increased **hepatotoxicity** of binimetinib in comparison to DTIC was proven by the laboratory data of the clinical development program as well as in Study CMEK162A2301. Elevated liver enzymes were reported for a substantially larger proportion of patients in the binimetinib than dacarbazine arm of Study CMEK162A2301 (B: 39.5% v. DTIC: 21.3%). This indicates a significantly increased hepatotoxicity which is clinical relevant as illustrated by the case of fatal liver failure in a patient during the development programm. Binimetinib's hepatotoxicity was also responsible for the safety protocol amendment reducing the dose to 45 mg binimetinib in trial X2201 (from initially 60 mg) (OC).

Although decreased haemoglobin was the most common newly occurring or worsening hematologic abnormality observed, in Study CMEK162A2301, decreases from baseline haemoglobin values were reported more frequently for dacarbazine-treated patients.

In Study CMEK162A2301, hypocalcaemia was observed in 23.4% of patients receiving binimetinib and in 0.4% of patients, the hypocalcaemia was grade 3 or 4. Although this difference met criteria for inclusion as a laboratory-associated ADR, because of the high incidence of hypoalbuminemia (32.3%), hypocalcaemia may be a measurement artefact. Corrected calcium was collected as a laboratory parameter in Study CMEK162A2301. The rate of corrected hypocalcemia in patients treated with binimetinib was 10.4% and in patients treated with dacarbazine was 7.0%. Given that correction for hypoalbuminemia is imperfect and given the large difference between the absolute rate of hypocalcaemia and corrected hypocalcaemia, it seems unlikely that binimetinib treatment is associated with an increased risk of true clinically relevant hypocalcaemia. After a further review of the clinical data, among the possible explanations for hypoalbuminemia, no specific aetiology has been found. The review failed to identify a clear relationship with the occurrence of oedema, the patients' concomitant medication profile, or the existence of current medical conditions. In Study CMEK162A2301, increased

prothrombin INR (prothrombin time/international normalized ratio [INR]) was observed in 7.1% of patients receiving binimetinib (1.1% grade 3 or grade 4). A clinical review of patients with increased prothrombin time/INR of grade 2 or 3 was conducted and showed that for 3 patients, no clear reason for the elevation was noted. In all 3 cases the event was an isolated value with normal values prior to and after the event. In the remaining patients, events of increased prothrombin time/INR were associated with ongoing thromboprophylaxis for atrial fibrillation, treatment of a thrombotic event, use of warfarin for an unknown indication or in one case, multi-organ failure, or a combination of these. In one patient, the increase in prothrombin time/INR occurred after the patient discontinued binimetinib and started ipilimumab. Thus, binimetinib treatment does not seem to be associated with significant increases in prothrombin time/INR in the absence of other precipitating factors

Of the 188 patients in the binimetinib arm with normal baseline LDH values, the majority (146 [77.7%] patients) experienced a shift to a high LDH value. In the dacarbazine arm, 21/81 (25.9%) patients with normal baseline LDH values experienced a shift to a high LDH value. Overall, 231 (85.9%) out of 269 patients in the binimetinib arm had at least 1 high LDH value (> 250 U/L) and 61 (53.5%) out of 114 patients in the dacarbazine arm had at least 1 high LDH value. Out of the 185 patients in the binimetinib arm who experienced disease progression, 165 reported high LDH values.Among the 269 patients in the binimetinib arm, the proportion reporting high LDH values (> 250 U/L) was higher prior to experiencing BIRC-confirmed PD (222 [82.5%] patients) compared to following PD (122 [45.4%] patients), including in patients who were allowed to continue study treatment following progression. Similarly, among the 114 patients in the dacarbazine arm, the proportion reporting high LDH values was higher prior to experiencing BIRC-confirmed PD (54 [47.4%] patients) compared to following PD (39 [34.2%] patients), although the difference was less pronounced than in the binimetinib arm.In summary, a greater proportion of patients in the binimetinib arm compared to the dacarbazine arm reported high LDH values during Study CMEK162A2301 (77.7% versus 25.9%). In both treatment arms, the incidence of high LDH values was higher prior to patients experiencing BIRC-confirmed PD compared to following PD, including in patients who could continue study treatment following progression. Regarding the presented data the high LDH levels might be attributed to treatment. As this issue is still unclear, the applicant is asked for further discussion and to implement this eventually in the SmPC/PIL.

Safety in special populations

Subgroups defined for the reporting of AEs were age (<65 vs. ≥65 years), gender and race (Caucasian vs. Asian vs. Other). No differences were observed, except in the all cancers (binimetinib any dose) population, patients of Asian ethnicity had a higher incidence of retinal detachment (38.7%), RPED (25.8%) and macular detachment (3.2%) compared to the Caucasian population (retinal detachment [8.1%], RPED [4.0%] and detachment of macular retinal pigment epithelium and macular detachment [0.2% each]). In the subgroup of Other, the PT of retinal detachment was reported in 9.7% of patients. Despite the high rate of these terms related to retinal detachment, the overall rate of visual impairment seems to be the same in the Caucasian and Asian subgroups.

Hepatic impairment: Data from trial CMEK162A2104 indicate that the exposure of binimetinib compared to healthy subjects is not significantly altered in subjects with mild hepatic impairment, but is increased 2-fold in subjects with moderate hepatic impairment. Based on the results of the clinical study, the dose in this population (moderate hepatic impairment) is proposed to be 30 mg BID. This proposal is not endorsed due to the intrinsic hepatotoxicity of binimetinib; a warning for patients with moderate and severe hepatic impairment should be considered (for further discussion please see above in the pharmacological overview)

Renal impairment: Renal impairment was investigated in a study ARRAY-162-106. The study had an abbreviated design in which, if no significant difference in PK (< 50% increase in the area under the curve [AUC]) was observed between subjects with severe renal impairment and matching healthy subjects, no further enrolment was required. Results from the severe impairment cohort (estimated Glomerular Filtration Rate [eGFR] ≤ 29 mL/min/1.73 m2) indicate a 29% increase in systemic exposure (AUC0-inf) and 21% increase in Cmax compared with matching healthy subjects. The increase in binimetinib exposure in subjects with severe renal impairment compared with the matching healthy subjects was below the protocol-specified 50% increase that would have required evaluation of the mild and moderate cohorts; therefore, no further enrolment to the study was required. Compared to the healthy subjects, the severe renal impairment cohort exhibited a 22% lower clearance and a slightly longer apparent terminal half-life (arithmetic means t1/2; 11.2 versus 9.16 hours). The observed differences were within the variability observed for these parameters in both cohorts of this study (25% to 49%) and the variability previously observed in patient clinical trials, hence these differences are unlikely to be clinically relevant and do not necessitate additional precautions for use. Section 5.2 reflects the results of Study ARRAY-162-106 in subjects with severe renal impairment

Immunological events

None reported.

Safety related to drug-drug interactions and other interactions

Binimetinib is a substrate of UGT1A1. It is suggested that a study with an inhibitor is not required but instead cautionary wording is proposed. This is not agreed. Data on the effect of polymorphisms is limited and there are few patients on UGT inhibitors in the POPPK analysis (n=20) and this is not as sensitive to determine an effect. The applicant should perform a study to determine the effect of UGT1A1 inhibitors on binimetinib.

Binimetinib is also a substrate for Pgp and BCRP, however an effect on biliary secretion is proposed to be unlikely based on non-clinical data and effects on absorption unlikely, due to high intestinal permeability. This too is not accepted and it is considered a clinical study should be performed to determine the effect of Pgp and BCRP inhibition.

In cocktail uptake studies binimetinib did not appear to be a substrate of hepatic uptake transporters. The concentration studied however is high, 15.3 µM compared to Cmax,u of 0.06µM, further studies are required at more physiologically relevant concentrations.

The target concentrations to rule out interactions of binimetinib based on plasma Cmax are 3 µM in plasma, 5.5 µM at the hepatic inlet and 40 µM in the gut.

Binimetinib does not inhibit CYPs with the exception of CYP 2B6 which had a Ki of 1.7 µM, however the mechanistic static model was used to rule out an interaction.

Binimetinib shows induction of CYP 3A4 in vitro and this was investigated in a clinical study. Induction of mRNA for CYP 1A2 and 2B6 is greater than 2 fold (16.5 and 2.6 fold respectively). This should be discussed.

Binimetinib is not an inhibitor of UGT1A1.

Binimetinib is not an inhibitor of Pgp, BCRP, OAT1, OCT1, OCT2, MATE-1, MATE-2k or BSEP. It is a weak inhibitor of OATP1B1 and 1B3, but it can be agreed this does not occur at clinically relevant concentrations. Binimetinib does inhibit OAT3 and further clarification should be provided to discount an effect on this transporter.

Discontinuation due to AES

AEs leading to study drug discontinuation

Table 20 presents a summary of AEs leading to study drug discontinuation, regardless of relationship to study drug, that were reported for > 1.0% of patients in the binimetinib arm of Study CMEK162A2301 by PT (overall and maximum grade 3/4) for the Broad Safety Set, including separate columns for data from the "all cancers (binimetinib any dose)", "all melanoma (binimetinib 45 mg)" and "Study CMEK162A2301" populations.

In Study CMEK162A2301, the incidence of patients who were discontinued from study drug due to an AE was higher in the binimetinib arm than in the dacarbazine arm (24.5% binimetinib vs. 7.9% dacarbazine). Grade 3/4 AEs were the cause of study drug discontinuation for 16.7% of patients in the binimetinib arm and 5.3% of patients in the dacarbazine arm. In the binimetinib arm, the AE that most frequently led to study drug discontinuation (> 2.0% patients) was ejection fraction decreased (3.7%). In the dacarbazine arm, no single AE preferred term resulted in study drug discontinuation for >1 patient.

Compared to the binimetinib arm of Study CMEK162A2301, a similar proportion of patients in the all melanoma (binimetinib 45 mg) and the all cancers (binimetinib any dose) populations discontinued study drug due to AEs (22.0% and 22.3% of patients, respectively).

In the all cancers (binimetinib any dose) population, the AESIs (regardless of study drug relationship) that resulted in the greatest number of study drug discontinuations were cardiac events, myopathy/rhabdomyolysis, dermatological events (rash), and liver events, reported for 19 (3.4%), 19 (3.4%), 12 (2.1%), and 11 (1.9%) patients, respectively.

In the binimetinib arm in Study CMEK162A2301, the AESIs (regardless of study drug relationship) that resulted in the greatest number of study drug discontinuations were cardiac events, myopathy/rhabdomyolysis, and dermatological events (rash), reported for 13 (4.8%), 11 (4.1%), and 7 (2.6%) patients, respectively (Safety Appendix Table 108-3).

In the all cancers (binimetinib any dose) population, compared to the first, second and third months of treatment, most discontinuations were reported in the fourth month or later (all grades: 33 (5.8%) patients, Grade 3/4: 17 (3.0%) patients), particularly for the AESIs of cardiac events (all grades: 8 (1.4%) patients, Grade 3/4: 5 (0.9%) patients), oedema events (all grades: 4 (0.7%) patients, Grade 3/4: 1 (0.2%) patient), and thrombotic and embolic events (all grades: 4 (0.7%) patients, Grade 3/4: 2 (0.4%) patients). In the all cancers (binimetinib any dose) population, most discontinuations were reported in the first month of treatment for the AESIs of liver events (all grades: 7 (1.2%) patients, Grade 3/4: 5 (0.9%) patients), gastrointestinal events (all grades: 6 (1.1%) patients, Grade 3/4: 1 (0.2%) patient), and dermatological events (rash) (all grades: 5 (0.9%) patients, Grade 3/4: 3 (0.5%) patients).

In the all cancers (binimetinib any dose) population, cardiac events (all grades) leading to study drug discontinuation occurring within the first, second, and third month were reported for 5 (0.9%), 3 (0.5%), and 3 (0.5%) patients, respectively; and myopathy/rhabdomyolysis events (all grades) leading to study drug discontinuation occurring within the first, second, and third month were reported for 3 (0.5%), 8 (1.4%), and 2 (0.4%) patients, respectively. Six (1.1%) patients reported myopathy/rhabdomyolysis events leading to study drug discontinuation that occurred in the fourth month or later.

In the binimetinib arm in Study CMEK162A2301, compared to the first, second and third months of treatment, most discontinuations were reported in the fourth month of treatment or later (all grades: 21 (7.8%) patients, Grade 3/4: 12 (4.5%) patients), particularly for the AESIs of cardiac events (all grades: 5 (1.9%) patients, Grade 3/4: 3 (1.1%) patients) and myopathy/rhabdomyolysis events (all grades: 5 (1.9%)

patients, Grade 3/4: 4 (1.5%) patients). In the binimetinib arm in Study CMEK162A2301, most discontinuations were reported in the first month of treatment for the AESI of dermatological events (rash) (all grades: 3 (1.1%) patients, Grade 3/4: 2 (0.7%) patients). In the binimetinib arm in Study CMEK162A2301, cardiac events (all grades) leading to study drug discontinuation occurring within the first, second, and third month were reported for 2 (0.7%), 3 (1.1%), and 3 (1.1%) patients, respectively; and myopathy/rhabdomyolysis events (all grades) leading to study drug discontinuation occurring within the first, second, and third month were reported for 1 (0.4%), 3 (1.1%), and 2 (0.7%) patients, respectively.

In the dacarbazine arm in Study CMEK162A2301, the AESIs that resulted in study drug discontinuation were fatigue/asthenia (2 [1.8%] patients), liver events (2 [1.8%]), gastrointestinal events (1 [0.9%]), and QTc prolongation (1 [0.9%]). AESIs (all grades) leading to study drug discontinuation occurred within the first, second, and third month for 3 (2.6%), 1 (0.9%), and 1 (0.9%) patients, respectively. No patients in the dacarbazine arm in Study CMEK162A2301 reported AESIs leading to study drug discontinuation that occurred in the fourth month or later.

In Study CMEK162AUS11, 26.4% of patients experienced AEs that resulted in permanent discontinuation of binimetinib treatment which was similar to that observed in the pivotal study CMEK162A2301, the all melanoma (binimetinib 45 mg) and the all cancers (binimetinib any dose) groups. The most common preferred term leading to discontinuation of binimetinib was blood CK increased, with fewer patients (< 2.0%) who discontinued treatment due to PTs of oedema peripheral, ejection fraction decreased, fatigue and nausea.

However, the most common reasons for discontinuation from study drug were locally assessed PD confirmed by BIRC (46.1% binimetinib versus 52.6% dacarbazine), AEs (20.8% versus 6.0%) and subject/guardian decision (10.0% versus 9.8%).

Death was reported as the primary reason for discontinuation in 13 (3.2%) patients overall, including 11 (4.1%) patients in the binimetinib arm and 2 (1.5%) patients in the dacarbazine arm.

Table 20: Adverse Events Leading to Study Drug Discontinuation, Regardless of Study Drug Relationship, by Preferred Term and Treatment - Overall and Maximum Grade 3 or 4 (> 1.0% in CMEK162A2301 Binimetinib) (Broad Safety Set)

	All cancers		All melanoma		Study CMEK162A2301			
	Binimetinib any dose N=566		Binimetinib 45 mg N=427		Binimetinib 45 mg N=269		DTIC N=114	
Preferred term	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	**126 (22.3)**	**84 (14.8)**	**94 (22.0)**	**66 (15.5)**	**66 (24.5)**	**45 (16.7)**	**9 (7.9)**	**6 (5.3)**
Ejection fraction decreased	15 (2.7)	8 (1.4)	14 (3.3)	7 (1.6)	10 (3.7)	5 (1.9)	0	0
Blood creatine phosphokinase increased	10 (1.8)	6 (1.1)	6 (1.4)	6 (1.4)	5 (1.9)	5 (1.9)	0	0
Retinal vein occlusion	7 (1.2)	5 (0.9)	7 (1.6)	5 (1.2)	5 (1.9)	4 (1.5)	0	0
Retinal detachment	4 (0.7)	0	4 (0.9)	0	4 (1.5)	0	0	0
Alanine aminotransferase increased	5 (0.9)	4 (0.7)	4 (0.9)	3 (0.7)	3 (1.1)	3 (1.1)	0	0
Aspartate aminotransferase increased	6 (1.1)	6 (1.1)	4 (0.9)	4 (0.9)	3 (1.1)	3 (1.1)	1 (0.9)	0
Dermatitis acneiform	7 (1.2)	5 (0.9)	5 (1.2)	4 (0.9)	3 (1.1)	2 (0.7)	0	0
General physical health deterioration	5 (0.9)	5 (0.9)	5 (1.2)	5 (1.2)	3 (1.1)	3 (1.1)	0	0
Muscular weakness	3 (0.5)	2 (0.4)	3 (0.7)	2 (0.5)	3 (1.1)	2 (0.7)	0	0

Adverse Events Leading to Dose Interruption or Adjustment

Table 21 presents a summary of AEs requiring dose adjustment or study-drug interruption, regardless of relationship to study drug, that were reported for > 1.0% of patients in the binimetinib arm of Study CMEK162A2301 by PT (overall and maximum grade 3/4) for the Broad Safety Set including separate

columns for data from the “all cancers (binimetinib any dose)”, “all melanoma (binimetinib 45 mg)” and “Study CMEK162A2301” populations.

In Study CMEK162A2301, a higher incidence of patients in the binimetinib arm experienced AEs requiring dose adjustment or study-drug interruption as compared to the dacarbazine arm (69.5% binimetinib vs. 36.0% dacarbazine). Grade 3/4 AEs were the cause of dose adjustment or study-drug interruption for 43.1% of patients in the binimetinib arm and 20.2% of patients in the dacarbazine arm. In the binimetinib arm, the PTs that most frequently required dose adjustment or study-drug interruption (> 5.0% of patients) were blood CK increased (18.2%), rash (9.3%), dermatitis acneiform (7.1%), ejection fraction decreased (6.3%), vomiting (5.9%) and diarrhoea and retinal detachment (5.6% each). Grade 3/4 AEs requiring dose adjustment or study-drug interruption in > 2.0% patients in the binimetinib arm were blood CK increased (14.5%), rash (4.1%) and hypertension (3.0%). In the dacarbazine arm, the PTs that most frequently required dose adjustment or study-drug interruption (> 5.0% of patients) were neutropenia (13.2%), thrombocytopenia (10.5%), platelet count decreased (7.0%) and neutrophil count decreased (6.1%). Grade 3/4 AEs requiring dose adjustment or study-drug interruption in > 2.0% patients in the dacarbazine arm were neutropenia (7.9%) and neutrophil count decreased and thrombocytopenia (2.6% each).

Compared to the binimetinib arm of Study CMEK162A2301, patients in the all melanoma (binimetinib 45 mg) and the all cancers (binimetinib any dose) populations experienced AEs requiring dose adjustment or study-drug interruption at a similar rate.

In Study CMEK162AUS11, 61.8% of patients experienced AEs that resulted in a dose adjustment or interruption. AEs that most frequently required dose adjustment or study drug interruption (> 5.0% of patients) by PT were fatigue (7.3%), blood CK increased and diarrhoea (6.4% each) and dyspnoea (5.5%).

Table 21: Adverse Events Requiring Dose Adjustment or Study-drug Interruption, Regardless of Study Drug Relationship, by Preferred Term and Treatment - Overall and Maximum Grade 3 or 4 (> 1.0% in CMEK162A2301 Binimetinib) (Broad Safety Set)

	All cancers		All melanoma		Study CMEK162A2301			
	Binimetinib any dose N=566		Binimetinib 45 mg N=427		Binimetinib 45 mg N=269		DTIC N=114	
Preferred term	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	**379 (67.0)**	**224 (39.6)**	**283 (66.3)**	**176 (41.2)**	**187 (69.5)**	**116 (43.1)**	**41 (36.0)**	**23 (20.2)**
Blood creatine phosphokinase increased	94 (16.6)	80 (14.1)	78 (18.3)	67 (15.7)	49 (18.2)	39 (14.5)	0	0
Rash	33 (5.8)	13 (2.3)	29 (6.8)	11 (2.6)	25 (9.3)	11 (4.1)	0	0
Dermatitis acneiform	32 (5.7)	8 (1.4)	28 (6.6)	7 (1.6)	19 (7.1)	5 (1.9)	0	0
Ejection fraction decreased	26 (4.6)	7 (1.2)	24 (5.6)	7 (1.6)	17 (6.3)	3 (1.1)	0	0
Vomiting	27 (4.8)	7 (1.2)	19 (4.4)	5 (1.2)	16 (5.9)	3 (1.1)	0	0
Diarrhea	29 (5.1)	4 (0.7)	23 (5.4)	4 (0.9)	15 (5.6)	3 (1.1)	0	0
Retinal detachment	24 (4.2)	0	18 (4.2)	0	15 (5.6)	0	0	0
Nausea	25 (4.4)	5 (0.9)	18 (4.2)	3 (0.7)	13 (4.8)	2 (0.7)	1 (0.9)	1 (0.9)
Edema peripheral	20 (3.5)	0	19 (4.4)	0	13 (4.8)	0	0	0
Asthenia	12 (2.1)	2 (0.4)	12 (2.8)	2 (0.5)	11 (4.1)	2 (0.7)	2 (1.8)	2 (1.8)
Hypertension	16 (2.8)	13 (2.3)	15 (3.5)	12 (2.8)	11 (4.1)	8 (3.0)	0	0
Aspartate aminotransferase increased	14 (2.5)	4 (0.7)	10 (2.3)	2 (0.5)	8 (3.0)	1 (0.4)	2 (1.8)	0
Myalgia	11 (1.9)	2 (0.4)	9 (2.1)	2 (0.5)	7 (2.6)	2 (0.7)	0	0
Fatigue	13 (2.3)	8 (1.4)	10 (2.3)	7 (1.6)	6 (2.2)	4 (1.5)	0	0
Muscular weakness	10 (1.8)	2 (0.4)	7 (1.6)	2 (0.5)	6 (2.2)	2 (0.7)	0	0
Pyrexia	13 (2.3)	1 (0.2)	10 (2.3)	0	6 (2.2)	0	1 (0.9)	0
Dyspnea	12 (2.1)	3 (0.5)	11 (2.6)	2 (0.5)	5 (1.9)	1 (0.4)	0	0
Eyelid edema	6 (1.1)	0	6 (1.4)	0	5 (1.9)	0	0	0
General physical health deterioration	5 (0.9)	2 (0.4)	5 (1.2)	2 (0.5)	5 (1.9)	2 (0.7)	1 (0.9)	0
Intraocular pressure increased	5 (0.9)	0	5 (1.2)	0	5 (1.9)	0	0	0
Alanine aminotransferase increased	12 (2.1)	5 (0.9)	7 (1.6)	4 (0.9)	4 (1.5)	2 (0.7)	3 (2.6)	1 (0.9)
Detachment of retinal pigment epithelium	9 (1.6)	0	5 (1.2)	0	4 (1.5)	0	0	0
Periorbital edema	4 (0.7)	1 (0.2)	4 (0.9)	1 (0.2)	4 (1.5)	1 (0.4)	0	0
Rash pustular	4 (0.7)	2 (0.4)	4 (0.9)	2 (0.5)	4 (1.5)	2 (0.7)	0	0
Vision blurred	9 (1.6)	1 (0.2)	5 (1.2)	1 (0.2)	4 (1.5)	1 (0.4)	0	0
Abdominal pain	3 (0.5)	0	3 (0.7)	0	3 (1.1)	0	1 (0.9)	1 (0.9)
Erythema	4 (0.7)	1 (0.2)	3 (0.7)	1 (0.2)	3 (1.1)	1 (0.4)	0	0
Myoglobin blood increased	3 (0.5)	1 (0.2)	3 (0.7)	1 (0.2)	3 (1.1)	1 (0.4)	0	0
Peripheral swelling	3 (0.5)	2 (0.4)	3 (0.7)	2 (0.5)	3 (1.1)	2 (0.7)	0	0
Pulmonary embolism	3 (0.5)	3 (0.5)	3 (0.7)	3 (0.7)	3 (1.1)	3 (1.1)	0	0
Retinal disorder	3 (0.5)	1 (0.2)	3 (0.7)	1 (0.2)	3 (1.1)	1 (0.4)	0	0
Skin infection	4 (0.7)	4 (0.7)	4 (0.9)	4 (0.9)	3 (1.1)	3 (1.1)	0	0
Subretinal fluid	5 (0.9)	0	5 (1.2)	0	3 (1.1)	0	0	0
Visual impairment	12 (2.1)	1 (0.2)	8 (1.9)	1 (0.2)	3 (1.1)	0	0	0

To sum it up, the higher toxicity of binimetinib compared with DTIC is confirmed by a significantly higher rate of discontinued from study drug due to an AE (B: 24.5% versus DTIC:7.9). Also findings regarding AEs requiring dose adjustment or study-drug interruption confirm this view (69.5% binimetinib vs. 36.0% dacarbazine).

The discontinuation rate of 24.5% for binimetinib seems to indicate mainly drug associated risks and the high level may be illustrated by a comparison of discontinuation rate in a similar melanoma population [e.g.: in the pivotal trial MEK114267 for Trametinib (Mekinist) discontinuation is reported with 12%].

3.4.8. Discussion on clinical safety

The safety of binimetinib is based on pooled safety data from 4 clinical studies and a total of 566 patients including 427 patients with metastatic melanoma treated with single-agent binimetinib 45 mg BID. In addition, safety data of 2 studies, that were not included in the pool, were reviewed and taken into account in the analysis.

Study CMEK162A2301 provides comparative safety data in 269 patients treated with binimetinib relative to the active control of dacarbazine. The overall rate and severity of AEs is similar in Study

CMEK162A2301 and across pooled data sets. Study drug exposure was similar across all 3 binimetinib-treated populations, with a median duration of exposure of 12.0 weeks in the all cancers (binimetinib any dose) population, 12.7 weeks in the all melanoma (binimetinib 45 mg) population and 12.6 weeks for patients in Study CMEK162A2301. Median exposure for patients treated with dacarbazine in Study CMEK162A2301 was 9.0 weeks. In the pool of 427 patients with metastatic melanoma treated with single-agent binimetinib at 45 mg BID (all melanoma [binimetinib 45 mg] population), 22.7% of patients were exposed for greater than or equal to 24 weeks and 3.5% were exposed for greater than or equal to 48 weeks. Median relative dose intensity across all 3 binimetinib-treated populations ranged from 84% to 88%. In the all melanoma [binimetinib 45 mg] population, the median age was 64.0 years, 63.7% were male, and 93.0% were Caucasian. Due to the known demographics and epidemiology of melanoma, other races were, as expected, underrepresented in the data set. The median age in the all cancers (binimetinib any dose) population was 61.5 years, 61.8% were male and 89.0% were Caucasian.

The incidence of on-treatment deaths in Study CMEK162A2301 was higher in the binimetinib arm compared to the dacarbazine arm (8.6% binimetinib vs 2.6% dacarbazine). Most on-treatment deaths in the binimetinib arm (7.1%) and all in the dacarbazine arm were due to progression of metastatic melanoma. Patients in Study CMEK162A2301 were allowed (with Sponsor approval) to continue on study drug treatment after disease progression. AEs resulting in death for patients in the binimetinib arm of Study CMEK162A2301 included sepsis (0.7%) and multi-organ failure associated with a rhabdomyolysis and embolism (0.4% each). Compared to the binimetinib arm of Study CMEK162A2301, on-treatment deaths occurred in a similar proportion of patients in the all melanoma (binimetinib 45 mg) population (10.8%) and in the all cancers (binimetinib any dose) population (11.5%). Similar to Study CMEK162A2301, the majority of on-treatment deaths in these binimetinib-treated populations were attributable to disease progression.

In Study CMEK162A2301, the incidence of patients with SAEs was higher in the binimetinib arm than in the dacarbazine arm (33.8% binimetinib vs. 21.9% dacarbazine).

In the binimetinib arm of Study CMEK162A2301, AEs were reported most frequently (> 20.0% of patients) under the PTs of blood CK increased (42.0%), diarrhoea (40.1%), rash (36.4%), oedema peripheral (36.1%), dermatitis acneiform (35.3%), nausea (29.4%), fatigue (22.3%) and vomiting (21.2%). PTs that were reported at an incidence of ≥ 10% more patients in the binimetinib arm and with an incidence of ≥ 5% more patients in the binimetinib arm as compared to the dacarbazine arm were blood CK increased, rash, dermatitis acneiform, oedema peripheral, diarrhoea, retinal detachment, skin fissures, hypertension, pruritus, vomiting, AST increase, Ejection fraction decrease and dyspnoea.

Subgroup analyses of AEs were performed in the subgroups of age, race and gender in the all cancers (binimetinib any dose) population and in the subgroup of patients who received prior immunotherapy for unresectable or metastatic disease (per stratification factor) in Study CMEK162A2301. No safety trends were observed by age, gender or prior immunotherapy for unresectable or metastatic disease. For the subgroup of race, it was observed that patients of Asian ethnicity had a higher incidence of retinal-related events compared to the Caucasian population; however, the overall rate of visual impairment seemed to be the same in the Caucasian and Asian subgroups, suggesting that the detachment finding was poorly correlated with visual impairment overall.

The most important risks associated with binimetinib treatment defined by ADRs in the proposed patient population are described below.

Left ventricular dysfunction: is a class effect of MEK. Left ventricular dysfunction occurred in 10% (44/427) of patients treated at the recommended dose, with a maximum severity of grade 3 (in 4.4% of patients). It frequently led to dose modification or treatment discontinuation. LVEF was routinely monitored with MUGA or echocardiography across the clinical program. The safety of binimetinib has not been established in patients with a baseline LVEF that is either below 50% or below the institutional lower limits of normal. It is recommended that there be assessment of LVEF by ECHO or MUGA scan before initiation of binimetinib, 1 month after initiation, and then at 2 to 3-month intervals while on treatment. Binimetinib should be interrupted for up to 3 weeks if absolute LVEF value decreases by 10% from pre-treatment values and is less than the lower limit of normal. Binimetinib should be permanently discontinued for symptomatic left ventricular dysfunction or persistent, asymptomatic left ventricular dysfunction that does not resolve within 3 weeks.

According the non-clinical data binimetinib has no **electrophysiological effects in the heart** and lack of effects on cardiac waveform and intervals (including QTc) at doses as high as 10 mg/kg (mean Maximum Concentration [Cmax] 2.7 µM, range 1.04 to 7.05 µM) in monkeys. QT prolongation was routinely monitored and classified as an AESI. This is confirmed by the clinical data in the different safety sets (restricted and broad). In the pivotal trial QTc prolongation events occurred with similar frequency in patients in both arms (binimetinib: 3.3% versus DTIC: 3.5%). All events were asymptomatic and none of the patients had presyncope, syncope or loss of consciousness associated with the QT prolongation, potentially indicating dangerous arrhythmias (e.g. “torsade de pointes”).

Hypertension: New-onset hypertension or worsening of hypertension was seen with binimetinib treatment in 16% (68/427) of patients at the recommended dose, with grade 3 in 8% of patients. It was generally manageable with antihypertensive medications and rarely required treatment discontinuation. Patients should be monitored for hypertension and temporary suspension of binimetinib is recommended in case of severe hypertension, until hypertension is controlled. The significantly high frequency for increases of creatinine (82.0%) indicating a decrease in renal function may explain at least partially this finding. It seems very likely that the increase in cardiac events was also triggered by hypertension results.

RPED and RVO: the ocular toxicities of binimetinib can in rare instances be sight threatening although no cases of permanent blindness have been reported. Visual impairment, including vision blurred and reduced visual acuity, occurred in 13% (56/427) of patients and was generally reversible. RPED is a characteristic adverse effect of MEK inhibition and was closely monitored in the binimetinib clinical program. While evidence of retinopathy was detected frequently, in 31.6% of patients treated at the recommended dose, i.e., all melanoma binimetinib 45 mg group, it was often asymptomatic (grade 1 in 18% of patients) or mildly symptomatic (grade 2 in 12% of patients) and could be managed without need for dose modification. RVO was seen infrequently (1.6% [9/566 patients in the all cancers (binimetinib any dose) population]), but is a potentially sight-threatening event. Patients with RVO were discontinued from treatment with binimetinib and the majority with available follow-up showed evidence of recovery. The safety of binimetinib has not been established in patients with a history of or current evidence of RVO or current risk factors for RVO including uncontrolled glaucoma, or a history of hyperviscosity or hypercoagulability syndromes. Binimetinib has to be discontinued with the occurrence of RVO. Binimetinib is not recommended in patients with a history of RVO.

Skin-related “rash” events were observed very common and reported in 81.4 % of patients treated with binmetinib monotherapy. Most cases were grade 1 or 2 severity but 68% were requiring additional therapy. Taking into account that these events often results in an impairment of infection protection and the binimetinib is also a TNF inhibitor, the increase rates of infections and cases of

sepsis observed may be also seen as drug related complications. As the median time of onset was 0.4 month for these events, more clarification of potential dangerous consequences of these very frequent events and early occurring AE is needed.

Dermatologic "non-rash" events occurred in 42.4% of patients in the binimetinib arm. The median time of onset of this toxicity was 1.4 month, additional therapy was required in 24%. In addition approx. 25% of the patients showed - often secondary to other dermatologic events- a skin infection; 3.3% of these events were resulting in hospitalization. **Muscular toxicity:** blood CK increase was a very commonly reported AE with binimetinib treatment (in 43.3% of patients treated at the recommended dose). This was rarely associated with symptoms, although symptoms were more common with higher reported grades of CK elevation. It was the most frequent cause of dose adjustment or treatment interruption. Frank rhabdomyolysis, defined by published criteria of high CK, evidence of end organ damage and muscle symptoms was infrequent, with only a single documented case meeting case defining criteria based on published literature and regulatory guidance. CK and creatinine levels should be monitored prior to initiating binimetinib, periodically during treatment, and as clinically indicated, and ensure that the patient is adequately hydrated. In case of rhabdomyolysis treatment should be discontinued. Depending on CK elevation, dose interruption or discontinuation of binimetinib may be required. Renal complications and clinical symptoms of myopathy are often clinically not very impressive, but their impact on overall morbidity and mortality should not be underestimated.

Liver related events: Liver enzyme abnormalities are also common (ALT in 9.6%; AST in 13.6% of patients treated at the recommended dose) with binimetinib treatment. Although liver enzyme monitoring was enhanced as a result of a case of hepatic failure in a single patient treated at the 60 mg BID dose of binimetinib, the applicant states that no Hy's law cases or other clear cases of drug-induced liver injury have been observed at the recommended 45 mg BID dose. Liver function abnormalities, mainly AST and ALT elevations, can occur with binimetinib. Liver laboratory tests should be monitored before initiation of binimetinib and monthly during treatment, or more frequently as clinically indicated. Grade 3 and 4 liver laboratory abnormalities should be managed with dose interruption, reduction, or discontinuation of binimetinib. With respect to overall tolerability hepatotoxicity observed indicate a critical safety issue which needed to be balanced by a clear benefit.

Gastro-intestinal disorders including diarrhoea and vomiting: in the 9-month repeat-dosing study in the monkey, the primary findings were gastrointestinal intolerance and inflammation. All large intestinal findings resolved after a treatment-free period. In the gastric irritation study in rats, there were no significant effects at the 10 and 30 mg/kg doses. At 100 mg/kg binimetinib, there was an increased incidence of superficial mucosal lesions and of haemorrhagic ulcers. ADRs reported most commonly by PT at the recommended dose were diarrhoea (43% of patients), nausea (30% of patients) and vomiting (20% of patients). Gastrointestinal events required dose adjustment or study drug interruption in 11% of patients and led to discontinuation of binimetinib in 1.2% of patients.

Venous thromboembolism: In melanoma patients treated at the recommended dose of binimetinib, VTE occurred in 4.2% (18/427) of patients receiving binimetinib, including 1.4% (6/427) of patients with pulmonary embolism. It is a common complication related to malignancy and there is generally a high degree of vigilance for signs and symptoms of VTE in cancer patients, and use of thromboprophylaxis in appropriate settings is recognized as a standard of care in oncology.

Haemorrhage: Although haemorrhage is classified as an AESI an occurred in 11.2 of patients in the binimetinib arm of the pivotal trial it seems that clinical relevant haemorrhage event beside epistaxis

were not observed. The INR increases reported were also classified in this category, but no clear reason for these elevations were found beside concomitant treatment with anticoagulants from the analyses. The PTs reported failed to indicate a clear signal for systemic impairment of haemostasis system or thrombocytes, although at the time being it cannot be completely excluded. The retinal haemorrhage (2.2% in the binimetinib arm) seems to reflect more a symptom of the retinal toxicity than really a bleeding disorder. Additionally haematuria (0.4% in the binimetinib arm) in the absence of a haemostatic impairment is often symptom of a urogenital infection like acute cystitis. In summary, the data presented seemed not to indicate a significantly increase bleeding risk during binimetinib treatment.

Pneumonitis: This was seen following binimetinib treatment in 1.4% of patients in the all cancers [binimetinib any dose] population) and is a well-recognized ADR associated with a number of kinase inhibitors, including MEK inhibitors. The underlying mechanism behind pulmonary toxicities, considered as being MEK inhibitor class effects, is not yet known. It has been hypothesized that the blockage of epidermal growth factor receptor (EGFR)-dependent epithelial proliferation by EGFR tyrosine kinase inhibitors augments pulmonary fibrosis (Min et al, 2011**,** Suzuki et al, 2003). However, it is notable that MEK inhibition may not have the same effect. For example, an *in vivo* study in mice demonstrated that the MEK inhibitor, selumetinib (ARRY-142886), prevented the progression of established pulmonary fibrosis associated with EGFR activation (Madala et al 2012).

Reproductive risk: based on findings from animal studies and its mechanism of action, binimetinib may cause foetal harm when administered to a pregnant woman. Binimetinib was embryotoxic and abortifacient in rabbits at doses greater than or equal to those resulting in exposures approximately 12 times the human exposure at the recommended clinical dose. The main risk factor is the women of child-bearing potential (i.e., pre or peri-menopausal) with exposure during the first trimester without effective method of contraception. The risk may be managed by highlighting in the patient information leaflet/summary of product characteristics that female patients of reproductive potential should use effective contraception during treatment with binimetinib and for 2 weeks after treatment.

Safety comparison with approved MEK inhibitors in advance melanoma population

Safety results observed in CMEK162A2301 and the entire binimetinib safety database is consistent regarding class effect toxicities known for other MEK inhibitors currently approved for marketing (trametinib and cobimetinib). However, binimetinib toxicities are clearly more pronounced in such a comparison as demonstrated below. The following table (Table 22) allows comparing the key characteristics safety of binimetinib with the trametinib, an MEK inhibitor approved already as single agent (and/or in combination with a BRAF inhibitor) for the treatment of advanced metastatic melanoma.

Table 22: Comparison Binimetinib (pivotal trial MEK162A2301) and Trametinib (pivotal trial MEK114267)

	Binimetinib (CMEK162A2301) (N=269)	Trametinib (MEK114267) (N=322)
Indication	Metastatic melanoma, NRAS Mutation pos.	Metastatic melanoma, BRAF Mutation +
Demographic aspects	61% male, 89% caucasian 65 years	54% male caucasian 54 years
Comparator		

	DTIC		DTIC / Paclitaxel	
Exposure (weeks)	12.6		> 16 (4.83 month)	
Dose intensitiy	83.78 %		91 %	
AEs leading to discontinuation	24.5 %		12 %	
AE leading to dose reduction and / or delays	In total 69.5%		32% 38%	
SAEs	33.8 %		24 %	
Adverse events (class effects)	Binimetinib		Trametinib	
	All grades n%	Grade ¾ n%	All grades n%	Grade ¾ n%
CK increased	42.0	19.3	*	na
Rhabdomyolysis	0.4	na	1.4	na
Rash	49.8	5.2	59	8
Dermatitis acneiforme	35.3	2.6	19	<1
Skin infections (secondary)	25.7	5.6	*	
Edema peripheral	38.3	0.4	29	1
Cardiac events	13	4.8	9	2
Hypertension				
RPED	33.1	1.1	-	-
Visual impairment	14.5	0.4	13%	<1
RVO	2.2	na	<1	na
Hepatic events	18.6	5.2	12	na
Increased ALT	8.2	2.6	9	na
Increased AST	13	2.2	10	na

*no explicit value available, SmPC section 4.8 states “common”, na not applicable

Elevation of creatine kinase (CK) values is a known class effect of MEK-Inhibition. As stated in the SmPC for trametinib (and cobimetinib) the appearance of increased CK values is common, but most cases resolve without further management (interruption or dose reduction). For Binimetib CK increases were very commonly reported with a frequency of 42.0%, with 21.1% CTCAE grade 3 and 4. A dose reduction was required in >18% and rhabdomyolysis caused the death in at least one patient. It is not clear whether increases of CK observed possibly mask cardiac myocyte damage.

Dermatologic events and edema events are a further class effect of the MEK inhibitors. Regarding the safety data concerning these issues the frequency and severity is comparable for the three MEK inhibitors. Regarding the cardiac events and hypertension binimetinib seems to be slightly more toxic than trametinib and cobemetinib. It is not clear whether the hypertension can be explained due by an increase in renal impairment or renal toxicity.

The comparison also retinal toxicity and hepatotoxicity are more frequent with binimetinib than with trametinib.

3.4.9. Conclusions on clinical safety

The overall safety results for binimetinib show ADRs consistent with the known safety profile of other drugs in this class. However, the incidences of some of the expected adverse events are more frequent that seen with other approved MEK inhibitors. Some of these ADRs are serious or potentially life

threatening (thromboembolic events, hypertension, serious skin toxicities and infections, left ventricular dysfunction, pneumonitis, liver function abnormalities and rhabdomyolysis), or are sight threatening (RVO) and are reflected in the deaths, SAEs and AEs leading to discontinuation across the safety sets.

Although an MEK inhibitor in principle is not cytotoxic, binimetinib's toxicity is more pronounced than that of standard chemotherapy. The sum of toxicities has a statistically significantly negative impact on deterioriation of ECOG PS >1, translating even into DFS (i.e. deterioration free survival), albeit currently not reaching the formal criterion of statistical significance.

High event rates for grade 3 and 4 events and the occurrence of fatal causes due to hepatotoxicity, rhabdomyolysis, cardiac insufficiency from decreased LVEF and many other class adverse events indicate an overall inferior safety profile with poor tolerability, even in comparison to cytotoxic therapy such as dacarbazine. Additionally, it should be considered that binimetinib is intended for permanent daily administration, while chemotherapy with DTIC is administered in cycles, which allow the patients to recover between the treatment phases. The high rates of drug discontinuation, dose interruptions and reductions raises concerns regarding tolerability in the intended target population.

In conclusion, the sum of risks due to binimetinib's high toxicity needs to be balanced by an adequate clinically relevant benefit.

3.5. Risk management plan

Safety Specification

The applicant identified the following safety concerns in the RMP:

Table 23: Summary of the Safety Concerns as proposed by the applicant.

Summary of safety concerns	
Important identified risks	• Left ventricular dysfunction • Hypertension • Severe dermatologic reactions • Rhabdomyolysis • Hepatotoxicity • Retinal vein occlusion • Retinal pigment epithelial detachment • Venous thromboembolism • Haemorrhage
Important potential risks	• Pneumonitis/Interstitial lung disease • Reproductive toxicity • Over-exposure in patients with moderate to severe hepatic impairment

Summary of safety concerns	
Missing information	• Use in patients with reduced cardiac function (LVEF <50%) or symptomatic chronic heart failure • Use in paediatric population aged 12 to 17 years

Pharmacovigilance Plan

Table 24: Ongoing and planned studies in the PhV development plan

Activity / Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,	Date for submission of interim or final reports (planned or actual)
Paediatric clinical study ARRAY 162-115 A Multicenter, Open-label Phase 1b Study of the Combination of Binimetinib and Encorafenib in Adolescents with Unresectable or Metastatic BRAF V600-mutant Melanoma (other category)	*Establish safety, preliminary evidence of anti-tumour activity and appropriate dose in adolescents.*	*Use in paediatric population aged 12-17 years*	*Planned*	*Planned completion date Dec 2021, CSR June 2022.*
Hepatic impairment study: CMEK162A2104 (other catehory)	*Evaluate safety, efficacy and appropriate dose in patients with moderate to severe hepatic impairment.*	*Over-exposure in patients with moderate to severe hepatic impairment*	*Completed*	*Final report: Q3 2017*
Renal impairment study: ARRAY-162-106 (other category)	*Evaluate safety, efficacy and appropriate dose in patients with severe renal impairment.*	*Use in patients with severe renal impairment*	*Completed*	*CSR: July 2017*

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

No studies (category 1-3) are being proposed by the applicant to address the product's safety concerns. The applicant presents three additional studies (classified as "other category"), as presented in the table above. These studies should be removed from the PhV plan, because only category 1-3 studies should be mentioned. Also, two of these "other category" studies are currently on the status "completed" which constitutes one additional reason to remove these studies from the pharmacovigilance plan, which should only include planned or ongoing studies. (OC)

Additionally, the applicant presents two paediatric studies in Part IV: Plans for post-authorisation efficacy studies, both part of the PIP approved in the assessment of the procedure EMEA-001454-PIP03-15. Considering that this section should contain only efficacy studies that are imposed as conditions to the MA or when included as specific obligations in the context of a conditional MA or a MA under exceptional circumstances, these studies should be removed from the RMP. (OC)

Risk minimisation measures for Mektovi

Table 25: Summary table of additional Risk Minimisation Measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Left ventricular dysfunction	Dose reduction and interruption recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PL section. Listed in Section 4.8 of the SmPC and relevant PL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products.	None
Hypertension	Dose reduction and interruption recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PL section. Listed in Section 4.8 of the SmPC and relevant PL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products.	None
Severe Dermatologic reactions	Dose reduction and interruption recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PL section. Listed in Section 4.8 of the SmPC and relevant PL section. Prescription only medicine. Treatment with binimetinib	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products.	
Rhabdomyolysis	Dose reduction and interruption recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PL section. Listed in Section 4.8 of the SmPC and relevant PL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products.	None
Hepatotoxicity	Dose reduction and interruption recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PL section. Listed in Section 4.8 of the SmPC and relevant PL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products.	None
Retinal vein occlusion	Discontinuation is recommended in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PL section. Listed in Section 4.8 of the SmPC and relevant PL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products.	None
Retinal pigment Epithelial detachment	Dose reduction and interruption recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PL section. Listed in Section 4.8 of the SmPC and relevant PL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products.	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Venous thromboembolism	Dose reduction and interruption recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PL section. Listed in Section 4.8 of the SmPC and relevant PL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products.	None
Haemorrhage	Dose reduction and interruption recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PL section. Listed in Section 4.8 of the SmPC and relevant PL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products.	None
Pneumonitis / Interstitial lung disease	Dose reduction and interruption recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PL section. Listed in Section 4.8 of the SmPC and relevant PL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products.	None
Reproductive toxicity	Warning in Section 4.6 of the SmPC and relevant PL section. Information provided in Section 5.3 of the SmPC. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products.	None
Over-exposure in patients with moderate to severe hepatic impairment	Dose reduction and interruption recommendations in Section 4.2 of the SmPC. Warning in Section 4.4 of the SmPC and relevant PL section. Information in Section 5.2 of the SmPC. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	responsibility of a physician experienced in the use of anticancer medicinal products.	
Use in patients with reduced cardiac function (<50%) or symptomatic chronic cardiac failure	Warning in Section 4.4 of the SmPC and relevant PL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products.	None
Use in paediatric population aged 12 to 17 years	Addressed in Section 4.2 of the SmPC and relevant PL section. Prescription only medicine. Treatment with binimetinib should be initiated and supervised under the responsibility of a physician experienced in the use of anticancer medicinal products.	None

The applicant proposes routine risk minimisation measures to address the product's safety specifications, which is considered acceptable.

As requested in the previous step of the assessment, the applicant discussed the reinforcement of the routine risk minimisation measures related to retinal events. Thereafter, the applicant proposes to reinforce the warnings to be included in the SmPC with regards to the risk of retinal pigment epithelium detachment, recommending the assessment of symptoms of new or worsening visual disturbances and further ophthalmologic examination, if appropriate. Guidance is also being proposed for the management of patients that experience the occurrence of symptomatic RPED. Concerning the risk of retinal vein occlusion, the applicant proposes to strengthen the message on the search for predisposing factors for RVO before initiating treatment with binimetinib. It is also proposed not to recommend binimetinib's use in patients with history of RVO.

Additionally, the applicant proposes the inclusion of a warning statement in the SmPC with regard to risk factors for myopathy/rhabdomyolysis, which is acceptable. However, the use of concomitant medications (such as statins) that are known to be associated with a higher post-baseline fraction of patients with grade 4 CK elevation was not considered. (OC)

PRAC outcome

The PRAC discussed the RMP aspects of the Mektovi D150 joint AR, during its November 2017 plenary meeting.

The PRAC fully endorsed the PRAC rapporteur's assessment of the applicant's responses to the D120 LoQ for the RMP aspects and the proposed LoOIs.

The PRAC endorsed the following points:

-the planned paediatric study and both the completed "Hepatic impairment study" and "Renal impairment study" should be removed from the pharmacovigilance plan, and

-the risk factors for rhabdomyolysis should be further characterised in the SmPC.

As a conclusion, the PRAC considered by consensus that the Mektovi RMP version 0.2 could be acceptable if all other concerns related to the RMP listed in section 6 are adequately resolved by the applicant.

Public summary of the RMP

The public summary of the RMP may require revision.

3.6. Pharmacovigilance system

The CHMP considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

4. Orphan medicinal products

N/A

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

The proposed indication for Mektovi is:

Mektovi monotherapy is indicated for the treatment of adult patients with unresectable or metastatic melanoma with NRAS Q61 mutation.

Malignant melanoma is the 19th most common cancer worldwide, with around 232,000 new cases (2% of the total) diagnosed in 2012 (Ferlay, 2013; Ferlay, 2015). Malignant melanoma is the ninth most common cancer in Europe, with more than 100,000 new cases (3% of the total) diagnosed in 2012 (Skin cancer incidence statistics). The European incidence of malignant melanoma varies from 3 to 5/100 000/year in Mediterranean countries to 12–25 (and rising) in Nordic countries.

Approximately 20% of patients with unresectable or metastatic melanoma have NRAS-mutation positive tumours; of these, substitutions at position Q61 of exon 2 account for approximately 90% of NRAS mutations (Jakob et al 2012; Colombino et al 2012; Lee et al 2011; Bucheit et al 2013). Metastatic melanoma patients with an NRAS mutation may represent a distinct clinical subset of melanoma with a more aggressive clinical course and shorter survival compared to wild-type and v-raf murine sarcoma viral oncogene homolog B1 (BRAF)-mutation positive melanoma (Devitt et al 2011; Eggermont and Robert 2011; Jakob et al 2012).

5.1.2. Available therapies and unmet medical need

In Europe, mutation testing for treatable mutations is mandatory in patients with advanced disease (unresectable stage III or stage IV), and highly recommended in high-risk resected disease (stage IIc, stage IIIb–IIIc). Tumour tissues, preferentially of metastatic lesions, should be screened for mutations of BRAF V600. If the melanoma is negative for BRAF V600 then further molecular testing can be

carried out for NRAS, c-Kit (mucosal and acrolentigenous primaries) GNA11 or GNAQ (uveal primary); this helps to direct patients to the appropriate targeted treatment or clinical trial. (*ref: Dummer et al, ESMO guidelines, 2015*).

No therapies have been approved in the EU specifically for patients with *NRAS* mutation-positive melanoma. Inadequate justification has been provided to claim that binimetinib fulfils an unmet medical need in these patients.

In the absence of a specific targeted treatment, *NRAS*-mutated melanoma is generally managed as *BRAF* wild-type disease. In patients with BRAF-wild-type (wt) disease, ipilimumab has been the standard treatment based on a survival benefit with a ~10% higher survival rate at 1, 2 and 3 years. Based on very recent randomised trial results, comparing anti-PD1 antibody therapies to ipilimumab, anti-PD1 antibody therapy is the preferred first-line treatment of patients with BRAF-wt disease. Anti-PD-1 therapies are also recommended as a second-line treatment, after ipilimumab failure.

5.1.3. Main clinical studies

Study CMEK162A2301 (the NEMO trial) provides the primary data for clinical efficacy claims for binimetinib in the treatment of unresectable or metastatic NRAS mutation-positive melanoma. Supportive efficacy data for the proposed indication are derived from study CMEK162X2201.

The NEMO trial (NRAS melanoma and MEK inhibitor) is a randomized Phase III, open label, multicentre, two-arm study comparing the efficacy of MEK162 (binimetinib) versus dacarbazine in patients with advanced unresectable or metastatic NRAS mutation-positive melanoma.

5.2. Favourable effects

Both, the pivotal CMEK162A2301 study and the supportive phase II CMEK162X2201 study show evidence of activity for binimetinib in a patient population with NRAS mutation positive melanoma. There is a statistically significant although numerically small prolongation of the progression free survival, compared to dacarbazine chemotherapy, shown in the pivotal trial. There is also a higher overall response rate seen with binimetinib in the pivotal trial and the results are in line with the ORR seen in the phase II trial.

The results of the primary analysis for PFS are supported by further ancillary analyses and sub-group analyses carried out for PFS.

Considering the options currently used in the treatment of the patients and possible detrimental effect in overall survival, the by 1.3-month prolonged median PFS compared to dacarbazine chemotherapy and an ORR of 15.2% for binimetinib, is of questionable clinical benefit.

5.3. Uncertainties and limitations about favourable effects

Though prolonged PFS has been seen with binimetinib compared to dacarbazine, the median is prolonged by only 1.32 months. This does not translate into an improvement in overall survival in the results presented. From the most recent OS analysis provided the curves cross over at around 12 months and may suggest a detrimental effect. Further the median overall survival seen in the dacarbazine arm of 10.09 months in the comparator arm is greater than that expected with dacarbazine treatment, provided one would expect that the subtype (NRAS positive) of advanced/ metastatic melanoma has a poorer prognosis than BRAF wild type, or according to mutations not selected tumours.

The improvement in PFS and the results showing tumour response also do not translate into an improvement in QoL or ECOG PS. On the contrary, QoL are not assessable but the ECOG performance scores show deterioration soon after starting treatment with binimetinib. Thus, the higher proportion of deterioration in the ECOG PS in the binimetinib arm compared to the dacarbazine arm is a concern and raises issues regarding the tolerability of binimetinib in the proposed population.

Further updated analyses for PFS, OS, ECOG PS (in terms of DFS) change measurement and for duration of response were requested. Updated results for PFS and ORR were provided from the cut-off date of the 16th of March 2016. These show results similar to that of the primary analysis. Results concerning DFS support the view that binimetinib deteriorates the clinical performance soon (and more dramatically compared to dacarbazine) after start of treatment.

. As discussed previously, this sub-group of patients are treated with other agents used to treat BRAF-wild type melanoma. These include ipilimumab and anti-PD1 therapies. Though not directly compared with binimetinib, the outcomes with these agents in the treatment of BRAF-wild-type melanoma appear better that the outcome with binimetinib in NRAS mutation positive melanoma. Hence, the claim that an unmet medical need in NRAS mutation positive melanoma is fulfilled by binimetinib, is not supported.

5.4. Unfavourable effects

The overall safety profile of binimetinib is consistent with the known safety profile of other drugs in this class. However, the incidence of some of these expected ADRs are higher than that seen with our drugs in this class.

The safety profile of binimetinib as monotherapy was consistent across the different safety sets (Broad set, restricted set (target population) and the pivotal trial MEK162A2301):

Myopathy / Elevation of CK values, skin events, ocular toxicities, hepatotoxicity and cardiac toxicities were the most prominent and dose limiting events.

In addition, there occurred hypertension events, haemorrhage events, oedema events, pneumonitis events and thrombotic events.

In summary binimetinib as monotherapy appears to be **less well tolerated compared with chemotherapy (dacarbazine)** as observed by the increased incidence of AEs (100% vs 91%, respectively), grade≥ 3 AEs (68% vs 46%), AEs leading to dose reduction (70% vs 36%), AEs requiring additional therapy (95% vs 64%) and **AEs leading to treatment discontinuation** (25% vs 8%), **serious advere events** (33.8% vs 27.5%) and **incidence of on-treatment-deaths** (8.6% vs 2.6%).

The PT of **general physical health deterioration** was reported most frequently as a SAE in the binimetinib arm (4.5% with 4.1% G3/4 vs 0 %).

The median duration of exposure to binimetinib was short (12.6 weeks); however, longer than in the median duration of exposure to dacarbazine (9.0 weeks). Study drug exposure was similar across all binimetinib-treated populations, with a median duration of exposure of 12.7 weeks in the all melanoma (binimetinib 45 mg) population and 12.0 weeks in the all cancers (binimetinib any dose) population. In the all melanoma (binimetinib 45 mg) population, 97 (22.7%) were exposed for ≥ 24 weeks and 15 (3.5%) were exposed for ≥ 48 weeks.

Myopathy events were very commonly reported (49.4% in the binimetinib of the pivotal trial) and **elevation of blood CK** was a very frequent laboratory finding (76.2% in the binimetinib arm of the

pivotal trial; in 20.8% of the cases grade ¾). In addition, 2 cases of rhabdomyolysis were reported in the Broad safety set. The median time of onset was 1.3 month.

Hepatic events were reported in around 19% of patients treated with binimetinib monotherapy compared with 10% in the dacarbazine arm. Increased ALT (8%) and AST (13%) were the most frequently reported hepatic events. Liver events were reported as SAEs in Study CMEK162A2301 for 1.1% of patients in the binimetinib arm, including events under the PTs of ALT increased, AST increased, ascites and hepatic failure (0.4% of patients each) and no patients in the dacarbazine arm

Cardiac related events, including reduction of ejection fraction and left ventricular dysfunction, were observed in 13% in the binimetinib arm compared to 1.8 % under dacarbazine therapy. 4.8% of the described cases in the binimetinib arm were grade ¾ toxicities, 4.5% of cases were leading to a discontinuation of therapy; in 6.7% a dose interruption or a dose adjustment was required. The median time of onset was 1.4 month.

Skin-related "rash" events were observed in 81.4 % of patients treated with binmetinib monotherapy compared with 3.5% of patients treated with dacarbazine in the pivotal trial (MEK162A2301). Most cases were grade 1 or 2 severity but 68% were requiring additional therapy. The median time of onset was 0.4 month.

Dermatologic "non-rash" events occurred in 42.4% of patients in the binimetinib arm and 8.8% of patients in the chemotherapy arm. The median time of onset of this toxicity was 1.4 month, additional therapy was required in 24%. In addition, approx. 25% of the patients showed - often secondary to other dermatologic events- a skin infection; 3.3% of these events were resulting in hospitalization. Furthermore, a photosensitivity reaction occurred in 1.5 % of the patients and was identified also as s a relevant toxicity of binimetinib in the non-clinical trials.

Retinal events (RPED) were observed in 33% of patients treated with binimetinib monotherapy and led to dose interruptions 10% of cases. **Visual impairment** occurred in 14.5%. Both events did not occur in the darcabazine arm. Grade 3/4 events were observed only in 1.1% of patients. Most events occurred in the early treatment and were transient, self-limiting and reversible. But in addition vascular events (RVO as a potentially sight-threatening event) were observed in 2.2% of the patients in the binimetinib arm.

Uncertainties and limitations about unfavourable effects

Missing information regarding safety includes information regarding use in patients with reduced cardiac function (LVEF <50%) or symptomatic chronic heart failure; safety in patients with severe renal impairment; safety in patients with severe hepatic impairment and safety in paediatric population (children less than 18 years).

The PT of **general physical health deterioration** was reported most frequently (> 2.0% of patients) as a SAE in the binimetinib arm. Although it is acknowledged that of the 17 binimetinib patients who had an SAE under the PT of general physical health deterioration, 11 patients experienced this SAE within days of declaration of PD and 2 patients died within days of this event, it seems to be very clear that the multiplicity of toxicities of binimetinib nevertheless had a significant negative impact on the patients' (physical) health: The efficacy endpoint ECOG PS (reported in the CSR as a safety endpoint) shows that the proportion of patients with a definitive 1-point deterioration in ECOG PS was higher in the binimetinib compared with the dacarbazine arm (30.9% vs. 11.4%). Please note that a definitive 1-point deterioration in the ECOG PS was considerably more frequent than a general physical health

deterioration reported as a SAE (for example, 30.9% and >2% in the binimetinib arm). Therefore the former is considered as the more sensitive (efficacy and) safety endpoint.

Increases of CK, ALT/AST and creatinine, all reflecting rhabdomyolysis as well as hepatotoxicity, were reported as very common biochemistry abnormalities in the binimetinib arm of Study CMEK162A2301 and in the other safety populations defined.

As a concerning deterioration of **left ventricular function** was observed and heart muscle cell damage may be masked by the increases of CK due to rhabdomyolysis, the applicant is requested to provide the analysis of the CK isoenzymes and troponin results. Moreover, it needs to be clarified whether the observed reduced LVEF was reversible after drug discontinuation or dose reduction of binimetinib. Additionally, regarding all subgroups with special cardiac risks, reported uncertainties due to the restricted number of patients investigated have to be considered. The applicant is requested to add a contraindication for Binimetinib in patients with a reduced LVEF under 50% or the institutional LLN and with severe hypertension.

Although the applicant has provided adequate analyses and descriptions of the **liver chemistry abnormalities** it seems difficult due to identify so called “Hy’s law” in the population investigated due to the complex situation in the severely ill target population. The details provided show at least one patient who developed severe liver toxicity following treatment, which highlights the intrinsic hepatotoxicity especially in patients with hepatic impairment. The dose recommendations in patients with hepatic impairment need further revision.

As the high degree of **cutaneous adverse events** may predispose patients for infectious complication finally leading to sepsis and on the other hand sepsis was an important reason for death, the applicant is requested to provide an analysis regarding the impact of dermatological infections and particular concomitant treatment of dermatological adverse event with corticosteroids was associated with the occurrence of systemic infections/sepsis in patients who died on-treatment.

5.5. Effects Table

Table 24: Effects Table for Mektovi (data cut-off: 24th August 2015).

Effect	Short Description	Treatment	Control	Uncertainties / Strength of evidence
Favourable Effects				
PFS	1.32 month improvement in median PFS Hazard ration: 0.62 (0.47, 0.80) p-value: <0.001	Binimetinib	Dacarbazine	No improvement in overall survival. 1.32-month improvement in PFS is in comparison to dacarbazine, but needs to be discussed in the context of a) other available agents currently used to treat the NRAS mutation positive melanoma b) no beneficial effect on OS c) prolonged progression free survival translated into shortened deterioration free survival.
Unfavourable Effects				

Effect	Short Description	Treatment	Control	Uncertainties / Strength of evidence	
	Deterioration in ECOG Performance status	Binimetinib	Dacarbazine	Favours the dacarbazine arm	
	Left ventricular dysfunction- 10%				
	Hypertension- 16%				
	RPED and RVO- 13%				
	Skin reactions- 44%				
	Muscular toxicity- CK level increase, -43.3%. One instance of frank rhabdomyolysis.				
	Liver toxicity- liver enzyme increase- 13.6%				
	GI toxicity Diarrhoea- 43% Nausea: 30% Vomiting: 20%				
	VTE: 4.2%				

5.6. Benefit-risk assessment and discussion

5.6.1. Importance of favourable and unfavourable effects

There are no agents approved specifically for the treatment of NRAS mutation positive melanoma, but there are effective treatment options currently available used to treat melanoma in general, and BRAF wild type in specific. The availability of an effective targeted agent specifically for this population of patients may be useful. However, there is insufficient evidence to justify that binimetinib fulfils an unmet medical need in these patients.

An improvement in PFS is considered relevant to the efficacy. However, the magnitude of improvement in PFS demonstrated in the pivotal study, i.e, 1.3-months is not considered clinically relevant on its own. The non-translation of the, by amount small, prolonged PFS, into an OS benefit is considered a critical issue. There is also a concern about a possible detrimental effect in the longer course of the disease (i.e. post progression, thus, eventually a detrimental effect on post progression therapy). Similarly, the detrimental effect on ECOG PS in the binimetinib arm, which does not correlate with the observed tumour responses - rather, contradicts (or is negatively correlated with) the PFS (assuming that progression is accompanied by a deterioration of health) result - and the observed safety results, raises issues regarding the tolerability of binimetinib in the proposed patient population.

Further, it is remarkable that the targeted treatment (binimetinib) is associated with a less favourable safety profile than the non-targeted chemotherapy (dacarbazine). It has to be kept in mind that, while

occurrence and severity of toxicity from chemotherapy has a cyclic character, binimetinib treatment is to be taken on a daily basis without cyclic relief.

The safety risks are reflected by the pronounced differences observed concerning the high rates for cardiotoxic adverse events (reduction in LVF early during treatment), rhabdomyolysis and skin events, as well as by a high degree of hepatotoxicity with a case of fatal liver failure during the clinical development. All these toxicities are very important and potentially life-threatening. As these toxicities were already observed early during the first 12 weeks of treatment and frequencies of AE occurrence increase significantly over this time, it remains uncertain at present whether binimetinib can be really tolerated from the target population for longer periods than currently evaluable. The high discontinuation and dose-reduction rate reported allows doubting this.

Beside other minor relevant and probably manageable risks (e.g. gastrointestinal AEs, hypoalbuminemia, oedema and others) the pronounced retinal toxicity is seen as an important concern, because it adheres to a clinical relevant risk for blinding. Even in an advance cancer population this is seen as an additional important burden for the patients, which seemed to be probably hardly tolerable with the expectation of a by 1, or 1.3-month prolonged duration to BIRC, but not patient, assessed PFS only

5.6.2. Balance of benefits and risks

The currently observed 1.32-month prolongation in median PFS over dacarbazine, without an improvement in overall survival is not considered sufficient evidence of benefit in the proposed patient population. The observed benefit does not override concerns regarding the tolerability of binimetinib in the proposed patient population and the possible negative impact on the health (+/- quality of life) of these patients.

5.6.3. Additional considerations on the benefit-risk balance

Currently there are other agents used to treat the proposed patient population. These are agents approved to treat BRAF-wild type melanoma and include ipilimumab, anti-PD1 therapies as well as their combinations and sequences in terms of lines.

In patients with BRAF-wild-type (wt) disease, ipilimumab has been the standard treatment based on a survival benefit with a ~10% higher survival rate at 1, 2 and 3 years. Based on very recent randomised trial results, comparing anti-PD1 antibody therapies to ipilimumab, anti-PD1 antibody therapy is the preferred first-line treatment of patients with BRAF-wt disease. These therapies also demonstrate efficacy for patients with BRAF mutations. Anti-PD1 therapies are also recommended as a second-line treatment, after ipilimumab failure. The anti-PD1 antibody nivolumab was compared with the reference chemotherapy dacarbazine in a double-blind randomised clinical trial with BRAF-wt patients. This trial showed a 1-year survival rate of 72.9% in the nivolumab group, compared with 42.1% in the dacarbazine group (HR for death, 0.42; P < 0.001). Opdivo and Keytruda were approved for treatment of advanced melanoma in the EU on 19 June 2015 and 17 July 2015, respectively.

5.7. Conclusions

The overall B/R of Mektovi in the proposed indication is considered negative.

Recommended conditions for marketing authorisation and product information

5.8. Conditions for the marketing authorisation

5.9. Summary of product characteristics (SmPC)

Attached separately

5.10. Labelling

Attached separately

5.11. Package leaflet (PL)

Attached separately

User consultation

Assessors comment Day 150:

Readability assessment (14 questions) was performed in November 2016 with the package leaflet proposed at initial submission. Following Day 120, an updated package leaflet was subjected to further focused assessment (5 questions) of those aspects that had been amended.

Both user tests passed the success criteria of 90 % of the subjects being able to locate the requested information, and of those, 90 % being able to give the correct answer in accordance with the Readability Guideline. Together with a justification for bridging the updated package leaflet to the original that was the subject of full user testing, the readability of the package leaflet is considered to have been acceptably demonstrated.

Further details are given in the annex attached