European (EU) Risk Management Plan (RMP) for EZMEKLY (mirdametinib)

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EU Qualified Person for Pharmacovigilance (EU QPPV)

EU QPPV name	Dr Eric Caugant
Electronic Signature:	*EU QPPV Oversight Declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.*

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

Table 1: List of Abbreviations

Abbreviation or Term	Definition/Explanation
ADR	Adverse drug reaction
AE	Adverse event
AESI	Adverse event of special interest
AKI	Acute kidney injury
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC Code	Anatomical therapeutic chemical Code
AUC	Area under the curve
BCRP	Breast cancer resistance protein
BID	Twice Daily
BMI	Body mass index
BRAF	v-Raf murine sarcoma viral oncogene homolog B
BSA	Body Surface Area
CES	Carboxylesterases
CIOMS	Council for International Organizations of Medical Sciences
CK	Creatine kinase
CLint	Intrinsic clearance
Cmaxss,u	Unbound steady-state maximum concentration
CNS	Central nervous system
CPK	Creatine phosphokinase

Abbreviation or Term	Definition/Explanation
CrCl	Creatinine clearance
CSR	Clinical study report
CUP	Compassionate use programme
CYP	Cytochrome P450
DDI	Drug-drug interactions
DILI	Drug Induced Liver Injury
ECG	Electrocardiogram
EEA	European Economic Area
EFD	Embryo-foetal development
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ERK	Extracellular regulated kinases
ERK1	Extracellular regulated kinase 1
ERK1/2	Extracellular regulated kinase 1 and Extracellular regulated kinase 2
ERK2	Extracellular regulated kinase 2
EC	European Commission
EU	European Union
GI	Gastrointestinal
GLP	Good Laboratory Practice
HEK	Human Embryonic Kidney
HEK293	Human Embryonic Kidney (HEK) 293 cell line
hERG	Human ether-a-go-go related gene
HIV	Human immunodeficiency virus

Abbreviation or Term	Definition/Explanation
IC50	Half-maximal inhibitory concentration
IIR	Investigator initiated research
INN	International non-proprietary name
IV	Intravenous
KRAS	Kirsten rat sarcoma virus protein homolog
L	Litre
LOAEL	Lowest observed adverse effect level
LVEF	Left ventricular ejection fraction
m	Metre
MAA	Marketing Authorisation Application
MAP	Mitogen-activated protein
MAPK	Mitogen-activated protein kinase
MATE1	Multidrug and toxin extrusion protein 1
MATE2K	Multidrug and toxin extrusion protein 2K
MDCK	Madin-Darby canine kidney
MDR1	Multi drug resistance mutation 1
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase kinase
MEK1/2	Mitogen-activated protein kinase kinases 1 and 2
MEKAR	Mitogen-activated protein kinase inhibitor-associated retinopathy
mg	Milligram
mL	Millilitre
MPNST	Malignant peripheral nerve sheath tumour

Abbreviation or Term	Definition/Explanation
MPP	1-methyl-4-phenylpyridinium
MTD	Maximum tolerated dose
NADPH	Nicotinamide adenine dinucleotide phosphate
NF1	Neurofibromatosis type 1
ng	Nanogram
NOAEL	No observed adverse effect level
OD	Right eye
OS	Left eye
OU	Both eyes
PASS	Post Authorisation Safety Study
PD-0325901	Mirdametinib
pERK	phospho-extracellular signal-regulated kinase
pERK 1/2	phospho-extracellular signal-regulated kinases 1/2
P-gp	P-glycoprotein
PIL	Package leaflet: Information for the patient
PK	Pharmacokinetics
PN	Plexiform Neurofibromas
popPK	Population pharmacokinetics
PRAC	Pharmacovigilance Risk Assessment Committee
PR	Partial response
PT	MedDRA Preferred term
PTH	Parathyroid hormone
QD	Once Daily

Abbreviation or Term	Definition/Explanation
QTc	Corrected QT interval
RAF-MEK-ERK	Rapidly accelerated fibrosarcoma (RAF)/mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK)
RAS	Rat sarcoma virus protein
RMP	Risk Management Plan
RPE	Retinal pigment epithelium
RPED	Retinal pigment epithelium detachment
RVO	Retinal vein occlusion
SAE	Serious adverse events
SAWP	Scientific Advice Working Party
SmPC	Summary of Product Characteristics
SMQ	Standardised Medical Dictionary for Regulatory Activities Queries
SOC	System organ class
SRD	Serous retinal detachments
StD	Standard deviation
TEAE	Treatment emergent adverse event
TK	Toxicokinetics
U	Units
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal
UV	Ultraviolet
WBC	White blood cells

Part I: PRODUCTS OVERVIEW

Table 2: Part I.1 Product Overview

Product Overview	
Active substance(s) (international nonproprietary name [INN] or common name)	Mirdametinib
Pharmacotherapeutic group(s) (anatomical therapeutic chemical [ATC] Code)	Antineoplastic agent; Mitogen-activated protein kinase (MEK) inhibitors ATC Code: L01EE05
Marketing Authorisation Applicant	SpringWorks Therapeutics Ireland Limited
Medicinal products to which this RMP refers	1
INVENTED NAME(s)	EZMEKLY
Brief Description of Product	Chemical class Mirdametinib is a selective, non-competitive inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2).
	Summary of mode of action Mirdametinib is a selective, non-competitive inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK1/2). Mirdametinib blocks MEK activity and the rat sarcoma (RAS)-rapidly accelerated fibrosarcoma (RAF)-MEK pathway. Therefore, MEK inhibition blocks proliferation and survival of tumour cells in which the RAF-MEK-extracellular related kinase (ERK) pathway is activated.
	Important information about its composition: None of relevance
Hyperlink to the Product Information	EZMEKLY SmPC
Indication(s) in the EEA	Current: EZMEKLY as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in

Product Overview	
	paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above.
	Proposed: Not applicable
Dosage	Adult and paediatric patients 2 years of age and above: Current: The recommended dose of EZMEKLY is 2 mg/m^2 of body surface area (BSA) twice daily (approximately every 12 hours) for the first 21 days of each 28-day cycle. The maximum dose is 4 mg twice daily. For paediatric patients 2 to <6 years of age and for patients who are unable to swallow capsules whole, Ezmekly is also available as a 1-mg dispersible tablet formulation that can be dispersed in water. Ezmekly oral suspension can also be administered via an enteral feeding tube. The recommended dose for patients with a BSA less than 0.40 m^2 has not been established.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Hard capsule: 1 mg hard capsules • Size 3 (approximately 16 mm × 6 mm) capsule comprised of a light green opaque body and cap with 'MIR 1 mg' printed in white ink on the cap. 2 mg hard capsules • Size 1 (approximately 19 mm × 7 mm) capsule comprised of a white opaque body and a blue-green opaque cap with 'MIR 2 mg' printed in white ink on the cap. Dispersible Tablet: 1 mg tablets • Oval, white to off-white tablets 6 × 9 mm diameter, debossed with 'S' on one side.
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: SAFETY SPECIFICATION

Part II: MODULE SI - Epidemiology of the indications and target population

Indication

EZMEKLY as monotherapy is indicated for the treatment of symptomatic, inoperable plexiform neurofibromas (PN) in paediatric and adult patients with neurofibromatosis type 1 (NF1) aged 2 years and above.

Incidence

NF1 is an autosomal dominant genetic disorder (Lee 2023) with a birth incidence of approximately 1 in 2,500 individuals (Children's Tumor Foundation 2023). Whilst data concerning the incidence of NF1 in the EU is limited, studies including patients with NF1 in England and Finland have proposed a birth incidence of approximately 1 in 2,000 to 1 in 3,000 (Evans 2010, Uusitalo 2015).

Prevalence

PNs are one of the most prevalent and impactful clinical manifestations of NF1, occurring in up to 50% of patients with NF1 (Choi 2022). While limited data concerning the prevalence of NF1 in the EU are available, a systematic review of patients with NF1 including those residing in the United Kingdom, Sweden, Finland, Israel, Germany, Italy, and Cuba has proposed a prevalence of 3.16 per 10,000 persons (Lee 2023).

Demographics of the population in the proposed indication

There are no known ethnic groups in which NF1 does not occur or is unusually common. The prevalence is somewhat higher in young children than in adults (Friedman 1999). In a Danish study, approximately 81% of patients with NF1 PN were adults while 19% were paediatric (Ejerskov 2023). There is no predilection for the male or female gender (Adil 2023).

The main existing treatment options

The approach to treatment of the various tumours associated with NF1 depends upon the type of tumour, its effect on adjacent tissues, and related complications. PNs usually involve multiple nerve fascicles, with serpiginous growth and significant vascularity. These lesions can be a significant challenge in surgical treatment and pain management, especially with progressive growth along the spinal column that may result in compression of the spinal cord (Gold 2013).

The optimal management of these complex lesions is unclear. Surgical resection is an option, and for large lesions, the main goal is to partially restore the normal appearance and function of the affected part and to ameliorate pain, when possible (Canavese 2011). However, up to 44% of tumours progress after the first surgery, most commonly in patients younger than ten years of age, with head and neck tumours that could not be completely resected (Needle 1997). Surgical resection often is limited to debulking of a specific area of a large lesion, for example,

when a component is impinging on the spinal cord or airway, or a large soft tissue component is removed to improve cosmesis. Various systemic therapies have been studied in patients with NF1 PN. Clinical trials in patients with NF1 PN with pegylated interferon alfa-2b (Jakacki 2017), the farnesyl transferase inhibitor tipifarnib (Widemann 2014), the mammalian target of rapamycin (mTOR) inhibitor sirolimus (Weiss 2014, Weiss 2015), and the fibroblast inhibitor pirfenidone (Widemann 2014b) have not demonstrated sufficient benefit to warrant clinical use.

Administration of the mitogen-activated protein kinase kinase (MEK) inhibitors trametinib and binimetinib as well as the tyrosine kinase inhibitors (TKI) imatinib (Robertson 2012) and cabozantinib (Fisher 2021) have resulted in shrinkage of PNs in a limited number of patients with NF1 PN, but tolerability challenges limited long term administrations. There is only one systemic treatment option approved for patients with NF1 PN: selumetinib (Koselugo® SmPC). In Europe, Koselugo obtained a conditional approval on 17Jun2021 for children aged 3 years and older. There are currently no approved treatments of NF1 PN in adults or children under 3 years of age in Europe.

Natural history of the indicated condition in the untreated population, including mortality and morbidity

Neurofibromatosis (NF) is classified into three major clinically and genetically distinct forms: NF type 1 (NF1), NF type 2 (NF2), and schwannomatosis. NF1, also known as von Recklinghausen disease, is the most common form of neurofibromatosis.

Approximately one-half of cases are inherited with the remainder being the result of de novo mutations in the *NF1* tumour suppressor gene, located at chromosome 17q11.2 (Evans 2010, Ledbetter 1989, Feldkamp 1998). NF1 is characterised by diverse, progressive cutaneous, neurological, skeletal, and neoplastic manifestations. The manifestation of the NF1 clinical diagnostic criteria typically appear in the order of café-au-lait macules, axillary and/or inguinal freckling, Lisch nodules (iris hamartomas), and finally neurofibromas (DeBella 2000). Most importantly, patients with NF1 develop both benign and malignant tumours at increased frequency throughout life (Gutmann 1997, Seminog 2013). Neurofibromas are non-malignant peripheral nerve sheath tumours that are a benign tumour composed of Schwann cells (the presumptive tumour progenitor), fibroblasts, endothelial cells, mast cells, and sometimes perineurial cells (Tucker 2011).

PNs are one of the most prevalent and impactful clinical manifestations of NF1, occurring in up to 50% of patients with NF1 (Choi 2022). PNs are multicellular tumours composed of tumorigenic Schwann cells, fibroblasts, perineural cells, macrophages, mast cells and secreted collagen. These tumours arise within nerves, grow rapidly during childhood and can lead to motor and sensory dysfunction, pain, and disfigurement in as many as 40% of patients with NF1. PNs can be life threatening when impinging on vital structures (such as the airway or spinal cord) and are associated with a 10-15% risk of transformation to malignant peripheral nerve sheath tumours (MPNST), an aggressive and often fatal sarcoma (Fisher 2021). Spontaneous PN shrinkage over time has been reported in some individuals, but mainly in

adults. Importantly, spontaneous PN volume decreases ≥20% per year have not been reported. They are a significant cause of morbidity (Fisher 2022).

Persons with NF1 appear to have a decrease in life expectancy of about 15 years compared with the general population, often due to soft tissue neoplasms or vascular disease (Rasmussen 2001).

Important co-morbidities

As tumour growth progresses, lesions produce dysfunction, pain, and cosmetic disfigurement and can compress vital structures such as the airway or spinal cord. Furthermore, PNs have the potential to undergo malignant transformation into malignant peripheral nerve sheath tumours (MPNSTs), which occur in an estimated 8-13% of patients with NF1 (Evans 2002, Hirbe 2014). MPNSTs are aggressive tumours that can metastasize, with a 5-year survival rate of 21-32% among patients with NF1 (Evans 2002, Porter 2009).

Part II: MODULE SII - Nonclinical part of the safety specification

The nonclinical safety profile of mirdametinib was evaluated in a series of exploratory toxicity studies in rats, dogs, and monkeys, with the definitive GLP studies conducted in rats and dogs based on mirdametinib's pharmacokinetic (PK) and metabolism properties compared across species. Studies were based on daily oral (gavage) dosing with a limited number of studies involving intravenous (IV) administration. Mirdametinib was administered to rats and dogs in repeat dose general toxicology studies up to 3 months in duration. A recovery period was assessed in the pivotal 1-month studies. Due to the toxicities observed in the 3-month studies at exposures below the predicted human efficacious exposure of mirdametinib, the 6-month rat and the 9-month dog studies were not conducted, as these studies would not provide any additional meaningful data. In addition, the long duration of treatment in the clinical programme suggests that the safety profile of mirdametinib is acceptable over longer term use (Part II: MODULE SIII - Clinical trial exposure), thus a long-term nonclinical repeat dose is unnecessary.

A 1-month mouse study was conducted to support a 6-month carcinogenicity study in transgenic mice. Embryo-foetal developmental (EFD) toxicity studies were conducted in rats and rabbits, and a fertility study was conducted in male and female rats. Due to severe embryotoxicity observed in the preliminary studies with mirdametinib and the dependency of MEK for normal development, neither definitive embryo-foetal development studies in rats and rabbits, nor pre- and post-natal development study in rats were conducted with mirdametinib. Similarly, juvenile animal studies were not conducted. An in vitro phototoxicity study and an in vivo chemical impurities study in rats were also conducted.

Safety pharmacology studies with mirdametinib assessed potential cardiac effects in Good Laboratory Practice (GLP) compliant in vitro human ether-à-go-go-related gene (hERG) and Purkinje fibre assays. GLP-compliant in vivo safety pharmacology studies were conducted in rats to assess central nervous system (CNS) and respiratory effects, and in telemetered monkeys to evaluate cardiovascular effects.

Two major metabolites of mirdametinib were identified and the PD effects of these metabolites were studied. PD-0315209 is the carboxylic acid metabolite of mirdametinib and showed similar potency as mirdametinib when assayed against purified MEK1, however it was shown to be significantly less potent than mirdametinib at reducing pERK in tumour cells. An in vivo evaluation in mice showed that PD-0315209 transiently suppressed pERK. PD-0315209 concentrations associated with target suppression and biological activity far exceed concentrations achieved following administration of mirdametinib at the clinical dose of 2 mg/m^2 BID. Therefore, it is not expected that PD-0315209 contributes significantly to the pharmacological activity of mirdametinib. PD-0315209 is considered to have negligible pharmacological activity when administered at the clinical dose of mirdametinib to patients with NF1 PN. The other metabolite, M22 (ASYM-130520), a secondary O-glucuronide, was assessed in an in vitro pERK assay and was found to be more than 100-fold less potent than the

parent mirdametinib. M22 is not expected to contribute to the pharmacological activity of mirdametinib.

The in vitro cytochrome P450 (CYP) inhibition and induction potential of mirdametinib was also evaluated, and mirdametinib was examined for in vitro effects on human drug transporters in cell lines expressing specific hepatic and renal transporters to guide drug interaction risk assessments. The metabolite PD-0315209 was tested in vitro in CYP inhibition and transporter studies. The potential of mirdametinib to inhibit UGTs was also evaluated.

Table 3: SII.1 Key Safety Findings from Nonclinical Studies and Relevance to Human Usage

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Safety Pharmacology Studies Conducted in in vitro systems and in rat and monkey. Summaries are presented below.	
Central Nervous System Two CNS studies in male Sprague-Dawley rats were conducted. Animals in one study were given a single oral dose of mirdametinib at 30 or 100 mg/kg. No treatment related effects were observed in grip strength, acoustic startle, catalepsy, hindlimb foot splay, analgesia, air-righting, or visual placing at 30 mg/kg. At 100 mg/kg, vertical movements and total distance covered decreased by 45% and 30%, respectively, at 24 hours post dose. Observational assessment at 100 mg/kg included salivation and red staining of the muzzle at approximately 1 and 24 hours post dose in 2 animals. The decreased locomotor activity at 100 mg/kg could not be differentiated between general toxicity and CNS effects. No CNS effects were observed at 30 mg/kg. Mirdametinib had no effect on corneal or pupillary reflexes. Dose dependent, although statistically nonsignificant, increase in failure in the inverted screen test was observed both at 1 and 24 hours post dose. In the second study the animals were given a single IV injection of mirdametinib at 30 or 150 mg/kg and did not show any CNS effects.	No safety findings relevant to human use were identified
Respiratory system In the respiratory study in male Sprague-Dawley rats, a single dose of mirdametinib was given by oral gavage at dose levels of 10, 30, or 100 mg/kg. No effects on respiratory rate or tidal volume were observed at 10 mg/kg dose. At 30 and 100 mg/kg, respiratory rate was increased and associated tidal volume was decreased. The changes in tidal volume were consistent with changes in respiratory rate.	No safety findings relevant to human use were identified.
Cardiovascular system (CV) In a monkey CV study, a single dose of vehicle or mirdametinib at 3 or 10 mg/kg was given by oral gavage using a 3-way crossover design with 7 days between treatments. Doses of mirdametinib up to 10 mg/kg had no effect on blood pressure, body temperature, heart rate, or any of the electrocardiography parameters including QT interval.	No safety findings relevant to human use were identified.

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
hERG assay An in vitro hERG study for mirdametinib and PD-0315209 was conducted at a nominal dose range of 10 mM to 100 µM. A reduction in hERG current amplitude was < 10% at 10 µM mirdametinib and not affected at 10 µM PD-0315209.	
Repeat Dose Toxicity Studies Conducted in mice, rat, dog, and monkeys. Target identified toxicities in these species are presented below.	
CNS Effects CNS effects were observed in the 3-month pivotal dog study in 4 high-dose dogs (2 males and 2 females treated at 0.4 mg/kg/day area under the curve [AUC values of 2910 and 2240 ng·h/mL in males and females, respectively]), with exposures approximately 1.4× that observed in humans. These 4 dogs were euthanized between Days 33 and 50 due to their moribund health status, with clinical signs of decreased activity, tremors, titubation/impaired balance, arched back associated with rigid extended limbs, and stiff neck and low head resulting in prostration. The treatment was suspended in the remaining animals given the high dose 0.4 mg/kg (1 male and 1 female) from Day 51 and 57, respectively. No CNS effects were observed in these surviving animals. The signs observed only in the euthanized moribund dogs were more likely a secondary effect due to pain within the tongue and oesophagus based on the inflammation noted in these tissues. There were no microscopic findings in the brains of these dogs nor in surviving animals. In shorter-term toxicology studies in dogs at higher doses (up to 1.5 mg/kg/day), there were no reported CNS effects. The brain was not evaluated microscopically in that study. In an oral dose-escalation dog study, the 1 male and the 1 female in the study were sacrificed in moribund condition after the 10 mg/kg dose. CNS effects were not present and the brain was not evaluated microscopically. CNS effects were not observed in the CNS safety pharmacology studies in rats (745-03552 and 745-03690) nor in the monkey studies (745-03694 and 745-03751) in which higher dose levels or higher exposures were tested (up to 30 mg/kg with $AUC_{(0-24)}$ approximately 21,000 ng·h/mL). There were no microscopic findings in the brains of the monkeys when evaluated in 1 of the studies.	The CNS is a potential target for human effects.
Skin Skin lesions were observed clinically at ≥0.1 mg/kg/day in the 1-month study and at 1.0 mg/kg/day in the 3-month pivotal study in rats. These lesions were microscopically characterised as epidermal ulceration. These changes were reversible following cessation of dosing. Similar skin lesions were observed in studies of mirdametinib in dogs, given 0.3 mg/kg/day for 1 month, and monkeys given 10 mg/kg/day for 2 weeks.	Skin and subcutaneous tissue disorders of Dry Skin, Alopecia, Pruritus, Eczema, Hair colour changes, Hair texture abnormal, Paronychia, Dermatitis acneiform, Rash, Rash maculo-papular, Rash pustular, Rash erythematous, Rash papular, Exfoliative rash, Papule, Rash

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
	macular and Rash pruritic are considered non-important identified risks for the mirdametinib risk management plan.
Intestine Gastrointestinal (GI) toxicity, characterised by erosion/ulceration of the mucosa was the dose-limiting toxicity in dogs and monkeys. Decreased goblet cells in the neck of colonic crypts occurred in rats at ≥ 3 mg/kg/day, and ulcers of the cecum and duodenum occurred in male rats at 30 mg/kg/day in a 2-week dose range-finding study. In the pivotal 3-month study, multifocal red discolouration of the oral mucosa occurred in dogs at 0.4 mg/kg, which correlated microscopically with superficial neutrophilic inflammation.	Gastrointestinal disorders of Diarrhoea, Abdominal Pain, Abdominal pain upper, Stomatitis, Mouth ulceration, Aphthous ulcer, Nausea, Vomiting, and Constipation are considered non-important identified risks for the mirdametinib risk management plan.
Eye In the pivotal 3-month study in rats, corneal opacities were detected mainly in males at all doses with the incidence being dose-dependent. Opacities were unilateral in occurrence at 0.1 mg/kg/day with a dose-dependent increase of bilateral opacities noted at ≥ 0.3 mg/kg/day. The fact that corneal opacities were detected almost exclusively in male rats in the 3-month study suggests that tissue mineral deposition was the likely cause. These effects are likely mediated by elevations in plasma 1,25-dihydroxyvitamin D levels that appear to be rat specific. In addition to focal corneal mineralisation in some males at 1.0 mg/kg/day, thinning or atrophy of the corneal epithelium was evident microscopically in both males and females at ≥ 0.3 mg/kg/day. There was no evidence of erosions, ulcerations, or inflammation of the corneal stroma. This histologic alteration may be secondary to effects on cell/keratinocyte turnover as a reflection of the pharmacology of the compound. The mechanism of this corneal toxicity is not fully identified. Corneal focal opacity was observed in dogs but was not considered treatment related in the study report.	These findings were primarily seen in male rats and thus no toxicity relevant to human use was identified.
Hepatic Effects In a 2 week dose range-finding study in rats, multifocal, coagulative hepatocellular necrosis (with or without mixed inflammatory cell infiltrates) was observed in male rats ≥ 3 mg/kg/day and in female rats at ≥ 10 mg/kg/day. Single cell necrosis of hepatocytes and sinusoid dilatation occurred at ≥ 10 mg/kg/day. Hepatic toxicity in the 2-week study occurred at mirdametinib mean plasma exposures area under the curve (AUC) 0-24 ≥ 4650 ng·h/mL (male rats). In longer term studies at lower doses, there was no evidence of hepatotoxicity.	Adequate safety margins above human exposure were established. AST increased, ALT increased, and Blood alkaline phosphatase increased are considered non-important identified risks for the mirdametinib risk management plan. The absence of correlation of blood alkaline phosphatase increased with other markers of liver injury in the clinical programme suggests that the

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
In an escalation dose study in two dogs at single doses up to 10 mg/kg, following euthanasia after the 10 mg/kg dose, the one male and one female dog had microscopic hepatocellular swelling and increased neutrophils in hepatic sinusoids. The male also had single cell necrosis of hepatocytes.	increase in alkaline phosphatase is not of liver origin, while the observations of bone lesions in rats, but not other species, in pre-clinical studies, and the finding of bone specific alkaline phosphatase upon fractionation in the clinical programme, suggest that the increase in alkaline phosphatase may be of bone origin. No reports of DILI were observed in human studies.
Musculoskeletal Administration of mirdametinib to rats resulted in bone lesions that included necrosis of the metaphysis and the ossifying zone of the physis and thickening of the zone of hypertrophying cartilage of the physis. The expansion of chondrocytes in the physis may be a response to the metaphyseal necrosis and loss of osteoprogenitor cells, possibly due to inhibition of angiogenesis by mirdametinib MEK inhibition.	Physeal dysplasia is considered an important potential risk for mirdametinib.
Systemic Mineralisation Systemic mineralisation observed in rats following administration of mirdametinib is consistent with vitamin D toxicity and dysregulation due to serum calcium and phosphorus homeostasis (Grant 1963, Morrow 2001). Elevated serum phosphorus concentrations (hyperphosphatemia) and decreased serum albumin were consistently observed in rats given mirdametinib. Although serum albumin concentrations are decreased in rats treated with mirdametinib, calcium values typically remain unchanged or slightly elevated in these rats, indicating that free, nonprotein-bound calcium is increased (Rosol and Capen 1997, Payne 1979). In the studies in rats, decreased parathyroid hormone (PTH) concentrations were observed. PTH plays a central role in the hormonal control of serum calcium and phosphorus. Elevations in serum calcium typically elicit decreased PTH concentrations as a result of the normal control of this endocrine system (Rosol and Capen 1997). Hyperphosphatemia in the presence of normo- or hypercalcemia can result in an increased (Ca × P) product, which is associated with systemic mineralisation (Block 2000). The elevated calcium appears related to significantly increased concentrations of plasma 1,25-dihydroxyvitamin D in mirdametinib-treated rats. This is the most potent form of vitamin D and the primary metabolite responsible for regulating serum calcium and phosphorus (Rosol and Capen 1997, Pierides 1981). Vitamin D is converted to 25-hydroxyvitamin D in the liver and then 1-hydroxylated to 1,25-dihydroxyvitamin D in the	These findings were uniquely seen in rats and thus no toxicity relevant to human use was identified.

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
kidney. 1,25-dihydroxyvitamin D acts by increasing absorption of calcium and phosphorus from the GI tract and can increase calcium and phosphorus reabsorption by renal tubules (Rosol and Capen 1997). Hyperphosphatemia and increased plasma 1,25-dihydroxyvitamin D concentrations in rats occurred 1 to 2 days prior to the detection of tissue mineralisation at doses ≤ 3 mg/kg/day.	
Other relevant toxicity studies were conducted and are presented below.	
Genotoxicity Mirdametinib was not genotoxic in a bacterial reverse mutation (Ames) assay or in an in vitro human lymphocyte chromosomal aberration assay but was equivocal in the in vivo micronucleus study and in vivo chromosomal aberrations study in rats. A genotoxic risk in humans could not be excluded.	Embryo-foetal toxicity is considered an important potential risk for the mirdametinib risk management plan.
Carcinogenicity Mirdametinib was not carcinogenic in transgenic mice at a dose of 5 mg/kg/day (3 times the human exposure). A genotoxicity risk in humans could not be excluded at clinical exposure. The currently ongoing 2-year carcinogenicity study in rats is testing dose levels that will produce exposures below the therapeutic clinical exposure because of tolerability issues in rats.	Carcinogenicity is considered an important potential risk for the mirdametinib risk management plan.
Reproductive and development toxicity The developmental and reproductive toxicology assessment of mirdametinib consisted of a fertility study in male and female rats and dose range-finding embryo-foetal development (EFD) toxicity studies in pregnant rats and rabbits. In a male and female rat fertility study, mirdametinib at a dose up to 1.0 mg/kg/day (approximately equivalent to the human exposure at the recommended dose based on AUC) did not affect mating performance or fertility in both sexes. In a 3-month repeat-dose toxicology study in rats, mirdametinib caused decreased ovarian organ weight and increased follicular cysts associated with decreases in the number of corpora lutea at doses ≥ 0.3 mg/kg/day (0.5 times the human exposure), as well as testicular hypocellularity and decreased weight of epididymides at 1 mg/kg/day (2.1 times the human exposure). Mirdametinib exhibits embryo-foetal toxicity after administration to pregnant rats and rabbits. In both rat and rabbit EFD studies, dose-dependent early resorptions, post-implantation loss, and decreased foetal weights were observed.	Embryo-foetal toxicity is considered an important potential risk for the mirdametinib risk management plan. Mirdametinib may impair fertility in males and females of reproductive potential, and as such, an effect on male and female fertility is a non-important potential risk for mirdametinib.
Phototoxicity Mirdametinib absorbs light in the 290 to 700 nm ultraviolet (UV) range and was not retained in the skin or eye based on the [^{14}C] mirdametinib rat study. The photo irritation potential was assessed as weak based on the in vitro Balb/c 3T3 assay.	Mirdametinib is not retained in the skin or eye and thus no toxicity relevant to human use was identified.

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Cardiac conduction A 1-month GLP dog study collected ECGs. ECGs were recorded pretest, Week 4 (predose and 2 hour), and Week 8 (reversal dogs, one from each dose group) on groups 1-8. No abnormal cardiac rhythms were noted for any animal. All measured parameters fell within acceptable limits. Purkinje fibre assay An in vitro assay using isolated canine Purkinje fibres and showed no effect on resting membrane potential at a range of 1 µM to 100 µM mirdametinib. Cardiac action potential was reduced at 10 µM and 100 µM and Vmax and amplitude were reduced at 100 µM. It is important to note that a mirdametinib concentration of 10 µM is approximately 2500-fold higher than the unbound steady-state maximum concentration (Cmaxss,u) of the clinical dose of mirdametinib in Study MEK-NF-201 at 2 mg/m^2 twice daily (BID); 4 mg BID maximum. In a secondary pharmacodynamic study conducted with mirdametinib at 1 and 10 µM against a panel of 87 targets, inhibition of the L-type calcium channel by 54% was observed at 10 µM (2500-fold higher than the human mirdametinib Cmaxss,u at the clinical dose).	Adverse effects on cardiac conduction is an important potential risk for the mirdametinib risk management plan.

Non-clinical Drug-Drug Interaction Studies

The potential for drug-drug interactions (DDI) with mirdametinib was investigated by evaluating the inhibition and induction of selected CYP isoenzymes, along with the evaluation of mirdametinib as a substrate or inhibitor of selected human drug transporters. A summary of the findings from these in vitro studies are presented below. No clinical studies assessing a drug interaction potential have been performed.

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
Nonclinical Drug-Drug Interaction Studies	
Potential to Inhibit CYP Enzymes The potential of mirdametinib and the metabolite, PD-0315209, to impair the metabolism of other agents by the direct inhibition of CYP isoforms was evaluated using probe substrates. Inhibition of substrate metabolism by mirdametinib was ≥ 3.3 µM across all the isoforms tested (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4). PD-0315209 exhibited a half-maximal inhibitory concentration (IC50) of 0.92 µM for CYP2C9, while the IC50 values for the remaining isoforms were >1.0 µM). The unbound fraction for PD-0315209 is <1%. In addition, the potential for mirdametinib (10 µM) and PD-0315209 (10 µM) to act as mechanism-based inhibitors of human CYP enzymes, time-dependent inhibition in the absence or presence of nicotinamide adenine dinucleotide phosphate (NADPH) as the cofactor was evaluated in HLMs. Time-dependent inhibition risk was determined and indicated a lack of time-dependent inhibition potential (ratio of shift of percent remaining enzyme activity without	There is a low risk for clinically relevant DDIs due to CYP inhibition.

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
NADPH over with NADPH were < 1.5) for CYP1A2, CYP2B6, CYP2C9, CYP2D6, CYP2C8, and CYP3A4 with clinical use. The ratio of shift of percent remaining enzyme activity without NADPH over with NADPH was 1.63-fold for CYP2C19.	
Potential to Induce CYP Enzymes The potential for mirdametinib to induce CYP enzymes was evaluated in 2 in vitro studies. Mirdametinib did not show induction potential in vivo for CYP isoforms CYP1A2, CYP2B6, CYP2C8, CYP2C9, and CYP2C19. While mirdametinib induced CYP3A4, the calculated predicted ratio of intrinsic clearance (CLint) values of a probe substrate in the absence and presence of an inducer value suggests that mirdametinib has a very low potential for CYP3A4 induction with clinical use at the proposed clinical dose. The calculated R3 value of 0.98 does not indicate that mirdametinib has induction potential in vivo.	There is a low risk for clinically relevant DDIs due to CYP induction.
Transporter Substrate Assessment: Efflux Transporters The substrate potential of mirdametinib and PD-0315209 was investigated using Madin-Darby canine kidney (MDCK) cell monolayers transfected with the MDR1 gene that encodes for human P-gp and in MDCK cells transfected with the breast cancer resistance protein (BCRP) gene that encodes for the BCRP transporter. Mirdametinib is a glycoprotein (P-gp) substrate, and PD-0315209 is not a P-gp substrate. Mirdametinib and PD-0315209 are both BCRP substrates	Drugs that alter P-gp or BCRP function may alter intracellular mirdametinib concentrations.
Transporter Substrate Assessment: Uptake Transporters Human embryonic kidney (HEK)293 cells, transfected with an individual uptake transporter gene (OATP1B1 and OATP1B3), were used to assess the substrate potential of mirdametinib and PD-0315209 toward the corresponding transporter. Uptake of atorvastatin (150 nM), a known substrate for hepatic uptake transporters OATP1B1 and OATP1B3, was used as a positive control to confirm active uptake. The influx ratio for mirdametinib and PD-0315209 was < 2.00, indicating that neither compound is a substrate of OATP1B1 or OATP1B3 transporters. These results indicate that in vitro, mirdametinib and PD-0315209 enter human hepatocytes by passive diffusion, and the hepatic uptake transporters, OATP1B1 and OATP1B3, are unlikely to contribute to the entry of either compound into hepatocytes.	There is a low risk for clinically relevant DDIs due to uptake transporter inhibition.
Transporter Inhibition Assessment: Efflux Transporters The potential of mirdametinib and PD-0315209 to inhibit the efflux transporter P-gp was evaluated in an in vitro study in multi drug resistance mutation 1(MDR1) (P-gp)-transfected MDCK cells using digoxin, a probe P-gp substrate, in the absence or presence of mirdametinib or PD-0315209. Under the conditions and at the test concentrations evaluated in this study, mirdametinib is not an inhibitor of P-gp with an extrapolated IC50 greater than 33.2 µM. For PD-0315209, the IC50 of 11.1 µM is 7400 greater than the	There is a low risk for clinically relevant DDI due to efflux transporter inhibition.

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
unbound Cmax of 0.0015 µM observed in humans at the proposed clinical dose of 2 mg/m^2 with a maximum of 4 mg BID. Therefore, PD-0315209 is not considered to present a DDI risk for P-gp inhibition. The potential of mirdametinib and PD-0315209 to inhibit the efflux transporter BCRP was evaluated in an in vitro study in BCRP-transfected MDCK cells using cladribine, a probe BCRP substrate, in the absence or presence of mirdametinib or PD-0315209. The data suggest that neither mirdametinib nor PD-0315209 would significantly inhibit BCRP at clinically relevant concentrations The intestinal concentration of mirdametinib (3.32 µM) is largely below the BCRP IC50 values of mirdametinib. The potential of mirdametinib and PD-0315209 to inhibit the efflux transporters, multidrug and toxin extrusion protein 1 (MATE1) and multidrug and toxin extrusion protein 2K (MATE2K), was evaluated in human Embryonic Kidney (HEK) 293 cell line (HEK293)-transfected cells using metformin, a probe MATE1 and MATE2K substrate, in the absence or presence of mirdametinib or PD-0315209. Extrapolated IC50 values for the inhibition of MATE1 and MATE2K were > 2.05 µM for mirdametinib and > 1.70 µM for PD-0315209. Under the conditions and at the test concentrations evaluated in this study, neither mirdametinib nor PD-0315209 appear to be an inhibitor of MATE1 or MATE2K	
<u>Transporter Inhibition Assessment: Uptake Transporters</u> The potential for mirdametinib and PD-0315209 to inhibit the hepatic uptake transporters OATP1B1 and OATP1B3 was evaluated in an in vitro study in HEK293 cells expressing OATP1B1 or OATP1B3 using atorvastatin, a prototypical probe substrate, in the absence or presence of mirdametinib or PD-0315209. Under the conditions of this study, mirdametinib is not an inhibitor of OATP1B1 or OATP1B3 (calculated IC50 of > 2.31 µM). In the same study, mirdametinib was reported to cause a dose-dependent inhibition of para aminohippurate uptake in OAT1-transfected HEK cells with an IC50 of 0.0418 µM, while PD-0315209 had an extrapolated IC50 > 1.70 µM (19SPRWP4). While mirdametinib is an inhibitor of OAT1, the geometric mean unbound Cmax at the clinical dose produces concentrations approximately 10-fold lower than the mirdametinib IC50 for OAT1 inhibition. In addition, the IC50 of 0.0418 µM is just above the 10 fold Cmax,u cut-off value indicated in the ICH draft guideline Drug Interaction studies M12 (ICH 2022). Mirdametinib caused a 2.62% inhibition of furosemide uptake in OAT3-transfected cells at the highest tested concentration (2.05µM) and showed no inhibition of 1-methyl-4-phenylpyridinium (MPP+) uptake in OCT2 transfected cells up to 2.05µM. In the presence of PD-0315209, the average influx rate of atorvastatin ranged from 1.43 to 8.70 pmol/min/mg protein via OATP1B1 and from 2.04 to 6.13 pmol/min/mg protein via OATP1B3, corresponding to 0% to 81.8% inhibition of OATP1B1	There is a low risk for clinically relevant DDI due to uptake transporter inhibition.

Key Safety Findings (from Nonclinical Studies)	Relevance to Human Usage
and 0% to 70.2% inhibition of OATP1B3. Under the conditions of this study, PD-0315209 is an inhibitor of OATP1B1 and OATP1B3 (calculated IC50 values of 12.0 and 12.6 µM, respectively). However, it should be noted that these IC50 values are largely above the ICH M12 cut-off for the metabolite based on the estimated unbound Cmax at the hepatic inlet. Experimentally, the unbound fraction of mirdametinib or PD-0315209 is less than 1%. Using the conservative fu,p of 0.01 (1%), the geometric mean unbound Cmax in humans after administration of 2 mg/m^2 of mirdametinib BID in MEK-NF-201 is approximately 0.0039 and 0.0015 µM for mirdametinib and PD-0315209, respectively. Therefore, there is low potential for clinical DDIs resulting from mirdametinib- or PD-0315209-mediated inhibition of drugs that are substrates for uptake and efflux transporters.	
Potential to Inhibit UGT Enzymes The potential of mirdametinib to impair the metabolism of other agents by the direct inhibition of UGT was evaluated against 7 major recombinant human UGT isozymes 1A1, 1A3, 1A4, 1A6, 1A9, 2B7, and 2B15 over a concentration range of 0.03 to 30 µM. No detectable or limited (< 50%) inhibition of UGT 1A1, 1A3, 1A4, 1A6, 1A9, 2B7, and 2B15 was observed at concentrations of up to 30 µM. Therefore, mirdametinib was considered to have low potential for DDI when co-administered with other drugs metabolised by UGT.	There is a low risk for clinically relevant DDI when co-administered with other drugs metabolised by UGT.

Safety margins are presented below in Table 4. The calculated safety margins for the definitive repeat-dose toxicity studies with mirdametinib were calculated by dividing the total AUC_{0-24} from the respective toxicology study at the NOAEL, lowest-observed-adverse-effect level (LOAEL), or maximum tolerated dose with the human total steady-state AUC_{0-24} (1862 ng·h/mL and 1362 ng·h/mL for mirdametinib and PD-0315209, respectively after administration of 2 mg/m^2 mirdametinib BID. The margins were based on exposures that were available at the end of the dosing period for the toxicity study. Because of minimal sex difference across species, the margins were determined using sex-combined exposures. Total exposures were used given that mirdametinib protein binding across species is similar.

Table 4: Part II: Module SII-1: Human Safety Margins for Mirdametinib

Study	Mirdametinib Dose (mg/kg/day)	Mirdametinib AUC_{0-24} (ng·h/mL)[a)]	Margin for Mirdametinib [b)]	PD-0315209 AUC_{0-24} (ng·h/mL)[a]	Margin for PD-0315209[c)]
Repeat-dose general toxicity studies					
1-Month mouse	10 (LOAEL)	13,250	7.1	3680	2.7
1-Month rat	0.1 (NOAEL)	213	0.11	182	0.13

Study	Mirdametinib Dose (mg/kg/day)	Mirdametinib AUC_{0-24} (ng·h/mL)[a)]	Margin for Mirdametinib [b)]	PD-0315209 AUC_{0-24} (ng·h/mL)[a]	Margin for PD-0315209[c)]
3-Month rat	0.1 (LOAEL)	342	0.18	380	0.27
1-Month dog	0.1 (NOAEL)	655	0.35	218	0.16
3-Month dog	0.1 (NOAEL)	633	0.34	213	0.16
Carcinogenicity					
6-Month mouse	5 (MTD)	6720	3.6	1105	0.81
Developmental and reproductive toxicity					
Rat fertility[d)]	1 (NOAEL)	2440	1.3	2315	1.7
Rat EFD[d]	0.3 (LOAEL)	769	0.41	824	0.60
Rabbit EFD	0.3 (LOAEL)	763	0.41	621	0.46

Abbreviations: AUC_{0-24}: area under the plasma concentration-time curve from 0 to 24 hours; BID: twice daily; EFD: embryo-foetal development; LOAEL: lowest-observed-adverse-effect level; MTD: maximum tolerated dose, NOAEL: no observed-adverse-effect level; popPK: population pharmacokinetic; TK: toxicokinetics.
[a)] The AUC values are an average of the reported male and female values at the end of the dosing period. [b)] The popPK report presents a mean steady-state AUC_{0-24} of 1862 ng·h/mL at 2mg/m^2 BID with maximum of 4 mg BID for mirdametinib (Mirdametinib popPK Report). [c)] The popPK report presents a mean steady-state AUC_{0-24} of 1362 ng·h/mL for metabolite PD-0315209 when administered mirdametinib at 2mg/m^2 BID with maximum of 4 mg BID (Mirdametinib popPK Report). [d)] TKs were not assessed in this study; therefore, the exposure was derived from the 1-month rat study.

Mirdametinib has been extensively studied in the non-clinical setting, including studies in safety pharmacology, exploratory toxicity, CYP inhibition and induction, effects on human drug transporters, and UGT inhibition. The overall nonclinical evidence does not support any important identified risks for mirdametinib. The nonclinical data do support an important potential risk for embryo-foetal toxicity in humans. (Table 5)

Table 5: SII.2 Conclusions on Nonclinical Data

Safety Concerns	
Important identified risks	None
Important potential risks	Embryo-foetal toxicity Physeal dysplasia Adverse effects on cardiac conduction Carcinogenicity
Missing information	None

Part II: MODULE SIII - Clinical trial exposure

Table 6 and Table 7 provide a summary of clinical studies with mirdametinib and from the compassionate use programme. As of the data cut off, approximately 577 participants have been exposed to mirdametinib.

The primary safety data (Pool 1) supporting the evaluation of the safety of mirdametinib for the treatment of participants with NF1 PN are Studies MEK-NF-201 (ReNeu) and NF-106 (Weiss) comprising both adult and paediatric cohorts (N=133).

Safety data from two Studies (Pool 2) conducted in adult participants with advanced cancer (A4581001 and A4581002) (N=113) further supports the evaluation of safety.

Additional supportive safety data informing the RMP includes the following:

- Three Phase 1 Studies (A4581004, MEK-NF-101, MEK-NF-102) in which healthy volunteers received single doses of mirdametinib (88 patients received mirdametinib in these three studies).
- The Global Pharmacovigilance database, which includes data from 8 studies in which mirdametinib was used in combination with other agents, or in which mirdametinib dosing and indication for treatment vary from the primary indication, as well as data from the compassionate use programme. An estimated 243 additional participants have received at least one dose of mirdametinib in these studies and the compassionate use programme.

Table 6: Mirdametinib Studies to Support Safety

Protocol Number/Study Design	Primary/Secondary Safety Objectives	Population	Treatment Arms	No. of Participants Exposed to Mirdametinib	Safety Conclusions
Pivotal Study					
MEK-NF-201 A Phase 2b Trial of the MEK 1/2 Inhibitor Mirdametinib in Adult and Paediatric Patients with Neurofibromatosis Type 1 (NF1)-Associated Inoperable Plexiform Neurofibromas (PNs) that are Causing Significant Morbidity	To evaluate the confirmed CR and PR rates of mirdametinib using volumetric MRI analysis, as assessed by a BICR, in participants with an inoperable NF1-associated PN that is causing significant morbidity. To evaluate safety and tolerability of mirdametinib.	Participants aged ≥2 years with NF1-associated inoperable PNs that caused significant morbidity	2 mg/m^2 BID (int) with a maximum of 4 mg BID	Total: 114 58 Adult 56 Paediatric	Mirdametinib had a manageable safety profile and was tolerated by the majority of adult and paediatric participants.
Pool 1 Studies (MEK-NF-201 and NF-106): Primary Safety Data in Adult and Paediatric Participants with NF1 PN – Monotherapy					
NF-106 A Phase 2 Trial of the MEK Inhibitor Mirdametinib in Adolescents and Adults with NF1-Associated Morbid Plexiform Neurofibromas	To evaluate the confirmed objective response rate based on volumetric magnetic resonance imaging analysis. To evaluate the feasibility, safety and toxicity of chronic mirdametinib administration in this population.	Participants aged ≥16 years and had a PN that was either progressive or causing significant morbidity.	2 mg/m^2 BID (int) with a maximum of 4 mg BID	Total: 19 17 Adult 2 Paediatric	Mirdametinib had a manageable safety profile and was tolerated by the majority of participants.

Protocol Number/Study Design	Primary/Secondary Safety Objectives	Population	Treatment Arms	No. of Participants Exposed to Mirdametinib	Safety Conclusions
Pool 2 Studies: Studies to Support Safety in Adult Oncology Participants -Monotherapy					
A4581001 A Multicenter, Open-Label, Noncomparative Phase 1-2 Clinical and Pharmacokinetic Study of Oral Mirdametinib in Patients with Advanced Cancer	Phase 1: To determine the safety profile, including DLTs, the MTD, RP2D, and schedule, the PK profile of oral mirdametinib and mirdametinib metabolite), including the impact of food on bioavailability, and the preliminary antitumour activity in participants with breast, colorectal, non-small cell lung cancer (NSCLC), or non-ocular melanoma. Phase 2: To determine the antitumour activity in participants with breast cancer, colon cancer, and melanoma.	Participants 18 years of age and older with histologically or cytologically documented breast, colorectal, NSCLC, or non-ocular melanoma refractory to standard therapy or for whom no standard therapy existed.	Phase 1: 1 mg QD (3 weeks on/1 week off) 1-30 mg BID (3 weeks on/1 week off) 10-20 mg BID (cont) 10 mg BID (5 days on/2 days off) Phase 2: Initial regimen: 20 mg BID (3 weeks on/1 week off) Amended regimen: 15 mg BID (3 weeks on/1 week off)	Total: 79 Phase 1: 66 Phase 2: 13	The study was terminated early due to the high rate of unexpected AEs. Events of retinal vein occlusion (RVO) were observed on two schedules (10 mg BID continuous and 10 mg BID, 5 days on/2 days off).

Protocol Number/Study Design	Primary/Secondary Safety Objectives	Population	Treatment Arms	No. of Participants Exposed to Mirdametinib	Safety Conclusions
A4581002 Phase 2 Study of the MEK Inhibitor Mirdametinib in Patients with Advanced Non-Small Cell Lung Cancer	To determine the activity of mirdametinib in advanced NSCLC participants as measured by the ORR, CR and PR by RECIST. To determine the safety profile of mirdametinib.	Participants ≥18 years with histologically or cytologically proven NSCLC with metastases or locally advanced disease with malignant pleural effusion.	Schedule 1: 15 mg BID (3 weeks on/1 week off) Schedule 2: 15 mg BID with food (5 days on/2 days off for 3 weeks/1 week off)	34	This study was terminated prematurely due to safety issues and lack of objective responses. Main treatment-related toxicities included diarrhoea, rash, fatigue, reversible visual disturbances (primarily subjects on the Schedule 1 dosing regimen), nausea, and vomiting.

Protocol Number/Study Design	Primary/Secondary Safety Objectives	Population	Treatment Arms	No. of Participants Exposed to Mirdametinib	Safety Conclusions
Healthy Volunteer Studies					
A4581004 A Phase 1 Open-Label Study to Evaluate the Effect of Food on Pharmacokinetics of Mirdametinib in Healthy Volunteers	To assess the effect of a high-fat, high-calorie meal and fasting on mirdametinib PK, and the effect of timing of meals relative to dosing of mirdametinib PK following a single oral dose in healthy volunteers. To evaluate the safety and tolerability of single dose mirdametinib when administered to healthy volunteers.	Healthy participants between 21 and 55 years old, inclusive.	20 mg single dose	23	Single 20-mg doses of mirdametinib were safe and well tolerated in both fed and fasted states.
MEK-NF-101 A Phase 1, Single-centre, Open-label, Pharmacokinetics, Metabolism, Mass Balance, and Safety Study of [^{14}C]-PD-0325901 (Mirdametinib) Following Single Oral Dose Administration in Healthy Male Volunteers	To evaluate the mass balance, routes of elimination, pharmacokinetics, and safety and tolerability of a single oral dose of mirdametinib, in healthy male volunteers	Healthy males between 18 and 50 (inclusive).	4 mg single dose	8	Mirdametinib was well-tolerated when administered as a 4 mg oral solution dose in healthy participants under fasted conditions.

Protocol Number/Study Design	Primary/Secondary Safety Objectives	Population	Treatment Arms	No. of Participants Exposed to Mirdametinib	Safety Conclusions
MEK-NF-102 A Thorough QT/QTc Study to Evaluate the Effect of Mirdametinib and Metabolite Exposures on Cardiac Repolarisation in Healthy Participants	To evaluate the relationship between mirdametinib plasma concentrations and time-matched, placebo-corrected, baseline-adjusted difference in QTc using Fridericia's formula (QTcF) (ΔΔQTcF). To describe the safety and tolerability of mirdametinib, the effects of mirdametinib on ECG parameters (QT, QTcF, PR, QRS, RR), and cardiac safety.	Healthy participants between 18 and 55 (inclusive).	Placebo, mirdametinib 6 mg or 14 mg single dose, or moxifloxacin 400 mg single dose	57	Administration of oral mirdametinib 6 and 14 mg single doses was generally safe and well tolerated by the healthy adult participants in this study.

BICR: blinded independent central review; BID: Twice daily; cont: continuous; CR: complete response; DLTs: dose-limiting toxicities; int: intermittent; MRI: magnetic resonance imaging; MTD: maximum tolerated dose; NF1: neurofibromatosis type 1; NSCLC: non-small cell lung cancer; ORR: objective response rate; RP2D: recommended Phase 2 dose; PK: pharmacokinetic; PN: plexiform neurofibroma; PR: partial response; QD: once daily; RECIST: Response Evaluation Criteria in Solid Tumours; RVO: retinal vein occlusion. Safety Population included all participants who received at least 1 dose of study treatment.

Table 7: Non Pooled Interventional Studies and Compassionate Use Programmes Used to Support the Safety Specification of Mirdametinib

Study Number	Status	Study Title[1]	Dosing	Number of Participants Exposed to Mirdametinib
B1271002 - combination	Terminated as a result of internal portfolio review	A Multi-arm Phase 1 Dose Escalation Study of the Safety, Pharmacokinetics, and Pharmacodynamics of the Dual PI3K/mTOR Inhibitors PF-04691502 and PF-05212384 in Combination with Experimental or Approved Anticancer Agents in Patients with Advanced Cancer	2 mg to 8 mg BID (int)	44
BGB-283/PD-0325901-AU-001 - combination	Ongoing	A Phase 1b, Open-Label, Dose-escalation and Expansion Study to Investigate the Safety, Pharmacokinetics and Antitumour Activities of a RAF Dimer Inhibitor BGB-283 (lifirafenib) in Combination with MEK Inhibitor mirdametinib in Patients with Advanced or Refractory Solid Tumours	2 mg QD to 4 mg BID (int)	44 as of 08Sep2023
SJ901 IIR - monotherapy	Ongoing	Phase 1/2 Evaluation of Single Agent mirdametinib, a Brain Penetrant MEK1/2 inhibitor, for the Treatment of Children, Adolescents, and Young Adults with Low-Grade Glioma	2 to 3 mg/m^2, BID (cont)	23 as of 08Sep2023
MEKRAF-AST-101 - combination	Ongoing	A Phase 1/2 Open-Label, Dose-Escalation and Expansion Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics and Efficacy of mirdametinib in Combination With BGB-3245 (brimarafenib) in Patients with Advanced Solid Tumours	2 mg to 4 mg BID (cont)	9 as of 08Sep2023
13-506 IIR – Combination	Completed	Phase I/II Study of the CDK4/6 Inhibitor Palbociclib (PD-0332991) in Combination with the MEK Inhibitor Mirdametinib for Patients with KRAS Mutant Non-Small Cell Lung Cancer and Other Solid Tumours	2 mg to 8 mg BID (int)	25

Study Number	Status	Study Title[1]	Dosing	Number of Participants Exposed to Mirdametinib
M13DAP IIR – Combination	Completed	Phase I/II Study with the Combination of Dacomitinib and Mirdametinib in Metastatic KRAS Mutation Positive Non-small Cell Lung Cancer	2 mg to 6 mg BID (int)	41
MErCuRIC1 IIR – Combination	Completed	A Sequential Phase I Study of MEK1/2 Inhibitors Mirdametinib or Binimetinib Combined With cMET Inhibitor PF-02341066 in Patients with RAS Mutant and RAS Wild Type (With Aberrant c-MET) Colorectal Cancer	2 mg to 8 mg BID (int)	25
21-288 IIR – Combination	Terminated due to poor enrolment	A Phase 1b/2a, Open-label Platform Study to Evaluate Mirdametinib as Monotherapy or in Combination with Other Anticancer Agents in Patients with Advanced Solid Cancers Harbouring MAPK-activating Mutations	Arm 1: 4 mg BID (cont) Arm 2 to 8 mg BID	Arm 1: 6 as of Oct2023 when the study was terminated. Arm 2: 0
Mirdametinib Compassionate Use Programme				
Mirdametinib Compassionate Use Programme	Ongoing	Not applicable	1 mg BID to 15 mg BID	26 as of 26Sep2023

[1]Study Title reference: clinicaltrials.gov.
BID: twice daily; cont: continuous; int: intermittent; IIR: investigator-initiated research; QD: daily.

As of 20 September 2023, the overall median duration of exposure in Pool 1 was 22 months (range 0.4 to 45.6), with 22 months (range 1.6 to 40.1) in the paediatric cohort and 19 months (range 0.4 – 45.6) in the adult cohort. Six paediatric participants and 10 adult participants have been exposed to mirdametinib for > 36 months.

Demographic and Exposure information for Pool 1 and Pool 2 is set out in Table 8, Table 9 and Table 10 below based upon a Data Lock Point of 20 Sept 2023.

Table 8: Demographics for Participants who Received Mirdametinib for Pool 1 and Pool 2

	Pool 1			**Pool 2**
	Paediatric NF1 PN 2 mg/m² BID (N = 58)	**Adult NF1 PN 2 mg/m² BID (N = 75)**	**Total NF1 PN 2 mg/m² BID (N = 133)**	**Total (N = 113)**
Age at Informed Consent (years)				
n	58	75	133	113
Mean (StD)	10.3 (4.55)	32.9 (12.48)	23.1 (14.95)	58.8 (12.43)
Median	10	30	21	59
Min, Max	2, 17	18, 69	2, 69	29, 86
Age Groups (years)				
Paediatric				
2 to <12	32 (55.2%)	N/A	N/A	N/A
12 to <18	26 (44.8%)	N/A	N/A	N/A
Adult				
18 to <40	N/A	57 (76.0%)	N/A	8 (7.1%)
40 to <65	N/A	16 (21.3%)	N/A	70 (61.9%)
≥65	N/A	2 (2.7%)	N/A	35 (31.0%)
Adult				
<65	N/A	73 (97.3%)	N/A	78 (69.0%)
≥65	N/A	2 (2.7%)	N/A	35 (31.0%)
Sex				
Male	27 (46.6%)	27 (36.0%)	54 (40.6%)	58 (51.3%)
Female	31 (53.4%)	48 (64.0%)	79 (59.4%)	55 (48.7%)

	Pool 1			Pool 2
	Paediatric NF1 PN 2 mg/m² BID (N = 58)	**Adult NF1 PN 2 mg/m² BID (N = 75)**	**Total NF1 PN 2 mg/m² BID (N = 133)**	**Total (N = 113)**
Race				
White	38 (65.5%)	56 (74.7%)	94 (70.7%)	100 (88.5%)
Black or African American	11 (19.0%)	10 (13.3%)	21 (15.8%)	9 (8.0%)
Asian	2 (3.4%)	4 (5.3%)	6 (4.5%)	1 (0.9%)
American Indian or Alaska Native	1 (1.7%)	0	1 (0.8%)	0
Native Hawaiian or Other Pacific Islander	0	0	0	0
Other	6 (10.3%)	5 (6.7%)	11 (8.3%)	3 (2.7%)
Ethnicity				
Hispanic or Latino	8 (13.8%)	3 (4.0%)	11 (8.3%)	1 (0.9%)
Not Hispanic or Latino	46 (79.3%)	66 (88.0%)	112 (84.2%)	65 (57.5%)
Missing/ Not Reported/ Unknown	4 (6.9%)	6 (8.0%)	10 (7.5%)	47 (41.6%)
Women who are of Child-Bearing Potential at Screening [1]				
Yes	15 (50.0%)	29 (78.4%)	44 (65.7%)	N/A
No	15 (50.0%)	8 (21.6%)	23 (34.3%)	N/A

BID: twice daily; Max: Maximum; Min: Minimum; N/A: not applicable; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibroma; StD: Standard deviation. Dose group is based on the assigned dose at baseline. Percentages are calculated using the number of participants in the corresponding cohort as the denominator except for Child-Bearing Potential which uses the number of females in that cohort as the denominator.
[1] Study MEK-NF-201 only.

A summary of exposure to mirdametinib in Pool 1 and Pool 2 is summarised in Table 9 and Table 10.

Table 9: Pool 1 Summary of Exposure

	Pool 1		
	Paediatric NF1 PN 2 mg/m²BID (N=58)	**Adult NF1 PN 2 mg/m²BID (N=75)**	**Total NF1 PN 2 mg/m²BID (N=133)**
Duration of Mirdametinib Exposure (Months)			
N	58	75	133
Mean (StD)	20.86 (10.690)	18.04 (13.002)	19.27 (12.087)
Median	21.87	18.66	21.85
Min, Max	1.6, 40.1	0.4, 45.6	0.4, 45.6
Total Duration of Exposure (years) for all Participants	100.8	112.7	213.5
Number of Participants who Received Study Treatment			
For at least 1 month	58 (100%)	70 (93.3%)	128 (96.2%)
For at least 2 months	57 (98.3%)	68 (90.7%)	125 (94.0%)
For at least 3 months	56 (96.6%)	68 (90.7%)	124 (93.2%)
For at least 6 months	51 (87.9%)	60 (80.0%)	111 (83.5%)
For at least 12 months	42 (72.4%)	41 (54.7%)	83 (62.4%)
For at least 24 months	24 (41.4%)	26 (34.7%)	50 (37.6%)
For at least 36 months	6 (10.3%)	10 (13.3%)	16 (12.0%)

BID: twice daily; m: meter; Max: Maximum; Min: Minimum; mg: milligram; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibromas; QD: once daily; StD: Standard deviation; TEAE: Treatment-Emergent Adverse Event. Dose group is based on the assigned dose at baseline. Planned dose is defined as the assigned dose at baseline. Percentages are calculated using the number of participants in the corresponding cohort as the denominator. Subcategories, shown by an indent, use the number of participants in the category as the denominator. Duration of study exposure in months is calculated as (last dose date – first dose date +1)/ 30.4375.

Table 10: Pool 2 Summary of Exposure

	Pool 2				
	1mg QD, 1mg, 2mg BID (N = 12)	**4mg BID (N = 4)**	**8, 10mg BID (N = 23)**	**15, 20 and 30mg BID (N = 74)**	**Total (N = 113)**
Duration of Mirdametinib Exposure (Months)					
N	12	4	23	74	113
Mean (SD)	2.46 (2.105)	3.14 (2.109)	2.44 (1.988)	2.47 (3.374)	2.49 (2.961)
Median	2.47	2.43	1.77	1.61	1.68
Min, Max	0.7, 8.3	1.6, 6.1	0.0, 8.3	0.1, 26.4	0.0, 26.4
Number of Participants who Received Study Treatment					
For at least 1 month	8 (66.7%)	4 (100%)	17 (73.9%)	54 (73.0%)	83 (73.5%)
For at least 2 months	7 (58.3%)	2 (50.0%)	10 (43.5%)	29 (39.2%)	48 (42.5%)
For at least 3 months	3 (25.0%)	2 (50.0%)	8 (34.8%)	17 (23.0%)	30 (26.5%)
For at least 6 months	1 (8.3%)	1 (25.0%)	1 (4.3%)	5 (6.8%)	8 (7.1%)
For at least 12 months	0	0	0	1 (1.4%)	1 (0.9%)
For at least 24 months	0	0	0	1 (1.4%)	1 (0.9%)
For at least 36 months	0	0	0	0	0

BID: twice daily; m: meter; Max: Maximum; Min: Minimum; mg: milligram; NF1: Neurofibromatosis Type 1; PN: Plexiform Neurofibromas; QD: once daily; StD: Standard deviation; TEAE: Treatment-Emergent Adverse Event. Dose group is based on the assigned dose at baseline. Planned dose is defined as the assigned dose at baseline. Percentages are calculated using the number of participants in the corresponding cohort as the denominator. Subcategories, shown by an indent, use the number of participants in the category as the denominator. Duration of study exposure in months is calculated as (last dose date – first dose date +1)/ 30.4375.

Part II: MODULE SIV - Populations not studied in clinical trials

The section below sets out the significant exclusion criteria for Study MEK-NF-201.

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Exclusion criteria:

- Participant has a Screening alanine transaminase (ALT) value of > 2.0 x upper limit of normal (ULN)
- Participant has a Screening total bilirubin value of > 1.5 x ULN (isolated bilirubin > 1.5 x ULN is acceptable if bilirubin is fractionated and direct bilirubin < 35%)
- Any clinically significant active or known history of liver disease or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome or asymptomatic gallstones).

Reason for exclusion:

In non-clinical studies in the rat, multifocal, coagulative, hepatocellular necrosis was observed at high doses. Changes in clinical laboratories included modest increases in AST and ALT levels, and decreases in albumin, which were reversible. Additionally, elevations of AST and ALT have been observed in paediatric patients treated with selumetinib, another MEK inhibitor. Participants with any liver function abnormality were therefore excluded from the clinical study as a precautionary measure.

Is it considered to be included as missing information?

Yes

Rationale:

Dedicated studies of mirdametinib in patients with hepatic impairment have not been conducted. Mirdametinib is highly metabolised via glucuronidation and oxidation (UDP-glucuronosyltransferase (UGT) and carboxylesterases (CES) enzymes, with less than 10% excreted unchanged. It is not known to what extent mirdametinib undergoes hepatic or extrahepatic metabolism. PopPK analyses indicated that no clinically meaningful relationships with mirdametinib or PD-0315209 PK parameters were observed for baseline liver enzymes. This suggests that the PK of mirdametinib is not expected to be altered in patients with mild hepatic impairment based on National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) classification system (NCI-ODWG Group B). Consequently, use in patients with moderate or severe hepatic impairment is unknown and should be considered to have potential effects on the PK of mirdametinib.

Exclusion criteria*:*

- Participant has a history of malignancy associated hypercalcemia

- Participant has an active parathyroid disorder, hyperphosphatemia at Screening (serum phosphorus > 1 x ULN), or serum calcium (mg/dL) x serum phosphorus (mg/dL) product > 70 at screening

Reason for exclusion:

Nonclinical toxicology studies in rats suggested that calcium and phosphorus dysregulation could lead to an increased risk of soft tissue mineralisation.

Is it considered to be included as missing information?

No

Rationale:

Nonclinical findings were uniquely seen in rats. Calcium and phosphorus dysregulation were not identified as adverse drug reactions in Pool 1 participants.

Exclusion criteria:

- Lymphoma, leukemia, or any malignancy (including malignant glioma or Malignant peripheral nerve sheath tumour (MPNST)) within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years
- Breast cancer within the past 10 years
- Participants with evidence of an active optic glioma or other low-grade glioma, requiring treatment with chemotherapy or radiation therapy. Participants not requiring treatment are eligible. Ophthalmological findings secondary to long-standing optic pathway glioma (such as visual loss, optic nerve pallor or strabismus) or long-standing orbito-temporal PN (such as visual loss, strabismus) will NOT be considered a significant abnormality for the purposes of the study).
- Participant has a history of a positive human immunodeficiency virus (HIV) antibody test
- Participant has a known malabsorption syndrome or preexisting gastrointestinal conditions that may impair absorption of PD-0325901 (e.g., gastric bypass, lap band, or other gastric procedures). Delivery of PD-0325901 via nasogastric tube or gastrostomy tube is not allowed

Reason for exclusion:

Confounding of safety findings of the study.

Is it considered to be included as missing information?

No

Rationale:

Baseline presence of these conditions in the targeted NF1 PN population would mask the effect of the intervention and/or interpretation of safety in the target population. In addition, studies in these populations are not feasible.

Exclusion criteria:

- Participant has abnormal QT interval corrected by Fridericia's formula (> 450 msec for male participants, > 470 msec for female participants, or > 480 msec for participants with bundle branch block) (triplicate ECG readings taken approximately 2 to 3 minutes apart and averaged) at screening.

Reason for exclusion:

Patients were excluded as a precautionary measure prior to the results of a thorough QT study.

Is it considered to be included as missing information?

No

Rationale:

MEK-NF-102, a Phase 1 double-blind, randomised crossover study concluded that mirdametinib and its primary metabolite (PD-0315209) had no effect on cardiac repolarisation as detected primarily by QT/QTc prolongation at single, supra-therapeutic oral doses of 6 and 14 mg. Adverse effects on cardiac conduction is an Important Potential Risk for mirdametinib.

Exclusion criteria:

- Participant has experienced any of the following within 6 months (24 weeks) of signing informed consent/assent: clinically significant cardiac disease, myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism
- Participant has recorded a LVEF < 55% at Screening or within 3 years of signing informed consent/assent, OR has a history of congestive heart failure

Reason for exclusion:

Participants were excluded for safety reasons as cardiac events were reported in clinical trials of mirdametinib in patients with advanced cancers.

Is it considered to be included as missing information?

No

Rationale:

Ejection fraction decreased is an Important Identified Risk that is well characterised in the intended treatment population in patients with NF1 PN.

Exclusion criteria:

- Participant has a history of, or evidence of, retinal pathology on ophthalmologic examination that is considered a risk factor for central serous retinopathy, retinal vein occlusion (RVO), or neovascular macular degeneration
- Participant has a history of glaucoma

Reason for exclusion:

Participants were excluded for safety reasons as retinal vein occlusion, central serous retinopathy, and neovascular macular degeneration have been observed with other MEK inhibitors. At the time of study MEK-NF-201 initiation, 3 participants had reported events of retinal vein occlusion in a study in adult participants with advanced cancers, all receiving doses of mirdametinib ≥5mg BID.

Is it considered to be included as missing information?

No

Rationale:

Ocular events (RVO, Retinal pigment epithelium detachment (RPED), Vision blurred) are an Important Identified Risk for mirdametinib.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

As presented in Module SIII, a total of 577 participants, including 148 with NF1 PN (n=133 in Pool 1, n=15 in NF1 compassionate use), have been exposed to mirdametinib across the 15 clinical studies and the compassionate use programme. The primary safety data (Pool 1) supporting the evaluation of the safety of mirdametinib for the treatment of participants with NF1 PN are studies MEK-NF-201 (ReNeu) and NF-106 (Weiss) comprising both adult and paediatric cohorts (N=133). Safety data from two studies (Pool 2) conducted in adult participants with advanced cancer (A4581001 and A4581002) (N=113) further supports the evaluation of safety. In Study MEK-NK-201, 6 paediatric and 10 adult participants have been exposed to mirdametinib for > 36 months. Accordingly, given the extent and duration of exposure in the clinical programme, some uncommon (≥1/1,000 to <1/100) adverse reactions may have been detected, while rare events (≥1/10,000 to <1/1,000) were unlikely to be detected. This is to be expected in any rare disease.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

As is typical for underrepresented populations in clinical development programmes, the clinical development programme for mirdametinib also has some of these special populations underrepresented. However, these few groups are not a limitation of the clinical development programme for mirdametinib, due to the rare nature of the indication. Specific details for each special population are shown below in Table 11.

Table 11: SIV.3 Exposure of special populations included or not in clinical trial development programmes

Type of Special Population	Exposure
Children	In Pool 1, 44% (58/133) of participants were 2 to 17 years of age, reflecting the epidemiology of the indication for study. No children were participants in Pool 2. Children less than 2 years of age have not been studied.
Elderly	In Pool 1, 2% (2/133) of participants were over 65 years of age, reflecting the epidemiology of the indication for study. In Pool 2, participants over 65 years of age were well represented with 31% (35/113) ≥65 years of age.
Pregnant or breastfeeding women	One participant in study MEK-NF-201 had a positive urine pregnancy test reported 31 days after the last dose of mirdametinib. The pregnancy ended in a first trimester spontaneous abortion. In study NF-106, there was one male partner pregnancy. The outcome of this pregnancy is unknown. There are no data regarding the presence of mirdametinib or its metabolites in either human or animal milk, its effects on a breastfed child, or on milk production. There were no reports of exposure to mirdametinib via lactation in Pool 1 or Pool 2.
Patients with relevant comorbidities	
Patients with hepatic impairment	Dedicated studies of mirdametinib in a population with hepatic impairment have not been conducted. Mirdametinib is highly metabolised via glucuronidation and oxidation (UGT and CES enzymes), with less than 10% excreted unchanged. It is not known to what extent mirdametinib undergoes hepatic or extrahepatic metabolism. There are two predominant metabolites, PD-0315209 and M22. PD-0315209 exhibited similar potency as mirdametinib when assayed against purified MEK1 but was significantly less potent than mirdametinib at reducing ERK phosphorylation in tumour cells. PD-0315209 concentrations associated with target suppression and biological activity far exceed concentrations achieved following administration of mirdametinib at the clinical dose of 2 mg/m^2 BID in patients with NF1 PN. Therefore, it is not expected that PD-0315209 contributes significantly to the pharmacological activity of mirdametinib. M22 is the O-glucuronide metabolite and was found to be significantly less potent than mirdametinib in an in vitro phospho-ERK pharmacodynamic assay across 3 tumour cell lines. The major route of elimination is renal excretion of glucuronide metabolites. In Study MEK-NF-201, exclusion criteria included any clinically significant active, or known history of, liver disease, or known hepatic or biliary abnormalities, or ALT > 2.0 x ULN or total bilirubin value of > 1.5 x ULN at screening. PopPK analyses indicated that no clinically meaningful relationships with mirdametinib or PD-0315209 PK parameters were observed for baseline liver enzymes. This suggests that the PK of mirdametinib is not expected to be altered in patients with mild hepatic impairment based on National Cancer Institute Organ Dysfunction

Type of Special Population	Exposure
	Working Group (NCI-ODWG) classification system (NCI-ODWG Group B). Use in patients with moderate or severe hepatic impairment is unknown and should be considered to have potential effects on the PK of mirdametinib. SpringWorks plans to conduct a hepatic impairment study to assess the effects of hepatic impairment on the PK of mirdametinib. This study will evaluate varying degrees of liver dysfunction based on multiple evaluation criteria.
Patients with renal impairment	A renal impairment PK study has not been performed. Enrollment of participants with CLCR indicative of mild renal impairment (60 to 89 mL/min) was allowed in Pool 1 Study MEK-NF-201. Participants with moderate renal impairment (CLCR of 30 to 60 mL/min) were included in Pool 2 Studies A4581001 and A4581002. PopPK analysis evaluated renal function-related covariates (CLCR on clearance of mirdametinib and PD-0315209). The major route of elimination for mirdametinib in humans is renal excretion of the glucuronide metabolites, with 67.7% recovered in urine and 27.3% recovered in faeces. Urinary elimination of unchanged mirdametinib is a minor route of excretion with less than 1% excreted as unchanged and less than 1% excreted as the carboxylic acid metabolite or the S-enantiomer. The O-glucuronide metabolite, M22, was found to be significantly less potent than mirdametinib in an in vitro phospho-ERK pharmacodynamic assay across 3 tumour cell lines. Renal elimination is not considered a substantial route of excretion for either mirdametinib or its primary active metabolite PD-0315209. Mirdametinib is highly protein bound (≥98.7%). The potential impact of renal impairment on the PK of mirdametinib is considered to be low. The estimated unbound fraction of mirdametinib is 0.3%, which suggests that hemodialysis is unlikely to result in additional elimination. PopPK analysis indicated that no relationship with mirdametinib PK parameters was observed for CLCR. Although an increase in PD-0315209 exposures for participants with moderate renal impairment is predicted, these predicted exposures are far below the concentrations associated with pERK inhibition in nonclinical experiments. Mild or moderate renal impairment is not expected to have a clinically meaningful effect on the PK of mirdametinib and PD-0315209.
Patients with cardiovascular impairment	Dedicated studies of mirdametinib in patients with cardiovascular impairment have not been conducted. In Study MEK-NF-201, participants were excluded if they had reported clinically significant cardiac disease, myocardial infarction, severe/unstable angina, coronary/peripheral artery bypass graft, cerebrovascular accident, transient ischemic attack, or symptomatic pulmonary embolism within 6 months (24 weeks) of signing informed consent/assent. Participants were also excluded if they had a recorded left ventricular ejection fraction (LVEF) <55% at screening or within 3 years of signing informed consent/assent or had a history of congestive heart failure. At the maximum

Type of Special Population	Exposure
	recommended dose of 4 mg BID, clinically significant QTc interval prolongation was not observed. Ejection fraction decreased is an Important Identified Risk for mirdametinib. Cardiomyopathy and cardiac failure are not identified risks for mirdametinib. Adverse effects on cardiac conduction is an Important Potential Risk for mirdametinib.
Patients with a disease severity different from inclusion criteria in clinical trials	Pool 1 studies focused on NF1 PN patients with symptomatic disease. No interventional study has been conducted in Adult or Paediatric NF1 PN patients who were asymptomatic or with malignant peripheral nerve sheath tumours.
Population with relevant different ethnic origin	In Pool 1, 71% (94/133) of the population in the clinical development programme were White, 16% (21/133) were Black or African American, 5% (6/133) were Asian, 1% (1/133) were American Indian or Alaska Native and 8% (11/133) were unspecified.
Subpopulations carrying relevant genetics	Only patients with Neurofibromatosis Type 1 were enrolled in Pool 1 studies. Genetics were not assessed in Pool 1.
Other	None

Part II: MODULE SV - Post-authorisation experience

Not applicable as mirdametinib is not currently approved for use in any territory worldwide.

SV.1.1 Method used to calculate exposure

Not applicable

SV.1.2 Exposure

Not applicable

Part II: MODULE SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

Mirdametinib crosses the blood brain barrier. No studies to assess the potential for drug abuse have been conducted. In both Pool 1 and Pool 2, there were no psychiatric treatment emergent adverse events (TEAEs) for euphoria, disinhibition, dissociation, or any other MedDRA Preferred Terms (PTs) that might suggest a psychoactive effect that could lead to drug abuse. Thus, mirdametinib is not expected to be subject to abuse or potential for misuse for illegal purposes.

Part II: MODULE SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

A summary of the identified and potential risks for mirdametinib with the rationale whether the risk is or is not considered important is included. Details for the important identified and potential risks and missing information that have potential impact on the risk-benefit assessment and/or public health or may require either further characterisation or evaluation, or implementation of specific risk minimisation activities are further characterised. Safety concerns for mirdametinib are derived from an assessment of all clinical and non-clinical data.

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

The following risks are not considered important for inclusion in the list of safety concerns in the RMP. These risks have been reported in Pool 1 in the NF1 PN population and are considered to be adverse drug reactions. Overall, these risks are not considered to have an impact on the overall benefit risk profile of mirdametinib or have an implication for public health.

Table 12: Risk with minimal clinical impact on patients (in relation to the severity of the indication treated)

Events	Supportive Information
Dry skin	In Pool 1, the incidence of TEAEs in paediatric, adult, and overall participants was 17.2%, 13.3% and 15.0%, respectively. There were no Grade ≥3 TEAEs.

Events	Supportive Information
Alopecia	In Pool 1, the incidence of TEAEs in paediatric, adult, and overall participants was 13.8%, 12.0%, and 12.8%, respectively. There were no Grade ≥3 TEAEs.
Pruritus	In Pool 1, the incidence of TEAEs in paediatric, adult, and overall participants was 12.1%, 13.3%, and 12.8%, respectively. There were no Grade ≥3 TEAEs.
Eczema	In Pool 1, the incidence of TEAEs in paediatric, adult, and overall participants was 13.8%, 2.7%, and 7.5%, respectively[1]. There were no Grade ≥3 TEAEs.
Hair colour changes	In Pool 1, the incidence of TEAEs in paediatric, adult, and overall participants was 12.1%, 1.3%, and 6.0%, respectively. There were no Grade ≥3 TEAEs.
Hair texture abnormal	In Pool 1, the incidence of TEAEs in paediatric, adult, and overall participants was 5.2%, 1.3%, and 3.0%, respectively. There were no Grade ≥3 TEAEs.
Nausea	In Pool 1, the incidence of TEAEs in paediatric, adult, and overall participants was 29.3%, 54.7%, and 43.6%, respectively. There were no Grade ≥3 TEAEs.
Vomiting	In Pool 1, the incidence of TEAEs in paediatric, adult, and overall participants was 39.7%, 37.3%, and 38.3%, respectively. There were no Grade ≥3 TEAEs.
Constipation	In Pool 1, the incidence of TEAEs in paediatric, adult, and overall participants was 10.3%, 18.7%, and 15.0%, respectively. There were no Grade ≥3 TEAEs.
Stomatitis*	In Pool 1, the incidence of TEAEs in paediatric, adult, and overall participants was 19.0%, 5.3%, and 11.3%, respectively[1]. There were no Grade ≥3 TEAEs.
Paronychia	In Pool 1, the incidence of TEAEs in paediatric, adult, and overall participants was 32.8%, 2.7%, and 15.8%, respectively[1]. There were no Grade ≥3 TEAEs.
Increased AST	In Pool 1, the incidence of increased AST in paediatric, adult, and overall participants was 8.6%, 16.0%, and 12.8%, respectively. There were no Grade ≥3 abnormalities.
Increased ALT	In Pool 1, the incidence of increased ALT in paediatric, adult, and overall participants was 20.7%, 6.7%, and 12.8%, respectively. There were no Grade ≥3 abnormalities.

Events	Supportive Information
Increased blood alkaline phosphatase	In Pool 1, the incidence of increased blood alkaline phosphatase in paediatric, adult, and overall participants was 27.6%, 13.3%, and 19.5%, respectively. There were no Grade ≥3 abnormalities.
Dry mouth	In Pool 1, the incidence of dry mouth in paediatric, adult, and overall participants was 0%, 6.7%, and 3.8% respectively. There were no Grade ≥3 TEAEs.
Oedema peripheral	In Pool 1, the incidence of oedema peripheral in paediatric, adult, and overall participants was 3.4%, 10.7%, and 7.5% respectively. There were no Grade ≥3 TEAEs.
Leucocyte count decreased	In Pool 1, the incidence of leucocyte count decreased in paediatric, adult, and overall participants was 51.7%, 6.7%, and 26.3% respectively. There were no Grade ≥3 shifts from baseline.

*Includes stomatitis, mouth ulceration, aphthous ulcer

Table 13: Known risks that require no further characterisation and is followed up via routine pharmacovigilance namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered by prescribers.

Events	Supportive Information
Dermatitis acneiform	In Pool 1, the incidence of TEAEs (Grade ≥3 TEAEs) in paediatric, adult, and overall participants was 43.1% (1.7%), 82.7% (6.7%), and 65.4% (4.5%), respectively.
Rash*	In Pool 1, the incidence of TEAEs (Grade ≥3 TEAEs) in paediatric, adult, and overall participants was 32.8% (1.7%), 17.3% (1.3%), and 24.1% (1.5%), respectively.
Diarrhoea	In Pool 1, the incidence of TEAEs (Grade ≥3 TEAEs) in paediatric, adult, and overall participants was 53.4% (5.2%), 54.7% (0%), and 54.1 (2.3%), respectively.
Abdominal pain**	In Pool 1, the incidence of TEAEs (Grade ≥3 TEAEs) in paediatric, adult, and overall participants was 39.7% (3.4%), 20.0% (4.0%), and 28.6% (3.8%), respectively.
Fatigue	In Pool 1, the incidence of TEAEs (Grade ≥3 TEAEs) in paediatric, adult, and overall participants was 12.1% (0%), 36.0% (1.3%), and 25.6% (0.8%).
Increased blood creatine phosphokinase (CPK)	In Pool 1, the incidence (Grade ≥3) of increased blood CPK in paediatric, adult, and overall participants was 58.6% (5.2%), 45.3% (2.7%), and 51.1% (3.8%), respectively. This risk is not considered

Events	Supportive Information
	important in view of the lack of reports of serious events, including no reports of rhabdomyolysis.
Decreased neutrophils	In Pool 1, the incidence (Grade ≥3) of decreased neutrophils in paediatric, adult, and overall participants was 29.3% (10.3%), 8.0% (1.3%), and 17.3% (5.3%), respectively. This risk is not considered important in view of the lack of reports of febrile neutropenia or opportunistic infections associated with decreased neutrophils in any participant in Pool 1.
Musculoskeletal pain***	In Pool 1, the incidence (Grade ≥3) of musculoskeletal pain in paediatric, adult, and overall participants was 41.1% (1.8%), 41.4%, (5.2%), and 41.2% (3.5%), respectively.
Headache	In Pool 1, the incidence of headache (Grade ≥3) in paediatric, adult, and overall participants was 36.2% (1.7%), 16.0% (1.3%), and 24.8% (1.5%), respectively.
Effect on male and female fertility	Based on findings in animals, mirdametinib may impair fertility in males and females of reproductive potential. The reversibility of the effects on male and female reproductive organs in animals is unknown. There are no data on the effect of mirdametinib on human fertility. The potential risk for humans is unknown.

*Includes Rash, Rash maculo-papular, Rash pustular, Rash erythematous, Rash papular, Exfoliative rash, Papule, Rash macular, Rash pruritic

**Includes abdominal pain and abdominal pain upper

***Includes Myalgia, Musculoskeletal pain, Pain in extremity, Back pain, Musculoskeletal Chest pain, Neck pain, Non-cardiac chest pain, Arthralgia, and Bone pain

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

SVII.1.2.1. Important Identified Risks

Important Identified Risk: Ocular events (RVO, RPED, Vision blurred)	
Scientific evidence for risk to be added in the safety specification	Several MEK inhibitors have been reported to cause ocular toxicities, such as central serous retinopathy, RVO or periorbital oedema. These ocular toxicities appear to be a class effect of MEK inhibition. MEK inhibitors have been reported to cause unique dose- and time-dependent MEK inhibitor-associated retinopathy (MEKAR), which is an umbrella term that includes serous retinopathy, central serous chorioretinopathy, serous retinal detachments (SRD), macular oedema, visual disturbance, retinopathy, chorioretinopathy and blurred vision (Stjepanovic 2016). Retinal vein occlusion (RVO) is an uncommon but

Important Identified Risk: Ocular events (RVO, RPED, Vision blurred)	
	potentially serious adverse event reported in initial clinical trials of several MEK inhibitors (Han 2023). In Pool 1, Eye disorders were reported in 11 (19%) paediatric participants and 21 (28%) adult participants. In Pool 2, Eye disorders were reported in 55 (48.7%) participants. In Pool 1, RVO has been observed in 2 (3%) adult participants. RVO was not observed in paediatric participants. In Pool 2, RVO was observed in 3 (3%) adult participants with advanced cancers receiving mirdametinib at doses ≥5mg BID. All participants who reported RVO had at least 1 predisposing factor including hypertension, diabetes, hypercholesterolaemia, COVID-19 vaccination, advanced cancer, or concomitant medications. In Pool 1, Vision blurred was reported by 4 (7%) paediatric and 7 (9%) adult participants. In Pool 2, Vision blurred was reported in 16 (14.2%) participants. In Pool 1, asymptomatic Retinal pigment epithelium detachment (RPED) was reported in 1 (1%) adult participant and was not reported in any paediatric participants. In Pool 2, no participant reported RPED. One participant in the compassionate use programme (CUP) with NF1 PN treated with mirdametinib 4 mg BID reported a non-serious event of RPED.
Risk-benefit impact	Additional information from a Post Authorisation Safety Study (PASS) will be conducted to further characterise the identified risk of Ocular events (RVO, RPED, Vision blurred) in patients initiating mirdametinib therapy.

Important Identified Risk: Ejection Fraction Decreased	
Scientific evidence for risk to be added in the safety specification	The MAPK signaling cascade is important for cardiac adaptation in response to stress; when inhibited, the heart cannot compensate by getting stronger or preventing cell death. Mice that lack ERK1/2 have normal cardiac size and function but are more susceptible to cardiomyocyte apoptosis and suffer greater cardiac damage in response to insult (Lips 2004). This finding suggests that susceptibility to MEK inhibitor associated injury does not occur due to drug exposure alone but requires a second source of injury (e.g., hypertension, ischemia, or other toxic drug exposure) (Banks 2017). MEK inhibition alone at lower doses in the NF1 paediatric patient population is also associated with cardiac AEs, primarily

Important Identified Risk: Ejection Fraction Decreased	
	cardiomyopathy/ejection fraction decrease and hypertension (Gross 2023). In Study MEK-NF-201, 20 events of asymptomatic ejection fraction decreased were observed in 15 (27%) paediatric participants and 13 events of were observed in 9 (16%) adult participants. The median (min, max) ejection fraction at baseline was similar between the cohorts, 65% (55%, 78%) in paediatric participants, and 62% (55%, 80%) in adult participants. For those participants still receiving mirdametinib after 1 year, the median (min, max) ejection fraction was largely unchanged from baseline at 63.2% (50%, 77%) in paediatric, and 60% (53%, 67%) in adult participants. In Study MEK-NF-201, 1 participant in each cohort was observed to have an event of ejection fraction decreased with a >10% absolute value decrease from their baseline value to an ejection fraction <50%. All events were asymptomatic and no events of cardiomyopathy or left ventricular dysfunction were reported.
Risk-benefit impact	Additional information from a Post Authorisation Safety Study (PASS) will be conducted to further characterise the identified risk of Ejection fraction decreased in patients initiating mirdametinib therapy.

SVII.1.2.2. Important Potential Risks

Important Potential Risk: Embryo-foetal toxicity	
Scientific evidence for risk to be added in the safety specification	Significant embryo-foetal development toxicities were observed in both the rat and rabbit range-finding studies, manifesting as foetal resorptions, post-implantation loss, and decreased foetal weights. There is a known requirement for MEK in embryonic development (Giroux 1999). The findings with mirdametinib are consistent with the embryo-foetal toxicity observed in nonclinical studies with other MEK inhibitors and are considered a class effect. Specifically, these findings from animal studies were noted with approved MEK inhibitors selumetinib (KOSELUGO SmPC), trametinib (MEKINIST® SmPC), binimetinib (MEKTOVI® SmPC), and cobimetinib (COTELLIC® SmPC), which clearly highlight the class effect of these compounds related to potential foetal harm if these agents are administered to pregnant women. Mirdametinib was not genotoxic in a bacterial reverse mutation (Ames) assay or in an in vitro human lymphocyte chromosomal aberration assay but was equivocal in the in vivo micronucleus study and in vivo chromosomal aberrations study in rats. A

Important Potential Risk: Embryo-foetal toxicity	
	genotoxicity risk in humans could not be excluded. One participant in Study MEK-NF-201 had a positive urine pregnancy test reported 31 days after the last dose of mirdametinib. The pregnancy ended in a first trimester spontaneous abortion.
Risk-benefit impact	Additional information from a Post Authorisation Safety Study (PASS) will be conducted to further characterise the potential risk of Embryo-foetal toxicity.

Important Potential Risk: Physeal dysplasia	
Scientific evidence for risk to be added in the safety specification	Administration of mirdametinib to rats resulted in bone lesions that included necrosis of the metaphysis and the ossifying zone of the physis and thickening of the zone of hypertrophying cartilage of the physis. The expansion of chondrocytes in the physis may be a response to the metaphyseal necrosis and loss of osteoprogenitor cells. These changes are characterised by localised injury to bone, which appear to be due to local ischaemia and/or necrosis. Skeletal vascular changes may be present in these animals, resulting in disruption of endochondral ossification. Skeletal lesions, including bone necrosis, can result from Vitamin D intoxication (Haschek 1978). In the pivotal 1- and 3-month studies in rats, hypocellularity in the metaphyseal region of the distal portion of the femur and/or proximal portion of the tibia occurred in males only at 1 mg/kg/day and was reversible following cessation of dosing in the 1-month study. In addition, thickening of the bony trabeculae in the femoral/tibial metaphyseal region was evident in all males at 1.0 mg/kg/day in the 3-month study. Bone lesions, like those observed in rats, have not been seen in dogs, monkeys, or mice given mirdametinib.
Risk-benefit impact	Additional information from a Post Authorisation Safety Study (PASS) will be conducted to further characterise the potential risk of physeal dysplasia among paediatric patients initiating mirdametinib therapy.

Important Potential Risk: Adverse effects on cardiac conduction	
Scientific evidence for risk to be added in the safety specification	In a GLP-compliant in vitro assay using isolated canine Purkinje fibres, mirdametinib reduced action potential duration at concentrations of 10 µM and 100 µM and reduced the maximum rate of depolarisation and amplitude at 100 µM. 10 µM is approximately 2500-fold higher than the unbound steady-state maximum concentration (Cmaxss,u) of mirdametinib at the clinical dose (2 mg/m^2 BID; [maximum dose of 4 mg BID]) in Study MEK-NF-201. In this assay, there was no meaningful effect on resting membrane potential at any tested concentrations of

Important Potential Risk: Adverse effects on cardiac conduction	
	mirdametinib. In a (GLP)-compliant in vitro study, mirdametinib and the metabolite PD-0315209 did not inhibit hERG current at a concentration of 10 µM. In a GLP-compliant cardiovascular study in telemetered monkeys, there were no mirdametinib-related effects in blood pressure, heart rate, body temperature, or electrocardiography parameters, including QT interval, for 24 hours after single oral doses up to 10 mg/kg. Mirdametinib exposure at the 10 mg/kg dose was 10-fold higher than the unbound exposure (Cmaxss,u) of mirdametinib at the clinical dose (2 mg/m^2 BID [maximum dose of 4 mg BID]) in Study MEK-NF-201. In a secondary pharmacodynamic study conducted with mirdametinib at 1 and 10 µM against a panel of 87 targets, inhibition of the L-type calcium channel by 54% was observed at 10 µM (2500-fold higher than the human mirdametinib Cmaxss,u at the clinical dose). In a thorough QT study conducted in healthy participants, no clinically significant effect of mirdametinib at supratherapeutic exposures (up to 6-fold higher than the Cmax,ss in Study MEK-NF-201) on baseline-adjusted QTcF or QTc prolongation was observed. There was also no statistically significant change observed in the QRS interval.
Risk-benefit impact	Additional information from a Post Authorisation Safety Study (PASS) will be conducted to further characterise the potential risk of adverse effects on cardiac conduction in patients initiating mirdametinib therapy.

Important Potential Risk: Carcinogenicity	
Scientific evidence for risk to be added in the safety specification	Mirdametinib was equivocal in the in vivo micronucleus study and in vivo chromosomal aberrations study in rats, and these findings may relate to a potential aneugenic mechanism that has been observed with other MEK inhibitors. Mirdametinib treatment resulted in equivocal findings in the in vivo genotoxicity studies in rats, was negative for carcinogenicity in transgenic mice, and the currently ongoing 2-year carcinogenicity study in rats is testing dose levels that will produce exposures below the therapeutic clinical exposure because of tolerability issues in rats.
Risk-benefit impact	Additional information from a Post Authorisation Safety Study (PASS) will be conducted to further characterise the potential risk of carcinogenicity in patients initiating mirdametinib therapy.,

SVII.1.2.3. Missing Information

Long term safety	
Evidence source	The overall median duration of exposure in Pool 1 was 22 months (range 0.4 to 45.6), with 22 months (range 1.6 to 40.1) in the paediatric cohort and 19 months (range 0.4 – 45.6) in the adult cohort. Six paediatric participants and 10 adult participants have been exposed to mirdametinib for > 36 months.
Risk benefit impact	Additional information from a PASS will be conducted to further characterise the missing information on long term safety of mirdametinib in paediatric and adult patients.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

Not applicable

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

SVII.3.1.1. Important Identified Risks

Important Identified Risk: Ocular events (RVO, RPED, Vision blurred)	
Potential mechanisms	The MAPK pathway contributes to the maintenance, protection, and repair of the retina and the retinal pigment epithelium (Méndez-Martínez 2019). MEK inhibition may block anti-apoptotic proteins, block natural retinal reactions to stress or oxidative injury, prevent repair of damaged retinal pigment epithelium cells, that ultimately leads to the accumulation of damage and the degeneration of cells (Van der Noll 2013). MEK pathway inhibition leads to disruption of aquaporin channels in membranes of the retinal pigment epithelium (RPE), leading to fluid accumulation. The accumulation of the drug at major vessels within the retina is thought to be responsible for the unique characteristic of MEKAR, causing bilateral macular foci of fluid without gravitational dependency, located between the RPE and interdigitation zone of the neural retina (Booth 2020). The microvascular abnormalities associated with NF1 may make this patient population susceptible to RVO (Moadel 1994, Mori 2001). RVO has been described in clinical trials of MEK inhibitors (Méndez-Martínez 2019).
Evidence source(s) and strength of evidence	Several MEK inhibitors have been reported to cause ocular toxicities, such as central serous retinopathy, RVO, or periorbital oedema. These ocular toxicities appear to be a class effect of MEK inhibition. MEK inhibitors have been reported to cause unique dose- and time-dependent MEKAR, which is an umbrella term that includes serous retinopathy, central serous chorioretinopathy, SRD, macular oedema, visual disturbance, retinopathy, chorioretinopathy, and blurred vision. (Stjepanovic 2016).

Important Identified Risk: Ocular events (RVO, RPED, Vision blurred)	
	Asymptomatic retinal changes may be present in a large percentage of MEK inhibitor treated patients (van Dijk 2018) and ocular toxicities with MEK inhibitors appear to be a class effect that is generally transient in nature (van der Noll 2013, Leijen 2012, LoRusso 2010, van Dijk 2018). Dose and dosing schedules may be important factors for the risk of RVO in patients treated with MEK inhibitors (van der Noll 2013). RVO has been described in clinical trials of trametinib, selumetinib, RO4987655, refametinib, pimasertib, and binimetinib (Méndez-Martínez 2019).
Characterisation of risk: Frequency	In Pool 1, Eye disorders were reported in 11 (19%) paediatric participants and 21 (28%) adult participants. In Pool 2, Eye disorders were reported in 55 (48.7%) participants. RVO: In Pool 1, RVO was reported in 2 (3%) adult participants. No events of RVO were reported in paediatric participants. In Pool 2, 3 (3%) participants with advanced cancers receiving mirdametinib at doses ≥5mg BID reported RVO. All participants who reported RVO had at least 1 predisposing factor including hypertension, diabetes, hypercholesterolemia, COVID-19 vaccination, advanced cancer, or concomitant medications. These participants are described below. In Pool 1, 1 participant who experienced RVO, a female in her 20's, reported the concomitant use of the hormonal contraceptive implant, Nexplanon, and recent COVID-19 vaccination (with the second vaccination dose administered 9 days prior to the onset of the event of RVO). A 2nd participant in Pool 1, a male in his 40's with a medical history of hyperlipidemia, a calculated BMI of 37 indicating obesity and recent COVID-19 vaccination 5 months prior to event onset, experienced 2 asymptomatic events of RVO approximately 2 years apart while receiving mirdametinib treatment. The events occurred in contralateral eyes, with the first event occurring approximately 1 year after initiation of mirdametinib. All of the participants in Pool 2 were receiving mirdametinib for the treatment of advanced cancers. One participant, a male in his 40's reported a medical history of arterial hypertension. A 2nd participant in Pool 2, a male in his 70's, reported a medical history of type 2 diabetes mellitus, hypertension, and hypercholesterolemia. The 3rd participant in Pool 2 experiencing RVO, a male in his 50's, reported no additional confounding factors than his malignant neoplasm. Vision blurred: In Pool 1, Vision blurred was reported in 11 (8%) participants: 4 (7%) paediatrics and 7 (9%) adults. In Pool 2, Vision blurred was reported in 16 (14.2%) participants. RPED: In Pool 1, asymptomatic RPED was reported in 1 (1%) adult participant. RPED was not reported in any paediatric participant. No participant in Pool 2 reported RPED. One participant in the CUP with NF1 PN treated with mirdametinib 4 mg BID reported a single non-serious event of RPED.
Seriousness	RVO: In Pool 1, one serious RVO was reported by an adult female participant

Important Identified Risk: Ocular events (RVO, RPED, Vision blurred)	
	with NF1 PN receiving mirdametinib at a dose of 4 mg BID. The participant reported non-serious acute onset of Vision blurred on Day 127 and subsequent onset of RVO on Day 130. Examination on Day 130 revealed a corrected visual acuity of 20/100 right eye (OD), 20/20 left eye (OS) (decreased from her baseline visual acuity of 20/20 OD, 20/20-1 OS), blurred optic disc margins, scattered retinal haemorrhages, and tortuous vessels in the right eye. She permanently discontinued treatment as a result of the event. No treatment was provided for this event. The event was resolved with sequelae of residual blurriness and decreased acuity to right eye on Day 435. At last follow-up on Day 469, the participant's visual acuity was reported as 20/30-2 OD, 20/20 OS, with no evidence of macular oedema, no residual dot blood haemorrhage, normal foveal contour and no fluid, but with nasal retinal thinning/atrophy of the right eye. In Pool 2, three serious RVOs were reported by participants receiving mirdametinib at doses ≥5mg BID. One male participant receiving 10 mg BID reported RVO with decreased vision in the right eye on Day 130. Mirdametinib was permanently discontinued and the RVO resulted in permanent central vision loss. One male participant receiving 5 mg BID reported Grade 3 bilateral RVO and Grade 2 bilateral papilloedema on Day 253. Mirdametinib was permanently discontinued and both events resolved on Day 292 and on Day 342, respectively. One male participant receiving 15 mg BID reported Grade 3 RVO with an episode of Vision blurred first in the left eye and subsequently in the right eye starting on Day 104. Mirdametinib was permanently discontinued, and the outcome was not resolved at last follow-up. Vision blurred: There were no serious events of Vision blurred in either Pool 1 or Pool 2. RPED: There were no serious events of RPED in either Pool 1 or Pool 2.
Severity	RVO: In Pool 1, there was one Grade 3 event and two Grade 1 events. In Pool 2, there were two Grade 3 events and one Grade 2 event. Vision blurred: In Pool 1 and Pool 2, all events of Vision blurred were Grade 1 or 2. There were no Grade ≥ 3 events. RPED: The 1 event of RPED in Pool 1 was Grade 1 and asymptomatic. There were no Grade ≥2 events in Pool 1. The 1 event in the CUP was Grade 2.
Risk factors and risk groups	RVO: A basic risk factor for RVO is advancing age. Further risk factors include systemic conditions such as hypertension, arteriosclerosis, diabetes mellitus, hyperlipidaemia, vascular cerebral stroke, blood hyperviscosity, and thrombophilia. A strong risk factor for RVO is metabolic syndrome (hypertension, diabetes mellitus, and hyperlipidemia). Individuals with end-organ damage caused by diabetes mellitus and hypertension have a greatly increased risk for RVO. Socioeconomic status seems to also be a risk factor. American blacks are more often diagnosed with RVO than non-Hispanic whites. Females are, according to some studies, at lower risk than men. The role of thrombophilic risk factors in RVO is still controversial. Congenital

Important Identified Risk: Ocular events (RVO, RPED, Vision blurred)	
	thrombophilic diseases including Factor V Leiden mutation, hyperhomocysteinemia and anticardiolipin antibodies increase the risk of RVO (Kolar 2014). Further, hypercoagulability induced by systemic malignancy has also been associated with RVO (Mishra 2023). RVO is an uncommon but potentially serious adverse event reported in initial clinical trials of several MEK inhibitors (Han 2023). Cigarette smoking also increases the risk of RVO as do systemic inflammatory conditions like vasculitis and Behcet disease. Ophthalmic risk factors for RVO are ocular hypertension and glaucoma, higher ocular perfusion pressure, and changes in the retinal arteries (Kolar 2014). Additionally, COVID-19 vaccination has been associated with an increased risk of RVO (Li 2023), and oral contraceptives have been implicated in the pathogenesis of occlusive retinopathy (Somisetty 2023). Vision blurred and RPED: Age, glomerular filtration rate, and history of ocular disease (particularly inflammatory eye disease) were associated with a risk of MEK inhibitor-induced retinopathy in a study of 247 patients treated with cobimetinib and vemurafenib (Booth 2020). However, these patients were participants in an advanced melanoma study and the same conclusions may not necessarily be applicable to the NF1 population. Additionally, NF1 mutations place patients at risk for the development of glaucoma, choroidal abnormalities including reduced choroid thickness or altered choroidal circulation due to the presence of nodules, and infrequently, retinal alterations which have been described in case reports as microvascular abnormalities. Finally, optic pathway glioma occurs frequently in patients with NF1, which can result in reduced visual acuity, visual field defects, oedema of the papilla, proptosis, and strabismus (Abdolrahimzadeh 2016).
Preventability	The product labelling will provide prescribers information regarding the need for patients to report any new visual disturbances, and recommend an ophthalmological evaluation prior to treatment initiation, at regular intervals during treatment, and at any time a patient reports new or worsening visual changes such as blurred vision. If RVO is diagnosed, treatment with mirdametinib should be permanently discontinued. If symptomatic RPED is diagnosed, treatment with mirdametinib should be interrupted until resolution and the dose reduced when treatment is resumed. The product labelling will inform patients that EZMEKLY can cause eye problems, that their doctor will check their vision before and during treatment, and to tell their doctor straight away if they get blurred vision, or any other changes to their vision, such as reduced vision, during treatment.
Impact on the risk-benefit balance of the product	Additional information from a Post Authorisation Safety Study (PASS) will be conducted to further characterise the identified risk of Ocular events (RVO, RPED, Vision blurred) in patients initiating mirdametinib therapy.
Public health impact	There is no public health impact of Ocular events associated with use of mirdametinib.

Important Identified Risk: Ejection fraction decreased	
Potential mechanisms	Several nonclinical studies demonstrate that the MEK-ERK pathway is critical for the hypertrophic response to stimulus or pressure overload, and dysregulation or modulation of MEK-ERK can impact cardiac or cardiomyocyte hypertrophy, interstitial fibrosis, contractility, cardiomyocyte apoptosis, and left ventricular (LV) systolic function (Bueno 2000, Muslin 2008, Purcell 2007, Streicher 2010). MEK inhibition could impair the beneficial effects produced by MEK signalling. The MAPK signalling cascade is important for cardiac adaptation in response to stress; when inhibited, the heart cannot compensate by getting stronger or preventing cell death. Mice that lack ERK1/2 have normal cardiac size and function but are more susceptible to cardiomyocyte apoptosis and suffer greater cardiac damage in response to insult (Lips 2004). This finding suggests that susceptibility to MEK inhibitor associated injury does not occur due to drug exposure alone but requires a second source of injury (e.g., hypertension, ischemia, or other toxic drug exposure) (Banks 2017).
Evidence source(s) and strength of evidence	Cardiotoxicity is a concern with the combination of v-Raf murine sarcoma viral oncogene homolog (BRAF) inhibitors and MEK inhibitors in melanoma patients with BRAF gene mutation, although cardiomyopathy or ejection fraction decrease appear to be attributed primarily to MEK inhibition (Banks 2017, Dolladille 2020, Glen 2022). MEK inhibition alone at lower doses in the NF1 PN paediatric patient population is also associated with cardiac AEs, primarily ejection fraction decrease and hypertension (Gross 2023). Decreased ejection fraction and cardiotoxicity have been described for the approved MEK inhibitors trametinib (Banks 2017) and selumetinib (Koselugo SmPC).
Characterisation of risk: Frequency	In Pool 1, asymptomatic ejection fraction decreased was observed in 15 (27%) paediatric participants and 9 (16%) adult participants. For those still receiving mirdametinib after 1 year, the median (min, max) ejection fraction was largely unchanged from baseline at 63.2% (50%,77%) in paediatric participants, and 60% (53%, 67%) in adult participants. One adult and one paediatric participant were observed to have an event of asymptomatic ejection fraction decreased with a >10% absolute value decrease from their baseline value to an ejection fraction <50%. In Pool 2, 5 (22%) participants receiving mirdametinib at the 8, 10 mg BID dose reported an event of asymptomatic ejection fraction decreased while 5 (6.8%) participants receiving the highest doses of mirdametinib, ranging from 15mg to 30mg BID reported an asymptomatic event. Among 7 (10%) participants with data available at Cycle 3 Day 1, the median (min, max) ejection fraction was similar to baseline at 64% (51%, 71%).
Seriousness	There were no serious adverse events of ejection fraction decreased in either Pool 1 or Pool 2.
Severity	In Pool 1, one paediatric participant had a Grade 3 event. No adult participant had a Grade ≥3 event. All events were asymptomatic and there were no Grade 4 events in Pool 1. No events of cardiomyopathy, cardiac failure, ventricular failure (non-specified, left, or right), or left ventricular dysfunction were reported in Pool 1.

Important Identified Risk: Ejection fraction decreased	
	In Pool 2, two participants had Grade 3 events. There were no Grade 4 events.
Risk factors and risk groups	None have been identified.
Preventability	The product labelling will advise prescribers that LVEF should be evaluated by echocardiogram before initiation of treatment to establish baseline values and that prior to starting EZMEKLY treatment, patients should have an ejection fraction above the institutional LLN. In addition, the label will advise that LVEF should be evaluated by echocardiogram every 3 months during the first year, then as clinically indicated thereafter. Decreased LVEF can be managed using treatment interruption, dose reduction or treatment discontinuation. Prescribes will be advised that asymptomatic, absolute decrease in LVEF of 10% or greater from baseline and less than the lower limit of normal to interrupt treatment until improvement and resume at reduced dose. For any absolute decrease in LVEF of 20% or greater from baseline to discontinue treatment permanently. The product labelling will inform patients that EZMEKLY can lower the amount of blood pumped by their heart, that in clinical trials of EZMEKLY at the recommended dose, this did not cause any symptoms, and their doctor will check how well their heart works before and during treatment with EZMEKLY.
Impact on the risk-benefit balance of the product	Additional information from a Post Authorisation Safety Study (PASS) will be conducted to further characterise the identified risk of Ejection fraction decreased in patients initiating mirdametinib therapy.
Public health impact	There is no public health impact of ejection fraction decreased associated with the use of mirdametinib.

SVII.3.1.2. Important Potential Risks

Important Potential Risk: Embryo-foetal toxicity	
Potential mechanisms	There is a known requirement for MEK in embryonic development (Giroux 1999).
Evidence source(s) and strength of evidence	Significant embryo-foetal development toxicities were observed in both the rat and rabbit range-finding studies manifesting as foetal absorptions, post-implantation loss, and decreased foetal weights. The findings with mirdametinib are consistent with the embryo-foetal toxicity observed in nonclinical studies with other MEK inhibitors and are considered a class effect. Specifically, these findings from animal studies were noted with approved MEK inhibitors selumetinib (KOSELUGO SmPC , trametinib (MEKINIST SmPC), binimetinib (MEKTOVI SmPC), and cobimetinib (COTELLIC SmPC), which clearly highlight the class effect of these compounds related to potential foetal harm if these agents are administered to pregnant women. Mirdametinib was not genotoxic in a bacterial reverse mutation (Ames) assay or in an in vitro human lymphocyte chromosomal aberration assay but was equivocal in the in vivo micronucleus study and in vivo chromosomal aberrations study in rats. A genotoxic risk in humans could not be excluded.

Important Potential Risk: Embryo-foetal toxicity	
Characterisation of risk: Frequency	One participant in Study MEK-NF-201 had a positive urine pregnancy test reported 31 days after the last dose of mirdametinib. The pregnancy ended in a first trimester spontaneous abortion. There was one case of a partner pregnancy reported for a 34-year-old male with NF1 PN treated with mirdametinib 4 mg BID. The outcome of the pregnancy is unknown.
Seriousness	One serious event of Abortion spontaneous occurred in a MEK-NF-201 participant more than 30 days after discontinuing study treatment.
Severity	The sole clinical event of Abortion spontaneous was Grade 4.
Risk factors and risk groups	Females of reproductive potential and their partners.
Preventability	The product labelling will advise prescribers that women of childbearing potential that EZMEKLY may cause foetal harm and to avoid becoming pregnant while receiving EZMEKLY. The label will also recommend that a pregnancy test should be performed on women of childbearing potential prior to initiating treatment, and that both female and male patients (of reproductive potential) should be advised to use effective contraception during treatment and for 6 months and 3 months, respectively, after the last dose. In addition, the label will communicate that the effect of mirdametinib on the exposure of systemically acting hormonal contraceptives has not been evaluated and therefore women using systemically acting hormonal contraceptives should be recommended to add a barrier method. The product labelling will inform patients that EZMEKLY is not recommended during pregnancy as it may cause harm to an unborn baby. It will also inform that if they may be pregnant or are planning to have a baby, to ask their doctor for advice before taking EZMEKLY. Additionally, patients will be informed that their doctor may ask them to take a pregnancy test before starting treatment, that they should not become pregnant while taking EZMEKLY, that if they or their partner are able to become pregnant, effective contraception (birth control) must be used, and that if they become pregnant during treatment, to tell their doctor straight away. Male patients will be informed that if their partner becomes pregnant while they are taking EZMEKLY, tell their doctor straight away.
Impact on the risk-benefit balance of the product	Additional information from a Post Authorisation Safety Study (PASS) will be conducted to further characterise the potential risk of Embryo-foetal toxicity.
Public health impact	There is no public health impact of embryo-foetal associated with the use of mirdametinib.

Important Potential Risk: Physeal dysplasia	
Potential mechanisms	The expansion of chondrocytes in the physis may be a response to the metaphyseal necrosis and loss of osteoprogenitor cells. These changes are characterised by localised injury to bone, which appear to be due to local ischaemia and/or necrosis. Skeletal vascular changes may be present in these animals, resulting in disruption of endochondral ossification. Skeletal lesions, including bone necrosis, can result from Vitamin D intoxication (Haschek 1978).
Evidence source(s) and strength of evidence	Administration of mirdametinib to rats resulted in bone lesions that included necrosis of the metaphysis and the ossifying zone of the physis and thickening of the zone of hypertrophying cartilage of the physis. In the pivotal 1- and 3-month studies in rats, hypocellularity in the metaphyseal region of the distal portion of the femur and/or proximal portion of the tibia occurred in males only at 1 mg/kg/day and was reversible following cessation of dosing in the 1-month study. In addition, thickening of the bony trabeculae in the femoral/tibial metaphyseal region was evident in all males at 1.0 mg/kg/day in the 3-month study. Bone lesions, like those observed in rats, have not been seen in dogs, monkeys, or mice given mirdametinib.
Characterisation of risk: Frequency	Physeal dysplasia has not been observed in human studies of mirdametinib.
Seriousness	Not applicable
Severity	Not applicable
Risk factors and risk groups	Paediatric patients with open growth plates.
Preventability	The product labelling will advise on the nonclinical findings in rats.
Impact on the risk-benefit balance of the product	With the implementation of routine risk minimisation measures, the risk-benefit of mirdametinib remains positive. Further characterisation of this potential risk will be evaluated through a long term safety study.
Public health impact	There is no public health impact of physeal dysplasia associated with the use of mirdametinib.

Important Potential Risk: Adverse effects on cardiac conduction	
Potential mechanisms	Mirdametinib reduced action potential duration at concentrations of 10 µM and 100 µM and reduced the maximum rate of depolarisation and amplitude at 100 µM. 10 µM is approximately 2500-fold higher than the unbound steady-state maximum concentration (Cmaxss,u) of mirdametinib at the clinical dose (2 mg/m^2 BID [maximum dose of 4 mg BID]) in Study MEK-NF-201.
Evidence source(s) and strength of evidence	In a (GLP)-compliant in vitro study, mirdametinib and the metabolite PD-0315209 did not inhibit hERG current at a concentration of 10 µM. In a GLP-compliant in vitro assay using isolated canine Purkinje fibres, there was no meaningful effect on resting membrane potential at any tested concentrations of mirdametinib. Mirdametinib did reduce action potential duration at high concentrations of 10 µM and 100 µM and reduced the maximum rate of depolarisation and amplitude at 100 µM. 10 µM is approximately 2500-fold higher than the unbound steady-state maximum concentration (Cmaxss,u) of mirdametinib at the clinical dose (2 mg/m^2 BID [maximum dose of 4 mg BID]) in Study MEK-NF-201 In a GLP-compliant cardiovascular study in telemetered monkeys, there were no mirdametinib-related effects in blood pressure, heart rate, body temperature, or electrocardiography parameters, including QT interval, for 24 hours after single oral doses up to 10 mg/kg. Mirdametinib exposure at the 10 mg/kg dose was 10-fold higher than the unbound exposure (Cmaxss,u) of mirdametinib at the clinical dose (2 mg/m^2 BID [maximum dose of 4 mg BID]) in Study MEK-NF-201. In a secondary pharmacodynamic study conducted with mirdametinib at 1 and 10 µM against a panel of 87 targets, inhibition of the L-type calcium channel by 54% was observed at 10 µM (2500-fold higher than the human mirdametinib Cmaxss,u at the clinical dose). In a thorough QT study conducted in healthy participants, no clinically significant effect of mirdametinib at supratherapeutic exposures (up to 6-fold higher than the Cmax,ss in Study MEK-NF-201) on baseline-adjusted QTcF or QTc prolongation was observed. There was also no statistically significant change observed in the QRS interval.
Characterisation of risk: Frequency	In Study MEK-NF-201, there were no major changes observed in electrocardiogram (ECG) parameters in any of the paediatric participants. In the adult cohort, 3 participants had QTc using Fridericia's formula (QTcF) between 450 and 480 msec throughout the study. One adult participant experienced an average QTcF of 480.50 msec on triplicate ECG on study day 178. This resolved without dose modification on a repeat ECG on study day 185 to an average QTcF of 446.01 msec, consistent with their baseline average QTcF of 447.45 msec. There was no QTcF change from baseline of >60 msec. One treatment-emergent adverse event (TEAE) of Grade 1 electrocardiogram QT prolonged was reported; this participant did not experience a QTcF >450 msec. There were no major changes observed in other ECG parameters, including QRS complex. In Pool 1, 4 (3.0%) participants, 1 (1.7%) paediatric and 3 (4.0%) adults, reported cardiac conduction defect TEAEs, and 14 (10.5%) participants, 7 (12.1%) paediatric and 7 (9.3%) adult participants, reported cardiac arrhythmia TEAEs. Most participants had predisposing concomitant conditions, including intercurrent illness, medical history, and pre-existing findings.

Important Potential Risk: Adverse effects on cardiac conduction	
	In Pool 2, 3 (2.7%) participants reported cardiac conduction defect TEAEs, and 20 (17.7%) participants reported cardiac arrhythmia TEAEs.
Seriousness	In Pool 1, no serious TEAEs associated with cardiac conduction or cardiac arrhythmias were reported. In Pool 2, participants reporting serious TEAEs associated with cardiac conduction or cardiac arrhythmias included atrial fibrillation (1.8%), tachycardia (1.8%), arrhythmia (0.9%), atrial flutter (0.9%), cardiac arrest (0.9%), ventricular fibrillation (0.9%), ventricular tachycardia (0.9%), and electrocardiogram repolarisation abnormality (0.9%).
Severity	All cardiac conduction and cardiac arrhythmia TEAEs in Pool 1 were Grade 1 or Grade 2. No TEAE was Grade ≥ 3. In Pool 2, 13 cardiac conduction or cardiac arrhythmia TEAEs were Grade ≥ 3.
Risk factors and risk groups	Patients with medical history of cardiac conduction disturbances or intercurrent illnesses associated with changes in cardiac conduction.
Preventability	Any risk for an adverse effect on cardiac conduction can only be prevented by choosing not to take mirdametinib.
Impact on the risk-benefit balance of the product	Additional information from a Post Authorisation Safety Study (PASS) will be conducted to further characterise the potential risk of Adverse effects on cardiac conduction in patients initiating mirdametinib therapy.
Public health impact	There is no public health impact of Adverse effects on cardiac conduction associated with the use of mirdametinib.

Important Potential Risk: Carcinogenicity	
Potential mechanisms	Mirdametinib was equivocal in the in vivo micronucleus study and in vivo chromosomal aberrations study in rats and these findings may relate to a potential aneugenic mechanism that has been observed with other MEK inhibitors.
Evidence source(s) and strength of evidence	Mirdametinib treatment resulted in equivocal findings in the in vivo genotoxicity studies in rats, was negative for carcinogenicity in transgenic mice, and the currently ongoing 2-year carcinogenicity study in rats is testing dose levels that will produce exposures below the therapeutic clinical exposure because of tolerability issues in rats.
Characterisation of risk: Frequency	In Pool 1, 10 participants (7.5%) reported a TEAEs within the system organ class (SOC) Neoplasms benign, malignant and unspecified (incl cysts and polyps). This includes 4 (6.9%) paediatric and 6 (8.0%) adult participants. The 4 paediatric participants reported tumour pain (6.9%). The 6 adult participants reported tumour pain (2.7%), fibrous histiocytoma (1.3%), haemangioma of skin (1.3%), neurofibroma (1.3%), seborrhoeic keratosis (1.3%), squamous cell carcinoma of skin (1.3%), and uterine leiomyoma (1.3%). In Pool 2, 5 participants (4.4%) reported a TEAEs within the SOC Neoplasms benign, malignant and unspecified (incl cysts and polyps). This includes tumour

Important Potential Risk: Carcinogenicity	
	pain (2.7%), colon cancer metastatic (0.9%), and metastases to central nervous system (0.9%).
Seriousness	In Pool 1, one (1.3%) adult participant reported a serious TEAE of squamous cell carcinoma of skin. In Pool 2, 3 (2.7%) participants reported serious TEAEs, including breast cancer metastatic (0.9%), colon cancer metastatic (0.9%), and metastases to central nervous system (0.9%).
Severity	All TEAEs in Pool 1 were Grade 1 or Grade 2. No TEAE was Grade ≥ 3 In Pool 2, 2 (1.8%) TEAEs were Grade 5. All other TEAEs were Grade 1 or Grade 2.
Risk factors and risk groups	None identified.
Preventability	The product labelling will advise on the nonclinical findings of the Carcinogenicity data of mirdametinib, and that a potential carcinogenicity risk in humans could not be excluded at the clinical exposure range.
Impact on the risk-benefit balance of the product	Additional information from a Post Authorisation Safety Study (PASS) will be conducted to further characterise the potential risk of carcinogenicity in patients initiating mirdametinib therapy.
Public health impact	There is no public health impact of Carcinogenicity associated with the use of mirdametinib.

SVII.3.2. Presentation of the missing information

Long term safety	
Evidence source	The overall median duration of exposure in Pool 1 was 22 months (range 0.4 to 45.6), with 22 months (range 1.6 to 40.1) in the paediatric cohort and 19 months (range 0.4 to 45.6) in the adult cohort. Six paediatric participants and 10 adult participants have been exposed to mirdametinib for > 36 months.
Population in need of further characterisation	Paediatric and adult patients treated with mirdametinib

Part II: MODULE SVIII - Summary of the safety concerns

Table 14: Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	Ocular events (RVO, RPED, Vision blurred) Ejection fraction decreased
Important potential risks	Embryo-foetal toxicity Physeal dysplasia Adverse effects on cardiac conduction Carcinogenicity
Missing information	Long term safety

Part III: PHARMACOVIGILANCE PLAN

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities consisting of adverse reaction collecting and reporting and signal detection will be employed as per all appropriate local pharmacovigilance requirements.

Specific adverse reaction follow-up questionnaires:

None

Other forms of routine pharmacovigilance activities

Not applicable

III.2 Additional pharmacovigilance activities

III.3 Summary table of additional pharmacovigilance activities

Table 15: Part III.1: On-going and planned additional pharmacovigilance activities

On-going and planned additional pharmacovigilance activities				
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation *(key to benefit risk)*				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances *(key to benefit risk)*				
Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study	Primary objectives: To estimate the incidence of physeal dysplasia in patients aged 2 to < 18 years (paediatric cohort) with NF1 for the treatment of symptomatic PNs, and long term safety based on the approved indication in the local labelling, treated with mirdametinib for up to 6 years. To further characterise the long-term safety in both adult and paediatric patients aged	Ocular events (RVO, RPED, Vision blurred) Ejection fraction decreased Adverse effects on cardiac conduction Embryo-foetal toxicity Physeal dysplasia in	Submission for Scientific Advice to SAWP/PRAC Submission of full protocol to PRAC Progress reports Final study report	July 2025 Approximately 5 months following EC decision Annually following start of data collection August 2033

On-going and planned additional pharmacovigilance activities				
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
	2 years and above (adult and paediatric cohort) for the treatment of symptomatic PNs based on the approved indication in the local labelling, treated with mirdametinib for up to 6 years.	paediatric patients Carcinogenicity Long term safety		
Category 3 - Required additional pharmacovigilance activities *(by the competent authority)*				
None				

Part IV: PLANS FOR POST AUTHORISATION EFFICACY STUDIES

Table 16: Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.				
Study Status	**Summary of Objectives**	**Efficacy uncertainties addressed**	**Milestones**	**Due date**
Efficacy studies which are conditions of the marketing authorisation				
None				
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
MEK-NF-201 (ongoing)	Efficacy and safety data with a longer follow-up	Long term efficacy and safety outcomes	Data cut-off of 22Dec2028	Clinical study report submitted by Jun2029

Part V: RISK MINIMISATION MEASURES (including evaluation of the effectiveness of risk minimisation activities)

V.1. Routine Risk Minimisation Measures

Table 17: Part V.1: Description of routine risk minimisation measures by safety concern

Description of routine risk minimisation measures by safety concern	
Safety concern	**Routine risk minimisation activities**
Ocular events (RVO, RPED, Vision blurred) **(Important Identified Risk)**	**Routine risk communication:** SmPC Section 4.2: Posology and method of administration. Section 4.4: Special warnings and precautions for use. Section 4.8: Undesirable effects. PIL Section 2: What you need to know before you take EZMEKLY. Section 4: Possible serious side effects.
	Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.2: Posology and method of administration. Section 4.4: Special warnings and precautions for use. PIL Section 2: What you need to know before you take EZMEKLY. Section 4: Possible serious side effects of EZMEKLY.
	Other routine risk minimisation measures beyond the Product Information: None
Ejection Fraction Decreased **(Important Identified Risk)**	**Routine risk communication:** SmPC Section 4.2: Posology and method of administration. Section 4.4: Special warnings and precautions for use. Section 4.8: Undesirable effects. PIL Section 2: What you need to know before you take EZMEKLY. Section 4: Possible serious side effects of EZMEKLY.
	Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.2: Posology and method of administration.

Description of routine risk minimisation measures by safety concern	
Safety concern	**Routine risk minimisation activities**
	Section 4.4: Special warnings and precautions for use. PIL Section 2: What you need to know before you take EZMEKLY.
	Other routine risk minimisation measures beyond the Product Information: None
Embryo-Foetal Toxicity (Important Potential Risk)	**Routine risk communication:** SmPC Section 4.4: Special warnings and precautions for use. Section 4.5: Interaction with other medicinal products and other forms of interaction. Section 4.6: Fertility, pregnancy, and lactation. Section 5.3: Preclinical safety data. PIL Section 2: What you need to know before you take EZMEKLY.
	Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC Section 4.4: Special warnings and precautions for use. Section 4.5 Interaction with other medicinal products and other forms of interaction. Section 4.6: Fertility, pregnancy, and lactation. PIL Section 2: What you need to know before you take EZMEKLY.
	Other routine risk minimisation measures beyond the Product Information: None
Physeal dysplasia (Important Potential Risk)	**Routine risk communication:** SmPC Section 5.3: Pre-clinical safety data.
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None
	Other routine risk minimisation measures beyond the Product Information: None
Adverse effects on cardiac conduction (Important Potential Risk)	**Routine risk communication:** None
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None
	Other routine risk minimisation measures beyond the Product Information: None

Description of routine risk minimisation measures by safety concern	
Safety concern	**Routine risk minimisation activities**
Carcinogenicity (Important Potential Risk)	Routine risk communication: SmPC Section 4.4: Special warnings and precautions for use. Section 5.3: Pre-clinical safety data.
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None
	Other routine risk minimisation measures beyond the Product Information: None
Long term safety (Missing Information)	**Routine risk communication:** None
	Routine risk minimisation activities recommending specific clinical measures to address the risk: None
	Other routine risk minimisation measures beyond the Product Information: None

V.2. Additional Risk Minimisation Measures

None

V.3 Summary of risk minimisation measures

Table 18: Part V.3 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern		
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
Ocular events (RVO, RPED, Vision blurred) (Important Identified Risk)	**Routine risk minimisation measures:** Routine risk communication: SmPC • Section 4.2: Posology and method of administration. • Section 4.4: Special warnings and precautions for use. • Section 4.8: Undesirable effects. PIL • Section 2: What you need to know before you take EZMEKLY. • Section 4: Possible serious side effects. Routine risk minimisation activities recommending specific clinical measures to address the risk:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern		
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
	SmPC • Section 4.2: Posology and method of administration. • Section 4.4: Special warnings and precautions for use. PIL • Section 2: What you need to know before you take EZMEKLY. • Section 4: Possible serious side effects EZMEKLY.	
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study
Ejection Fraction Decreased (Important Identified Risk)	**Routine risk minimisation measures:** Routine risk communication: SmPC • Section 4.2: Posology and method of administration. • Section 4.4: Special warnings and precautions for use. • Section 4.8: Undesirable effects. PIL • Section 2: What you need to know before you take EZMEKLY. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC • Section 4.2: Posology and method of administration. • Section 4.4: Special warnings and precautions for use. PIL	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern		
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
	• Section 2: What you need to know before you take EZMEKLY.	
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study
Embryo-Foetal Toxicity (Important Potential Risk)	**Routine risk minimisation measures:** Routine risk communication: SmPC • Section 4.4: Special warnings and precautions for use. • Section 4.5: Interaction with other medicinal products and other forms of interaction. • Section 4.6: Fertility, pregnancy, and lactation. • Section 5.3: Preclinical safety data. PIL • Section 2: What you need to know before you take EZMEKLY. Routine risk minimisation activities recommending specific clinical measures to address the risk: SmPC • Section 4.4: Special warnings and precautions for use. • Section 4.5: Interaction with other medicinal products and other forms of interaction. • Section 4.6: Fertility, pregnancy, and lactation. PIL • Section 2: What you need to know before you take EZMEKLY.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern		
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
		Multiple-Country Prospective Cohort Study
Physeal dysplasia (Important Potential Risk)	**Routine risk minimisation measures:** Routine risk communication: SmPC • Section 5.3: Pre-clinical safety data. Routine risk minimisation activities recommending specific clinical measures to address the risk: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study
Adverse effects on cardiac conduction (Important Potential Risk)	**Routine risk minimisation measures:** Routine risk communication: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study
Carcinogenicity (Important Potential Risk)	Routine risk minimisation measures: Routine risk communication: SmPC • Section 4.4: Special warnings and precautions for use. • Section 5.3: Pre-clinical safety data. Routine risk minimisation activities recommending specific clinical measures to address the risk: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern		
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
		Country Prospective Cohort Study
Long term safety (Missing Information)	**Routine risk minimisation measures**: None Routine risk minimisation activities recommending specific clinical measures to address the risk: None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None
	Additional risk minimisation measures: None	Additional pharmacovigilance activities: Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study

Part VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of the risk management plan for EZMEKLY

This is a summary of the risk management plan (RMP) for EZMEKLY. The RMP details important risks of EZMEKLY, how these risks can be minimised, and how more information will be obtained about EZMEKLY's risks and uncertainties (missing information).

EZMEKLY's Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how EZMEKLY should be used.

This summary of the RMP for EZMEKLY should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of EZMEKLY RMP.

I. The medicine and what it is used for

EZMEKLY as monotherapy is indicated for the treatment of symptomatic PN in adult and paediatric patients aged 2 years and above with neurofibromatosis type 1 who require systemic therapy. It contains mirdametinib as the active substance and it is given by the oral route.

Further information about the evaluation of EZMEKLY's benefits can be found in EZMEKLY EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of EZMEKLY, together with measures to minimise such risks and the proposed studies for learning more about the risks associated with EZMEKLY, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

1) Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
2) Important advice on the medicine's packaging;
3) The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
4) The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of EZMEKLY is not yet available, it is listed under missing information below.

II.A List of important risks and missing information

Important risks of EZMEKLY are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of EZMEKLY. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of Important Risks and Missing Information

Important identified risks	Ocular events (RVO, RPED, Vision blurred) Ejection fraction decreased
Important potential risks	Embryo-foetal toxicity Physeal dysplasia Adverse effects on cardiac conduction Carcinogenicity
Missing information	Long term safety

II.B Summary of important risks

Important Identified Risk: Ocular events (RVO, RPED, Vision blurred)	
Evidence for linking the risk to the medicine	Several MEK inhibitors have been reported to cause ocular toxicities, such as central serous retinopathy, RVO, or periorbital oedema. These ocular toxicities appear to be a class effect of MEK inhibition. MEK inhibitors have been reported to cause unique dose- and time-dependent MEKAR, which is an umbrella term that includes serous retinopathy, central serous chorioretinopathy, SRD, macular oedema, visual disturbance, retinopathy, chorioretinopathy, and blurred vision (Stjepanovic 2016). RVO is an uncommon but potentially serious adverse event reported in initial clinical trials of several MEK inhibitors (Han 2023). In Pool 1, Eye disorders were reported in 11 (19%) pediatric participants and 21 (28%) adult participants. In Pool 2, Eye disorders were reported in 55 (48.7%) participants.

Important Identified Risk: Ocular events (RVO, RPED, Vision blurred)	
	In Pool 1, RVO has been observed in 2 (3%) adult participants. RVO was not observed in paediatric participants. In Pool 2, RVO was observed in 3 (3%) adult participants with advanced cancers receiving mirdametinib at doses ≥ 5 mg BID. All participants who reported RVO had at least 1 predisposing factor including hypertension, diabetes, hypercholesterolemia, COVID-19 vaccination, advanced cancer, or concomitant medications. In Pool 1, Vision blurred was reported by 4 (7%) paediatric and 8 (11%) adult participants. In Pool 2, Vision blurred was reported in 16 (14.2%) participants. In Pool 1, asymptomatic RPED was reported in one (1%) adult participant and was not reported in any paediatric participant. In Pool 2, no participant reported RPED. One participant in the CUP with NF1 PN treated with mirdametinib 4 mg BID reported a nonserious event of RPED.
Risk factors and risk groups	RVO: A basic risk factor for RVO is advancing age. Further risk factors include systemic conditions such as hypertension, arteriosclerosis, diabetes mellitus, hyperlipidaemia, vascular cerebral stroke, blood hyperviscosity, and thrombophilia. A strong risk factor for RVO is metabolic syndrome (hypertension, diabetes mellitus, and hyperlipidemia). Individuals with end-organ damage caused by diabetes mellitus and hypertension have a greatly increased risk for RVO. Socioeconomic status seems to also be a risk factor. American blacks are more often diagnosed with RVO than non-Hispanic whites. Females are, according to some studies, at lower risk than men. The role of thrombophilic risk factors in RVO is still controversial. Congenital thrombophilic diseases including Factor V Leiden mutation, hyperhomocysteinaemia and anticardiolipin antibodies increase the risk of RVO (Kolar 2014). Further, hypercoagulability induced by systemic malignancy has also been associated with RVO (Mishra 2023). RVO is an uncommon but potentially serious adverse event reported in initial clinical trials of several MEK inhibitors (Han 2023). Cigarette smoking also increases the risk of RVO as do systemic inflammatory conditions like vasculitis and Behcet disease. Ophthalmic risk factors for RVO are ocular hypertension and glaucoma, higher ocular perfusion pressure, and changes in the retinal arteries (Kolar 2014). Additionally, COVID-19 vaccination has been associated with an increased risk of RVO (Li 2023), and oral contraceptives have been implicated in the pathogenesis of occlusive retinopathy (Somisetty 2023). Vision blurred and RPED: Age, glomerular filtration rate, and history of ocular disease (particularly inflammatory eye disease) were associated with a risk of MEK inhibitor-induced retinopathy in a study of 247 patients treated with cobimetinib and

Important Identified Risk: Ocular events (RVO, RPED, Vision blurred)	
	vemurafenib (Booth 2020). However, these patients were participants in an advanced melanoma study and the same conclusions may not necessarily be applicable to the NF1 population. Additionally, NF1 mutations place patients at risk for the development of glaucoma, choroidal abnormalities including reduced choroid thickness or altered choroidal circulation due to the presence of nodules, and infrequently, retinal alterations, which have been described in case reports as microvascular abnormalities. Finally, optic pathway glioma occurs frequently in patients with NF1, which can result in reduced visual acuity, visual field defects, oedema of the papilla, proptosis, and strabismus (Abdolrahimzadeh 2016).
Risk minimisation measures	SmPC • Section 4.2: Posology and method of administration. • Section 4.4: Special warnings and precautions for use. • Section 4.8: Undesirable effects. PIL • Section 2: What you need to know before you take EZMEKLY. • Section 4: Possible serious side effects. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study

Important Identified Risk: Ejection fraction decreased	
Evidence for linking the risk to the medicine	The MAPK signaling cascade is important for cardiac adaptation in response to stress; when inhibited, the heart cannot compensate by getting stronger or preventing cell death. Mice that lack ERK1/2 have normal cardiac size and function, but are more susceptible to cardiomyocyte apoptosis and suffer greater cardiac damage in response to insult (Lips 2004). This finding suggests that susceptibility to MEK inhibitor-associated injury does not occur due to drug exposure alone, but requires a second source of injury (e.g., hypertension, ischemia, or other toxic drug exposure) (Banks 2017). MEK inhibition alone at lower doses in the NF1 paediatric patient population is also associated with cardiac AEs, primarily cardiomyopathy/ejection fraction decrease and hypertension (Gross 2023). In Study MEK-NF-201, 20 events of asymptomatic ejection fraction decreased were observed in 15 (27%) paediatric participants, and 13 events were observed in 9 (16%) adult participants. The median (min, max) ejection fraction at baseline was similar between the cohorts: 65% (55%, 78%) in paediatric

Important Identified Risk: Ejection fraction decreased	
	participants and 62% (55%, 80%) in adult participants. For those participants still receiving mirdametinib after 1 year, the median (min, max) ejection fraction was largely unchanged from baseline at 63.2% (50%, 77%) in paediatric, and 60% (53%, 67%) in adult participants. In Study MEK-NF-201, 1 participant in each cohort was observed to have an event of ejection fraction decreased with a >10% absolute value decrease from their baseline value to an ejection fraction <50%. All events were asymptomatic and no events of cardiomyopathy or left ventricular dysfunction were reported.
Risk factors and risk groups	None have been identified.
Risk minimisation measures	SmPC • Section 4.2: Posology and method of administration. • Section 4.4: Special warnings and precautions for use. • Section 4.8: Undesirable effects. PIL • Section 2: What you need to know before you take EZMEKLY. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study

Important Potential Risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	Significant embryo-foetal development toxicities were observed in both the rat and rabbit range-finding studies manifesting as foetal absorptions, post-implantation loss, and decreased foetal weights. The findings with mirdametinib are consistent with the embryo-foetal toxicity observed in nonclinical studies with other MEK inhibitors and are considered a class effect. Specifically, these findings from animal studies were noted with approved MEK inhibitors selumetinib (KOSELUGO SmPC), trametinib MEKINIST SmPC , binimetinib MEKTOVI SmPC , and cobimetinib (COTELLIC SmPC) which clearly highlight the class effect of these compounds related to potential foetal harm if these agents are administered to pregnant women. Mirdametinib was not genotoxic in a bacterial reverse mutation (Ames) assay or in an in vitro human lymphocyte chromosomal aberration assay but was equivocal in the in vivo micronucleus study and in vivo chromosomal aberrations study in rats. A genotoxicity risk in humans could not be excluded. One participant in Study MEK-NF-201 had a positive urine pregnancy test reported 31 days after the last dose of mirdametinib. The pregnancy ended in a first trimester spontaneous abortion. There was one case of a partner pregnancy reported for a 34-year-old male with NF1 PN treated with mirdametinib 4 mg BID. The outcome of the pregnancy is unknown.
Risk factors and risk groups	Females of reproductive potential and their partners.
Risk minimisation measures	SmPC • Section 4.4: Special warnings and precautions for use. • Section 4.5: Interaction with other medicinal products and other forms of interaction. • Section 4.6: Fertility, pregnancy and lactation. • Section 5.3: Preclinical safety data. PIL • Section 2: What you need to know before you take EZMEKLY. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study

Important Potential Risk: Physeal dysplasia	
Evidence for linking the risk to the medicine	Administration of mirdametinib to rats resulted in bone lesions that included necrosis of the metaphysis and the ossifying zone of the physis and thickening of the zone of hypertrophying cartilage of the physis. The expansion of chondrocytes in the physis may be a response to the metaphyseal necrosis and loss of osteoprogenitor cells. These changes are characterised by localised injury to bone, which appear to be due to local ischaemia and/or necrosis. Skeletal vascular changes may be present in these animals, resulting in disruption of endochondral ossification. Skeletal lesions, including bone necrosis, can result from Vitamin D intoxication (Haschek 1978). In the pivotal 1- and 3-month studies in rats, hypocellularity in the metaphyseal region of the distal portion of the femur and/or proximal portion of the tibia occurred in males only at 1 mg/kg/day and was reversible following cessation of dosing in the 1-month study. In addition, thickening of the bony trabeculae in the femoral/tibial metaphyseal region was evident in all males at 1.0 mg/kg/day in the 3-month study. Bone lesions, like those observed in rats, have not been seen in dogs, monkeys, or mice given mirdametinib.
Risk factors and risk groups	Paediatric patients with open growth plates
Risk minimisation measures	SmPC • Section 5.3: Pre-clinical safety data. Additional risk minimisation measures: None

Important Potential Risk: Physeal dysplasia	
Additional pharmacovigilance activities	Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study

Important Potential Risk: Adverse effects on cardiac conduction	
Evidence for linking the risk to the medicine	Mirdametinib reduced action potential duration at concentrations of 10 µM and 100 µM and reduced the maximum rate of depolarisation and amplitude at 100 µM. 10 µM is approximately 2500-fold higher than the unbound steady-state maximum concentration (Cmaxss,u) of mirdametinib at the clinical dose (2 mg/m^2 BID [maximum dose of 4 mg BID]) in Study MEK-NF-201. In a (GLP)-compliant in vitro study, mirdametinib and the metabolite PD-0315209 did not inhibit hERG current at a concentration of 10 µM. In a GLP-compliant in vitro assay using isolated canine Purkinje fibres, there was no meaningful effect on resting membrane potential at any tested concentrations of mirdametinib. Mirdametinib did reduce action potential duration at high concentrations of 10 µM and 100 µM and reduced the maximum rate of depolarisation and amplitude at 100 µM. 10 µM is approximately 2500-fold higher than the unbound steady-state maximum concentration(Cmaxss,u) of mirdametinib at the clinical dose (2 mg/m^2 BID [maximum dose of 4 mg BID]) in Study MEK-NF-201 In a GLP-compliant cardiovascular study in telemetered monkeys, there were no mirdametinib-related effects in blood pressure, heart rate, body temperature, or electrocardiography parameters, including QT interval, for 24 hours after single oral doses up to 10 mg/kg. Mirdametinib exposure at the 10 mg/kg dose was 10-fold higher than the unbound exposure (Cmaxss,u) of mirdametinib at the clinical dose (2 mg/m^2 BID [maximum dose of 4 mg BID]) in Study MEK-NF-201. In a secondary pharmacodynamic study conducted with mirdametinib at 1 and 10 µM against a panel of 87 targets, inhibition of the L-type calcium channel by 54% was observed at 10 µM (2500-fold higher than the human mirdametinib Cmaxss,u at the clinical dose). In a thorough QT study conducted in healthy participants, no clinically significant effect of mirdametinib at supratherapeutic exposures (up to 6-fold higher than the Cmax,ss in Study MEK-NF-201) on baseline-adjusted QTcF or QTc prolongation was observed. There was also no statistically significant change observed in the QRS interval.
Risk factors and risk groups	Patients with medical history of cardiac conduction disturbances or intercurrent illnesses associated with changes in cardiac conduction
Risk minimisation measures	None

Important Potential Risk: Adverse effects on cardiac conduction	
Additional pharmacovigilance activities	Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study

Important Potential Risk: Carcinogenicity	
Evidence for linking the risk to the medicine	Mirdametinib was equivocal in the in vivo micronucleus study and in vivo chromosomal aberrations study in rats, and these findings may relate to a potential aneugenic mechanism that has been observed with other MEK inhibitors. Mirdametinib treatment resulted in equivocal findings in the in vivo genotoxicity studies in rats, was negative for carcinogenicity in transgenic mice, and the currently ongoing 2-year carcinogenicity study in rats is testing dose levels that will produce exposures below the therapeutic clinical exposure because of tolerability issues in rats.
Risk factors and risk groups	None identified
Risk minimisation measures	SmPC • Section 4.4: Special warnings and precautions for use. • Section 5.3: Pre-clinical safety data. Additional risk minimisation measures: None
Additional pharmacovigilance activities	Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study

Missing Information: Long term safety	
Risk minimisation measures	None
Additional pharmacovigilance activities	Post-Authorisation Safety Study of Paediatric and Adult Patients Initiating Mirdametinib: A Multiple-Country Prospective Cohort Study

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

None

II.C.2 Other studies in post-authorisation development plan

Post-authorisation safety study to estimate the incidence of physeal dysplasia in patients aged 2 to < 18 years (paediatric cohort) with NF1 for the treatment of symptomatic PNs, based on the approved indication in the local labelling, treated with mirdametinib for up to 6 years. In addition, the study will further characterise the long-term safety in both adult and paediatric patients aged 2 years and above (adult and paediatric cohort) for the treatment of symptomatic

PNs based on the approved indication in the local labelling, treated with mirdametinib for up to 6 years.

Annex 4 - Specific adverse drug reaction follow-up forms

None.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Draft/approved key messages of the additional risk minimisation measures

None.