NOVARTIS

Rydapt ®

Protein kinase inhibitor

Description and Composition

Pharmaceutical form

Soft capsules

Pale orange oblong capsules with red ink imprint 'PKC NVR'.

Certain dosage strengths and dosage forms may not be available in all countries.

Active substance

Each capsule contains 25 mg of midostaurin.

Excipients

Macrogolglycerol hydroxystearate/polyoxyl 40 hydrogenated castor oil, gelatin, macrogol 400/polyethylene glycol 400, glycerol, ethanol anhydrous/dehydrated alcohol, corn oil mono-di-triglycerides, titanium dioxide (E171), all-rac-alpha-tocopherol/Vitamin E, iron oxide yellow/ferric oxide (E172), iron oxide red/ferric oxide (E172), carmine (E120), hypromellose 2910, propylene glycol, purified water.

Pharmaceutical formulations may vary between countries.

INDICATIONS

RYDAPT is indicated:

- in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by Rydapt single agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukemia (AML) who are FLT3 mutation-positive (see CLINICAL STUDIES).
- for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL).

DOSAGE REGIMEN AND ADMINISTRATION

Treatment with RYDAPT should be initiated by a physician experienced in the use of anticancer therapies.
Before taking midostaurin, AML patients must have confirmation of FLT3 mutation using a validated test.

Dosage regimen

Target population

Recommended dose in AML

The recommended dose of RYDAPT is 50 mg twice daily. RYDAPT is dosed on days 8-21 of induction and consolidation chemotherapy cycles and then for patients in complete response twice daily as single agent maintenance therapy until relapse. In the clinical study, maintenance therapy was continued for up to 12 cycles of 28 days each. In patients receiving a haematopoietic stem cell transplant (SCT) Rydapt should be discontinued 48 hours prior to the conditioning regimen for SCT.

Recommended dose in ASM, SM-AHN and MCL

The recommended starting dose of RYDAPT is 100 mg twice daily.

Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.

Dose modifications

Dose modifications in AML

Recommendations for dose modifications of RYDAPT in patients with AML are provided in Table 1.

Table 1 RYDAPT dose interruption, reduction, and discontinuation recommendations in patients with AML

Phase	Criteria	Rydapt dosing
Induction, consolidation and maintenance	Grade 3/4 pulmonary infiltrates	Interrupt Rydapt for the remainder of the cycle. Resume Rydapt at the same dose when infiltrate resolves to Grade ≤1.
	Other Grade 3/4 non-haematological toxicities	Interrupt Rydapt until toxicities considered at least possibly related to Rydapt have resolved to Grade ≤2, then resume Rydapt.
	QTc interval >470 msecs and ≤500 msecs	Decrease Rydapt to 50 mg once daily for the remainder of the cycle. Resume Rydapt at the initial dose in the next cycle provided that QTc interval improves to ≤470 msecs at the start of that cycle. Otherwise continue Rydapt 50 mg once daily.
	QTc interval >500 msecs	Withhold or interrupt Rydapt for the remainder of the cycle. If QTc improves to ≤470 msecs just prior to the next cycle, resume Rydapt at the initial dose. If QTc interval is not improved in time to start the next cycle do not administer Rydapt during that cycle. Rydapt may be held for as many cycles as necessary until QTc improves.
Maintenance only	Grade 4 neutropenia (ANC <0.5 x 10^9/l)	Interrupt Rydapt until ANC ≥1.0 x 10^9/l, then resume at 50 mg twice daily. If neutropenia (ANC <1.0 x 10^9/l) persists >2 weeks and is suspected to be related to Rydapt, discontinue Rydapt.
	Persistent Grade 1/2 toxicity	Persistent Grade 1 or 2 toxicity that patients deem unacceptable may prompt an interruption for as many as 28 days.
ANC: Absolute Neutrophil Count		

Dose modifications in ASM, SM-AHN and MCL

Recommendations for dose modifications of RYDAPT in patients with ASM, SM-AHN and MCL are provided in Table 2.

Table 2 RYDAPT dose interruption, reduction, and discontinuation recommendations in patients with ASM, SM-AHN and MCL

Criteria	Rydapt dosing
ANC <1.0 x 10^9/l attributed to Rydapt in patients without MCL, or ANC less than 0.5 x 10^9/l attributed to Rydapt in patients with baseline ANC value of 0.5-1.5 x 10^9/l	Interrupt Rydapt until ANC ≥1.0 x 10^9/l, then resume at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily. Discontinue Rydapt if low ANC persists for >21 days and is suspected to be related to Rydapt.
Platelet count less than 50 x 10^9/l attributed to Rydapt in patients without MCL, or platelet count less than 25 x 10^9/l attributed to Rydapt in patients with baseline platelet count of 25-75 x 10^9/l	Interrupt Rydapt until platelet count greater than or equal to 50 x 10^9/l, then resume Rydapt at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily. Discontinue Rydapt if low platelet count persists for >21 days and is suspected to be related to Rydapt.
Haemoglobin less than 8 g/dl attributed to Rydapt in patients without MCL, or life-threatening anaemia attributed to Rydapt in patients with baseline haemoglobin value of 8-10 g/dl	Interrupt Rydapt until haemoglobin greater than or equal to 8 g/dl, then resume Rydapt at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily. Discontinue Rydapt if low haemoglobin persists for >21 days and is suspected to be related to Rydapt.
Grade 3/4 nausea and/or vomiting despite optimal anti-emetic therapy	Interrupt Rydapt for 3 days (6 doses), then resume at 50 mg twice daily and, if tolerated, gradually increase to 100 mg twice daily.
Other Grade 3/4 non-haematological toxicities	Interrupt Rydapt until event has resolved to Grade ≤2, then resume Rydapt at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily. Discontinue Rydapt if toxicity is not resolved to Grade ≤2 within 21 days or severe toxicity recurs at a reduced dose of Rydapt.
ANC: Absolute Neutrophil Count CTCAE severity: Grade 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms.	

Special populations

Renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment. Clinical experience in patients with severe renal impairment is limited. No data are available in patients with end-stage renal disease (see section CLINICAL PHARMACOLOGY).

Hepatic impairment

No dose adjustment is required in patients with mild, moderate or severe (Child-Pugh A, B or C) hepatic impairment (see section CLINICAL PHARMACOLOGY).

Pediatric patients (below 18 years)

The safety and efficacy of RYDAPT in pediatric patients (0 to less than 18 years) have not been established (see section CLINICAL PHARMACOLOGY). Rydapt should not be used in combination with intensive pediatric AML combination chemotherapy regimens including

anthracyclines, fludarabine and cytarabine (see sections WARNINGS AND PRECAUTIONS and CLINICAL STUDIES).

Geriatric patients (65 years or above)

No dosage regimen adjustment is required in patients over 65 years of age (SEE SECTION CLINICAL PHARMACOLOGY). Clinical studies in AML with RYDAPT did not include sufficient numbers of patients aged 60 years and over to determine whether they respond differently from younger patients. There is limited experience with midostaurin in AML patients aged 60-70 years and no experience in AML patients above 70 years. In patients aged ≥60 years, RYDAPT should be used only in patients eligible to receive intensive induction chemotherapy with adequate performance status and without significant comorbidities.

Method of administration

RYDAPT should be taken orally, twice daily at approximately 12 hour intervals. RYDAPT should be taken with food to reduce the risk of nausea and vomiting (see section CLINICAL PHARMACOLOGY).

Prophylactic anti-emetics should be administered in accordance with local medical practice as per patient tolerance.

RYDAPT capsules should be swallowed whole with a glass of water. RYDAPT capsules should not be opened, crushed or chewed.

If a dose is missed, the dose should not be made up and the patient should only take the next scheduled dose at the scheduled time.

If vomiting occurs, the patient should not take an additional dose of RYDAPT, but should take the next scheduled dose.

Monitoring during treatment with Rydapt

Interval assessments of QT by ECG should be considered if Rydapt is taken concurrently with medicinal products that can prolong the QT interval.

CONTRAINDICATIONS

RYDAPT is contraindicated in patients with hypersensitivity to midostaurin or to any of the excipients.

Concomitant administration of potent CYP3A4 inducers, e.g. rifampicin, St. John's Wort (*Hypericum perforatum)*, carbamazepine, enzalutamide, phenytoin (see section INTERACTIONS).

WARNINGS AND PRECAUTIONS

Neutropenia / Infections

Neutropenia has occurred in patients receiving RYDAPT as monotherapy and in combination with chemotherapy (see section ADVERSE DRUG REACTIONS). Severe neutropenia (ANC less than 0.5 x 10^9/L) was generally reversible by withholding RYDAPT until recovery or discontinuation in the ASM, SM-AHN and MCL studies. White blood cells (WBCs) should be monitored regularly, especially at treatment initiation.

In patients who develop unexplained severe neutropenia, treatment with RYDAPT should be interrupted until ANC is greater than or equal to 1.0 x 10^9/L, as recommended in Table 1 and

Table 2. RYDAPT should be discontinued in patients who develop recurrent or prolonged severe neutropenia that is suspected to be related to RYDAPT (see section DOSAGE REGIMEN AND ADMINISTRATION).

Any active serious infections should be under control prior to starting treatment with RYDAPT monotherapy. Patients should be monitored for signs and symptoms of infection and if a diagnosis of infection is made, appropriate treatment should be instituted promptly, including as needed, the discontinuation of RYDAPT.

Cardiac dysfunction

Patients with symptomatic congestive heart failure were excluded from clinical studies. In the ASM, SM-AHN and MCL studies with RYDAPT, cardiac dysfunction such as congestive heart failure (CHF), some of which were fatal, and transient decreases in left ventricular ejection fraction (LVEF) occurred. Fatal cardiac failure was reported in patients in the ASM, SM-AHN and MCL studies while no difference in CHF or LVEF dysfunction was observed between the RYDAPT + chemotherapy and placebo + chemotherapy arms in the randomized AML study. In patients at risk, RYDAPT should be used with caution and patients should be closely monitored (at baseline and during treatment).

An increased frequency of QTc prolongation was noted in midostaurin–treated patients (see section ADVERSE DRUG REACTIONS), however, a mechanistic explanation for this observation was not found. Caution is warranted in patients at risk of QTc prolongation (e.g. due to concomitant medicinal products and/or electrolyte disturbances). Interval assessments of QT by ECG should be considered if RYDAPT is taken concurrently with medicinal products that can prolong QT interval.

Pediatric patients

Rydapt should not be used in combination with intensive pediatric AML combination chemotherapy regimens including anthracyclines, fludarabine and cytarabine because of the risk of prolonged hematological recovery (such as prolonged severe neutropenia and thrombocytopenia) (see section CLINICAL STUDIES)

Pulmonary toxicity

Interstitial lung disease (ILD) and pneumonitis, some of which have been fatal, have occurred in patients treated with RYDAPT monotherapy or in combination with chemotherapy. Patients should be monitored for pulmonary symptoms indicative of ILD/pneumonitis and RYDAPT should be discontinued in patients who experience pulmonary symptoms indicative of ILD/pneumonitis without an infectious etiology which are ≥Grade 3 (NCI CTCAE).

Embryo-fetal toxicity and lactation

Based on findings from animal studies, RYDAPT can cause fetal harm when administered to pregnant women. Administration of midostaurin to pregnant rats and rabbits during the period of organogenesis resulted in embryo-fetal toxicity. Pregnant women should be advised of the potential risk to a fetus; Females of reproductive potential should be advised to have a pregnancy test within 7 days prior to starting treatment with Rydapt and to use effective contraception during treatment with RYDAPT and for at least 4 months after stopping treatment.

Because of the potential for serious adverse effects in nursing infants from RYDAPT, nursing women should be advised to discontinue breastfeeding during treatment with RYDAPT and for at least 4 months after stopping treatment (see section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL).

Severe hepatic impairment

Caution is warranted when considering the administration of midostaurin in patients with severe hepatic impairment and patients should be carefully monitored for toxicity (see section PHARMACOKINETICS).

Interactions

Caution is required when concomitantly prescribing with midostaurin medicinal products that are strong inhibitors of CYP3A4, such as, but not limited to, antifungals (e.g. ketoconazole), certain antivirals (e.g. ritonavir), macrolide antibiotics (e.g. clarithromycin) and nefazodone because they can increase the plasma concentrations of midostaurin especially when (re-)starting with midostaurin treatment (see section INTERACTIONS). Alternative medicinal products that do not strongly inhibit CYP3A4 activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for midostaurin-related toxicity.

ADVERSE DRUG REACTIONS

AML - Summary of the safety profile

The safety evaluation of RYDAPT (50 mg twice daily) in patients with newly diagnosed FLT3 mutated AML is based on a phase III, randomized, double-blind, placebo-controlled study. A total of 717 patients were randomized (1:1) to receive RYDAPT or placebo sequentially (on days 8 to 21) in combination with standard daunorubicin (60 mg/m^2 on days 1 to 3) / cytarabine (200 mg/m^2 on days 1 to 7) induction and high dose cytarabine (3 g/m^2 on days 1, 3, 5) consolidation, followed by maintenance with continuous RYDAPT or placebo treatment according to initial assignment for up to 12 cycles (28 days/cycle). The overall median duration of exposure was 42 days (range 2 to 576 days) for patients in the RYDAPT plus standard chemotherapy arm versus 34 days (range 1 to 465 days) for patients in the placebo plus standard chemotherapy arm. For the 205 patients (120 in RYDAPT arm and 85 in placebo arm) who entered the maintenance phase, the median duration of exposure in maintenance was 11 months for both arms (16 to 520 days for patients in the RYDAPT arm and 22 to 381 days in the placebo arm).

The most frequent (incidence ≥30%) adverse drug reactions (ADRs) in the RYDAPT plus standard chemotherapy arm were febrile neutropenia, nausea, exfoliative dermatitis, vomiting, headache, petechiae and pyrexia. The most frequent Grade 3/4 ADRs (incidence ≥10%) were febrile neutropenia, lymphopenia, device related infection, exfoliative dermatitis, and nausea.

Serious AEs occurred in 46.3 % of patients in the RYDAPT plus standard chemotherapy arm versus 51.8 % in the placebo plus standard chemotherapy arm. The most frequent serious AEs in patients in the RYDAPT plus standard chemotherapy arm was febrile neutropenia (15.7%) and this occurred at a similar rate in the placebo arm (15.9%).

Discontinuation due to any adverse event occurred in 9.2% of patients in the RYDAPT arm versus 6.2% in the placebo arm. The most frequent Grade 3/4 adverse event leading to discontinuation in the RYDAPT arm was exfoliative dermatitis (1.2%).

Deaths occurred in 4.3% of patients in the RYDAPT plus standard chemotherapy arm versus 6.3% in the placebo plus standard chemotherapy arm. The most frequent cause of death in the RYDAPT plus standard chemotherapy arm was sepsis (1.2%) and occurred at a similar rate in the placebo arm (1.8%).

Tabulated summary of adverse reactions from clinical trials in AML

Table 3 presents the frequency category of ADRs reported in the phase-III study in patients with newly diagnosed FLT3 mutated AML. ADRs are listed according to MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each ADR: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Table 4 presents the key laboratory abnormalities from the same phase-III study in patients with newly diagnosed FLT3 mutated AML.

Table 3 Adverse drug reactions reported in AML clinical study

Adverse drug reactions	All grades		Grades 3/4		Frequency category
	RYDAPT + chemo n=229[1] %	Placebo + chemo n=226[1] %	RYDAPT + chemo n=345[1] %	Placebo + chemo n=335[1] %	
Infections and infestations					
Device related infection	24	17.3	15.7	9.9	very common
Upper respiratory tract infection	5.2	3.1	0.6	0.9	common
Neutropenic sepsis	0.9	0.4	3.5	0.3	uncommon
Blood and lymphatic system disorders					
Febrile neutropenia	83.4	80.5	83.5	83.0	very common
Petechiae	35.8	27	1.2	0.6	very common
Lymphopenia[2]	16.6	18.6	20	22.7	very common
Immune system disorders					
Hypersensitivity	15.7	14.2	0.6	1.2	very common
Metabolism and nutrition disorders					
Hyperuricaemia	8.3	6.2	0.6	0.6	common
Psychiatric disorders					
Insomnia	12.2	8	0	0.3	very common
Nervous system disorders					
Headache	45.9	38.1	2.6	3	very common
Syncope	5.2	4.9	4.6	3	common
Tremor	3.9	1.8	0	0	common
Eye disorders					
Eyelid oedema	3.1	0.4	0	0	common
Cardiac disorders					
Hypotension	14.4	15	5.5	3	very common
Sinus tachycardia	9.6	8	1.2	0	common
Hypertension	7.9	5.8	2.3	0.9	common

Adverse drug reactions	All grades		Grades 3/4		Frequency category
	RYDAPT + chemo n=229[1] %	Placebo + chemo n=226[1] %	RYDAPT + chemo n=345[1] %	Placebo + chemo n=335[1] %	
Pericardial effusion	3.5	1.3	0.6	0	common
Respiratory, thoracic and mediastinal disorders					
Epistaxis	27.5	23.5	2.6	0.6	very common
Laryngeal pain	11.8	9.7	0.6	0.9	very common
Pneumonitis[3]	11.4	12.8	4.9	6.6	very common
Dyspnoea	10.9	12.4	5.5	3.9	very common
Pleural effusion	5.7	3.5	0.9	0.9	common
Nasopharyngitis	8.7	6.6	0	0	common
Acute respiratory distress syndrome	2.2	0.4	2.3	0.9	common
Gastrointestinal disorders					
Nausea	83.4	70.4	5.8	10.1	very common
Vomiting	60.7	52.7	2.9	4.5	very common
Stomatitis	21.8	14.2	3.5	2.7	very common
Abdominal pain upper	16.6	14.6	0	0.3	very common
Haemorrhoids	15.3	10.6	1.4	0	very common
Anorectal discomfort	7	4	0.9	0	common
Abdominal discomfort	3.5	0.9	0	0	common
Skin and subcutaneous tissue disorders					
Dermatitis exfoliative	61.6	60.6	13.6	7.5	very common
Hyperhidrosis	14.4	8	0	0	very common
Dry skin	7	5.3	0	0	common
Keratitis	6.6	4.9	0.3	0.6	common
Musculoskeletal and connective tissue disorders					
Back pain	21.8	15.5	1.4	0.6	very common
Arthralgia	14	8	0.3	0.3	very common
Bone pain	9.6	9.7	1.4	0.3	common
Pain in extremity	9.6	8.8	1.4	0.6	common
Neck pain	7.9	4	0.6	0	common
General disorders and administration site conditions					
Pyrexia	34.5	35.4	3.2	2.7	very common
Catheter-related thrombosis	3.5	1.3	2	1.8	common
Investigations					

Adverse drug reactions	All grades		Grades 3/4		Frequency category
	RYDAPT + chemo n=229[1] %	Placebo + chemo n=226[1] %	RYDAPT + chemo n=345[1] %	Placebo + chemo n=335[1] %	
Hyperglycaemia	20.1	16.8	7	5.4	very common
Electrocardiogram QT prolonged[3]	19.7	16.8	5.8	5.4	very common
Activated partial thromboplastin time prolonged	12.7	8.4	2.6	1.8	very common
Weight increased	6.6	3.1	0.6	0.3	common

[1]For trial sites in North America, all grades were collected for 13 pre-specified adverse events, For all other adverse events, only grades 3 and 4 were collected. Therefore all grade AEs are summarized only on patients in Non North American trial sites whereas grade 3 and 4 are summarized on patients in all trial sites.

[2]Higher frequency with RYDAPT observed during maintenance phase, please see paragraph below "Safety profile during maintenance phase".

[3]These ADRs were detected during the AML clinical study and were included after identification in the post-marketing setting.

Table 4 Percentage of patients with Grade 3 and 4 laboratory abnormalities

Laboratory abnormality	RYDAPT 50 mg twice daily (N=345) Grade 3/4 %	Placebo (N=335) Grade 3/4 %	Frequency category (based on all grades)
Absolute neutrophils decreased	85.8	86.9	very common
Haemoglobin decreased	78.6	77.6	very common
Platelets decreased	95.9	94.3	Very common
Aspartate aminotransferase (AST) increased	6.4	6.0	very common
Alanine aminotransferase (ALT) increased	19.4	14.9	very common
Hypercalcaemia	0.6	0.3	common
Hypokalaemia	13.9	14.3	very common
Hypernatraemia	1.2	1.8	very common

Safety profile during maintenance phase

While Table 3 provides the incidence for ADRs over the total duration of the study, when the maintenance phase (single agent RYDAPT or placebo) was assessed separately, a difference in the type and severity of ADRs was observed. The overall incidence of ADRs during the maintenance phase was also generally lower. Adverse drug reactions during the maintenance phase with at least ≥5% difference between the RYDAPT and placebo arms were: nausea (46.4% vs 17.9%), hyperglycaemia (20.2% vs 12.5%), vomiting (19% vs 5.4%), lymphopenia (16.7% vs 8.9%) and QT prolongation (11.9% vs 5.4%).

Most of the haematological abnormalities reported occurred during the induction and consolidation phase when the patients received RYDAPT or placebo in combination with chemotherapy. The most frequent grade 3/4 haematological abnormalities reported in patients during the maintenance phase with RYDAPT were absolute neutrophil count decrease (20.8% vs 18.9%) and leukopenia (7.5% vs 5.9%).

ADRs reported during the maintenance phase led to discontinuation of 1.2% of patients in the Rydapt arm and none in the placebo arm.

Description of selected adverse drug reactions

Gastrointestinal disorders

In AML patients during the maintenance phase, low grade nausea and vomiting were observed. Low grade diarrhea was also observed. These were well managed with supportive prophylactic medication and led to treatment discontinuation in 2 patients, one in each treatment group.

Adverse events in elderly AML patients

An interim analysis was conducted on 145 patients (99 patients were ≤ 60 years of age; 46 were > 60 to 70 years of age) enrolled into the first cohort of a phase II study. The most frequent adverse events observed across all grades and based on system organ class were blood/lymphatic system disorders (e.g. anemia, febrile neutropenia) and gastrointestinal disorders (e.g. nausea, vomiting). The incidence of adverse events when compared between the younger and older age groups (≤ 60, >60 to 70 years of age) appear to be similar in general. The frequency of treatment-related severe adverse events (≥ grade 3) and the frequency of serious adverse events were slightly higher in the older age group (85% vs. 80% and 72% vs. 62%, respectively). Although this is an interim analysis, the overall incidence of all treatment

related adverse events as well as Grade 3/4 adverse events appear to be consistent with that observed in Study A2301. The rates of death occurring during study treatment and within the 30-day follow-up period were higher in older compared to younger patients (22% and 6%, respectively).

ASM, SM-AHN and MCL - Summary of the safety profile

The safety of RYDAPT (100 mg twice daily) as a single agent in patients with ASM, SM-AHN and MCL was evaluated in 142 patients in two single-arm, open-label, multicenter studies. The median duration of exposure to RYDAPT was 11.4 months (range: 0 to 81 months).

The most frequent ADRs (incidence ≥30%) were nausea, vomiting, diarrhoea, peripheral oedema, and fatigue. The most frequent Grade 3/4 ADRs (incidence ≥6%) were fatigue, sepsis, pneumonia, febrile neutropenia, and diarrhoea. The most frequent non-haematologic laboratory abnormalities (incidence ≥30%) were glucose increased, total bilirubin increased, lipase increased, AST increased, and ALT increased while the most frequent haematologic laboratory abnormalities (incidence ≥25%) were absolute lymphocyte decreased and neutrophils decreased. The most frequent Grade 3/4 laboratory abnormalities (incidence ≥10%) were absolute lymphocyte decreased, absolute neutrophils decreased, glucose increased, and lipase increased.

Dose modifications (interruption or adjustment) due to ADRs occurred in 31% of patients. The most frequent ADRs that led to dose modification (incidence ≥5%) were nausea and vomiting.

Adverse events that led to treatment discontinuation occurred in 23.9% of patients. The most common AEs leading to discontinuation were GI related events (5.6%).

Deaths occurred in 18.3% of patients. The most frequent causes of death were disease progression and sepsis.

Tabulated summary of adverse reactions from clinical trials in ASM, SM-AHN and MCL

Table 5 presents the frequency category of ADRs based on pooled data from two studies in patients with ASM, SM-AHN and MCL. ADRs are listed according to MedDRA system organ class. Within each system organ class, the ADRs are ranked by frequency, with the most frequent reactions first. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each ADR: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Table 5 presents the key laboratory abnormalities based on pooled data from two studies in patients with ASM, SM-AHN and MCL.

Table 5 Adverse drug reactions reported in ASM, SM-AHN and MCL studies

Adverse drug reaction	RYDAPT (100 mg twice daily) N=142			Frequency category
	All grades %	Grade 3 %	Grade 4 %	
Infections and infestations				
Urinary tract infection	13	2.1	0.7	very common
Upper respiratory tract infection	11	1.4	0	very common
Pneumonia	8.5	7.0	0	common
Sepsis	7.7	2.1	5.6	common
Bronchitis	5.6	0	0	common

Adverse drug reaction	RYDAPT (100 mg twice daily) N=142 All grades %	Grade 3 %	Grade 4 %	Frequency category
Oral herpes	4.9	0	0	common
Cystitis	4.2	0	0	common
Sinusitis	4.2	0.7	0	common
Erysipelas	3.5	1.4	0	common
Herpes zoster	3.5	0.7	0	common
Blood and lymphatic system disorders				
Febrile neutropenia	7.7	6.3	0.7	common
Immune system disorders				
Hypersensitivity	2.1	0	0	common
Anaphylactic shock	0.7	0	0.7	uncommon
Nervous system disorders				
Headache	26	1.4	0	very common
Dizziness	13	0	0	very common
Disturbance in attention	7	0	0	common
Tremor	6.3	0	0	common
Ear and labyrinth disorders				
Vertigo	4.9	0	0	common
Vascular disorders				
Hypotension	9.2	2.1	0	common
Haematoma	6.3	0.7	0	common
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	18	4.2	1.4	very common
Cough	16	0.7	0	very common
Pleural effusion	13	4.2	0	very common
Epistaxis	12	2.1	0.7	very common
Oropharyngeal pain	4.2	0	0	common
Interstitial lung disease*	1.4	0	0	Common
Pneumonitis*	0.7	0	0	Uncommon
Gastrointestinal disorders				
Nausea	82	4.9	0.7	very common
Vomiting	68	4.9	0.7	very common
Diarrhoea	51	6.3	0	very common
Constipation	29	0.7	0	very common
Dyspepsia	5.6	0	0	common
Gastrointestinal haemorrhage	4.2	2.8	0.7	common
General disorders and administration site conditions				
Oedema peripheral	35	3.5	0	very common
Fatigue	31	7.0	1.4	very common
Pyrexia	27	4.2	0	very common
Asthenia	4.9	0	0.7	common
Chills	4.9	0	0	common
Oedema	4.2	0.7	0	common
Investigations				
Electrocardiogram QT prolonged*	10.6	0.7	0	very common
Weight increased	5.6	2.8	0	common

Adverse drug reaction	RYDAPT (100 mg twice daily) N=142 All grades %	Grade 3 %	Grade 4 %	Frequency category
Injury, poisoning and procedural complications				
Contusion	6.3	0	0	common
Fall	4.2	0.7	0	common

[*]These ADRs were detected during the Advanced SM studies and were included after identification in the post-marketing setting.

Table 6 presents the frequency of laboratory abnormalities reported in the ASM, SM-AHN and MCL trials.

Table 6 Percentage of patients with key laboratory abnormalities in the ASM, SM-AHN and MCL studies

Key laboratory abnormality	RYDAPT (100 mg twice daily) N=142 Grade 3 %	Grade 4 %	Frequency category (based on all grades)
Glucose increased*	18.3	0.7	very common
Absolute neutrophils decreased	15.5	11.3	very common
Absolute lymphocyte decreased	38.7	7.0	very common
Aspartate aminotransferase (AST) increased	2.1	0.7	very common
Alanine aminotransferase (ALT) increased	3.5	0	very common
Total bilirubin increased	4.9	0	very common
Amylase increased	4.2	2.8	very common
Lipase increased	14.8	2.8	very common
Anaemia	37.3	6.3	very common
Thrombocytopenia	20.4	16.9	very common

**non fasting*

Adverse drug reactions from spontaneous reports and literature cases (frequency not known)

The following adverse drug reactions have been derived from post-marketing experience with Rydapt via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Table 7 ADRs from spontaneous reports and literature cases

Adverse drug reaction	Frequency category
Respiratory, thoracic and mediastinal disorders	
Interstitial lung disease[*]	Not known

**Applicable only for AML indication*

Description of selected adverse drug reactions

Gastrointestinal disorders

In the ASM, SM-AHN and MCL patient population 17 (12%) patients had a dose adjustment or interruption for nausea, 13 (9.2%) for vomiting, and 7 (4.9%) for diarrhoea. The treatment discontinuation rate was low with 3 (2.1%) patients discontinued for nausea, 2 (1.4%) patients for vomiting, and 1 (0.7%) patient for diarrhoea. Most of the events occurred within the first 6 months of treatment and were well managed with supportive prophylactic medication.

INTERACTIONS

Midostaurin undergoes extensive hepatic metabolism through CYP3A4 enzymes which are either induced or inhibited by a number of concomitant drugs. Based on *in vivo* and in *vitro* data, midostaurin and/or its metabolites have the potential to inhibit and to induce CYP enzymes. Therefore, RYDAPT may be a victim or a perpetrator of drug-drug interactions *in vivo*.

Effect of other drugs on RYDAPT

Drugs or substances known to affect the activity of CYP3A4 may affect the plasma concentrations of midostaurin and therefore the safety and/or efficacy of RYDAPT.

Strong CYP3A4 inhibitors

Strong CYP3A4 inhibitors may increase midostaurin blood concentrations. In a study with 36 healthy subjects, co-administration of the strong CYP3A4 inhibitor ketoconazole to steady-state with a single dose of RYDAPT led to a significant increase in midostaurin exposure (1.8-fold C_{max} increase and 10-fold AUCinf increase) while the peak concentrations of the active metabolites, CGP62221 and CGP52421, decreased by half (see section CLINICAL PHARMACOLOGY). Another study evaluated the concomitant administration of multiple dose midostaurin 50 mg twice daily with the strong CYP3A4 inhibitor itraconazole at steady-state in a subset of patients (N=7), and showed that itraconazole increased midostaurin steady-state exposure (C_{min}) by only 2.09-fold. During the induction phase of the AML study, up to 62% of patients received midostaurin concomitantly with strong inhibitors of CYP3A4. Upon co-administration with CYP3A4 inhibitors, a 1.44-fold increase in midostaurin exposure (C_{min}) was observed. No impact was observed for CGP62221 and CGP52421. Caution should be advised when concomitantly administering with midostaurin, medicinal products that are strong inhibitors of CYP3A4, such as, but not limited to, antifungals (e.g., ketoconazole), certain antivirals (e.g., ritonavir), macrolide antibiotics (e.g., clarithromycin), and nefazodone. Alternative therapeutics that do not strongly inhibit CYP3A4 activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for toxicity.

Strong CYP3A4 inducers

Concomitant use of Rydapt with strong inducers of CYP3A4 (e.g. carbamazepine, rifampicin, enzalutamide, phenytoin, St. John's Wort [*Hypericum perforatum*]) is contraindicated (see section CONTRAINDICATIONS). Strong CYP3A4 inducers may decrease midostaurin and its active metabolites (CGP52421 and CGP62221). In a study in healthy subjects, co-administration of the strong CYP3A4 inducer rifampicin (600 mg daily) to steady state with a 50mg single dose of midostaurin decreased midostaurin C_{max} by 73% and AUC_{inf} by 96%, respectively. Both metabolites, CGP62221 and CGP52421, exhibited a similar pattern. The

concomitant use of RYDAPT with strong CYP3A4 inducers (e.g., carbamazepine, rifampin, St. John's Wort) should be avoided.

Effect of RYDAPT on other drugs

Substrates of CYP enzymes

In healthy subjects, co-administration of a single dose of bupropion (CYP2B6 substrate) with multiple doses of midostaurin (50 mg twice daily) at steady-state decreased bupropion AUCinf and AUClast by 48% and 49% respectively and Cmax by 55% compared to administration of bupropion alone. This indicates that midostaurin is a mild inducer of CYP2B6. Medicinal products with a narrow therapeutic range that are substrates of CYP2B6 should be used with caution when administered concomitantly with midostaurin, and may need dose adjustment to maintain optimal exposure.

Based on *in vitro* data, midostaurin and its active metabolites, CGP52421 and CGP62221, are considered as inhibitors of CYP1A2 and CYP2E1 and inducers of CYP1A2. Therefore, medicinal products with a narrow therapeutic range that are substrates of CYP1A2 and CYP2E1 should be used with caution when administered concomitantly with midostaurin, and may need dose adjustment to maintain optimal exposure.

In healthy subjects, co-administration of a single dose of midazolam (CYP3A substrate) with multiple doses of midostaurin (50 mg twice daily) at steady-state decreased midazolam AUCinf and AUClast by 3% and 4% respectively and increased Cmax by 10% compared to administration of midazolam alone. Therefore, midostaurin has neither inhibitory nor inducing effect on CYP3A substrates.

In healthy subjects, co-administration of a single dose of pioglitazone (CYP2C8 substrate) with multiple doses of midostaurin (50 mg twice daily) at steady-state did not cause any clinically significant decrease in pioglitazone exposure (6% decrease in AUCinf and AUClast respectively, and 10% decrease in Cmax) compared to the administration of pioglitazone alone. Clinically relevant drug-drug interactions between midostaurin and CYP2C8 substrates are unlikely to occur.

In healthy subjects, co-administration of a single dose of dextromethorphan (CYP2D6 substrate) with a single dose of midostaurin (100 mg) did not cause any increase in dextromethorphan exposure (13% decrease in AUCs and 28% decrease in Cmax) compared to administration of dextromethorphan alone. Therefore, midostaurin has no inhibitory effect on CYP2D6 and clinically relevant drug-drug interactions between midostaurin and CYP2D6 substrates are unlikely to occur.

Substrates of transporters

In healthy subjects, co-administration of a single dose of rosuvastatin (BCRP substrate) with a single dose of midostaurin (100 mg) increased rosuvastatin AUCinf and AUClast by 37% and 48% respectively; Cmax was approximately doubled (2.01 times) compared to administration of rosuvastatin alone. This indicates that midostaurin has a mild inhibitory effect on BCRP substrates. Medicinal products with a narrow therapeutic range that are substrates of the transporter BCRP should be used with caution when administered concomitantly with midostaurin, and may need dose adjustment to maintain optimal exposure.

In healthy subjects, co-administration of a single dose of digoxin (P-gp substrate) with a single dose of midostaurin (100 mg) increased digoxin AUCinf and AUClast by 23% and 21% respectively, and Cmax by 20% compared to administration of digoxin alone. This indicates that midostaurin has a minor inhibitory effect on P-gp substrates. Clinically relevant drug-drug interactions between midostaurin and P-gp substrates are unlikely to occur.

Hormonal contraceptives

There was no clinically significant pharmacokinetic drug-drug interaction between multiple doses of midostaurin (50 mg twice daily) at steady-state and oral contraceptives containing ethinyl estradiol and levonorgestrel in healthy women. Therefore it is not anticipated that the contraceptive reliability of this combination will be compromised by co-administration of midostaurin.

Drug-food interactions

See absorption sub-section in section CLINICAL PHARMACOLOGY.

PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Pregnancy

Risk summary

RYDAPT can cause fetal harm when administered to a pregnant woman.

There are no adequate and well-controlled studies in pregnant women. Reproductive studies in rats and rabbits demonstrated that midostaurin induced fetotoxicity. An increase in number of late resorptions, a reduction in fetal weight and reduced skeletal ossification were observed in rats and rabbits following prenatal exposure to midostaurin at concentrations over 50–fold below the exposure in humans at the recommended doses of 50 and 100 mg twice daily based on AUC. RYDAPT should not be used in women who are pregnant or contemplating pregnancy.

Animal data

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of midostaurin at 3, 10, and 30 mg/kg/day and at 2, 10 and 20 mg/kg/day, respectively, during the period of organogenesis. An increase in number of late resorptions was observed at all dose levels and a reduction in fetal weight and skeletal ossification was observed in rats at the high dose of 30 mg/kg/day; no maternal toxicity was observed. In rabbits, maternal toxicity was observed at all dose levels. Mortality in dams, reduced fetal weight and delayed ossification was observed at 10 and 20 mg/kg/day. The concentrations at which maternal and fetal toxicity occurred in both species are over 50-fold below the human therapeutic exposures at the recommended doses of 50 and 100 mg twice daily based on AUC comparisons across species.

In a pre- and post-natal developmental study, rats were given oral doses of 5, 15, and 30 mg/kg/day during gestation through lactation up to weaning. Maternal toxicity including signs of dystocia and reduced litter size were observed at 30 mg/kg/day. Lower body weights, a delay in eye opening and auricular startle ontogeny were noted in the rat pups (F1 generation) exposed to midostaurin at 30 mg/kg/day. Maternal systemic exposure at 30 mg/kg (based on AUC) was over 17 to 20-fold below the human therapeutic exposures at the human doses of 50 and 100 mg twice daily.

Lactation

It is unknown whether midostaurin or its active metabolites are transferred in human milk. There are no data on the effects of RYDAPT on the breastfed child or the effects of RYDAPT on milk production. Studies show that orally administered midostaurin and its active metabolites pass into the milk of lactating rats. Because many drugs are transferred in human milk and because of the potential for serious adverse reactions in nursing infants from

RYDAPT, a nursing woman should be advised on the potential risks to the child and breast-feeding should be discontinued during treatment with RYDAPT and for at least 4 months after stopping treatment.

Females and males of reproductive potential

Pregnancy testing

Sexually-active females of reproductive potential are advised to have a pregnancy test within seven days prior to starting treatment with RYDAPT.

Contraception

Females of reproductive potential should be advised that animal studies show RYDAPT to be harmful to the developing fetus. Sexually-active females of reproductive potential are advised to have a pregnancy test within 7 days prior to starting treatment with RYDAPT and that they should use effective contraception (methods that result in less than 1% pregnancy rates) when using RYDAPT and for at least 4 months after stopping treatment with RYDAPT.

Sexually-active males taking RYDAPT should use a condom during intercourse with females of reproductive potential or pregnant women and for at least 4 months after stopping treatment with RYDAPT to avoid conception or embryo-fetal harm.

Infertility

Based on findings in animals, RYDAPT may impair fertility in humans. It is not known whether these effects on fertility are reversible. Oral administration of midostaurin at 10, 30 and 60 mg/kg/day was associated with reproductive toxicity in male and female rats at doses ≥60 mg/kg/day. In males, testicular degeneration and atrophy, alterations in sperm motility, a decrease in sperm counts, and a decrease in reproductive organ weights were observed. In females, increased resorptions, decreased pregnancy rate, number of implants and live embryos were observed at 60 mg/kg/day. Inhibition of spermatogenesis was seen in dogs at doses ≥3 mg/kg/day. The concentrations in rats at 60 mg/kg/day and dogs at 3 mg/kg/day are 8- and 100-fold below the human therapeutic exposures at the recommended doses of 50 or 100 mg twice daily based on AUC.

OVERDOSAGE

Reported experience with overdose in humans is very limited. Single doses of up to 600 mg have been given with acceptable acute tolerability.

General supportive measures should be initiated in all cases of overdose.

CLINICAL PHARMACOLOGY

Pharmacotherapeutic group, ATC

Protein kinase inhibitors, ATC code: L01XE39.

Mechanism of action (MOA)

Midostaurin inhibits multiple receptor tyrosine kinases, including FLT3 and KIT kinase. Midostaurin inhibits FLT3 receptor signaling and induces cell cycle arrest and apoptosis in leukemic cells expressing ITD and TKD mutant receptors or overexpressing wild type

receptors. Midostaurin inhibits both the wild type and D816V mutant KIT, leading to interference with the aberrant signaling of KIT and inhibits mast cell proliferation and survival, and histamine release.

In addition, it inhibits several other receptor tyrosine kinases such as PDGFR or VEGFR2, as well as members of the serine/threonine kinase family PKC (protein kinase C). Midostaurin binds to the catalytic domain of these kinases and inhibits the mitogenic signaling of the respective growth factors in cells, resulting in growth arrest.

Midostaurin in combination with many chemotherapeutic agents (with the exception of methotrexate) resulted in synergistic growth inhibition in FLT3-ITD expressing AML cell lines.

Pharmacodynamics (PD)

Two major metabolites have been identified in murine models and humans.

In proliferation assays with FLT3-ITD expressing cells, CGP62221 showed similar potency compared to the parent compound, whereas CGP52421 was approximately 10 fold less potent.

Cardiac Electrophysiology

A dedicated QT study in 192 healthy subjects with a dose of 75mg twice daily did not reveal clinically significant prolongation of QT by midostaurin and CGP62221 and the study duration was not long enough to estimate the QTc prolongation effects of the long-acting metabolite CGP52421. Therefore, the change from baseline in QTcF with the concentration of midostaurin and both metabolites was further explored in a phase II study in 116 patients with ASM, SM-AHN and MCL. At the median peak Cmin concentrations attained at a dose of 100 mg twice daily, neither midostaurin, CGP62221 nor CGP52421 showed a potential to cause clinically significant QTcF prolongation, since the upper bounds of predicted change at these concentration levels were less than 10 msecs with 5.8, 2.4, and 4.0 msecs, respectively. In the ASM, SM-AHN and MCL population, 25.4% of patients had at least one ECG measurement with a QTcF greater than 450 ms and 4.7% greater than 480 ms.

Pharmacokinetics (PK)

Absorption

In humans, the absorption of midostaurin is rapid after oral administration, with T_{max} of total radioactivity observed at 1 to 3 hours post dose. In healthy subjects, the extent of midostaurin absorption (AUC) was increased by an average of 22% when RYDAPT was co-administered with a standard meal, and by an average of 59% when co-administered with a high-fat meal. Peak midostaurin concentration (C_{max}) was reduced by 20% with a standard meal and by 27% with a high-fat meal versus on an empty stomach. Time to peak concentration was also delayed in presence of a standard meal or a high-fat meal (median T_{max} = 2.5 hrs to 3 hrs). In clinical studies, midostaurin was administered with a light meal, in order to decrease potential nausea and vomiting events and it is recommended that midostaurin is administered to patients with food.

Distribution

Midostaurin has a high tissue distribution of geometric mean Vz/F= 95.2 L. Midostaurin and its metabolites are distributed mainly in plasma rather than red blood cells. *In vitro* data showed midostaurin is greater than 98% bound to plasma protein mainly to alpha-1-acid glycoprotein (AGP).

Biotransformation/metabolism

Midostaurin is metabolized by CYP3A4 mainly via oxidative pathways and the major plasma components included midostaurin and two major active metabolites; CGP62221 and CGP52421 accounting for 27.7± 2.7% and 37.97± 6.6% respectively of the total plasma exposure. O-demethylation, oxidation at benzene ring, oxidation at pyrrolidinine ring, amide bond hydrolysis, and N-demethylation were the major pathways of metabolism in man, leading to formation of 16 metabolites. CYP1A1, CYP3A4, and CYP3A5 were found capable of metabolizing both CGP62221 and CGP52421.

Elimination

The median terminal half-lives of midostaurin, CGP62221 and CGP52421 in plasma are approximately 20.9, 32.3 and 471 hours. The Human Mass Balance study results indicate that fecal excretion is the major route of excretion (78% of the dose), and mostly as metabolites (73% of the dose) while unchanged midostaurin accounts for 3% of the dose. Only 4% of the dose is recovered in urine. At least 16 radiolabeled metabolites were characterized and quantitated in the excreta. In feces, the predominant metabolite was P29.6B (26.7%). In urine, the predominant metabolite was P6B (hippuric acid).

Linearity/non-linearity

In general, midostaurin and its metabolites showed no major deviation from dose-proportionality after a single dose in the range of 25 mg to 100 mg. However, there was a less than dose-proportional increase in exposure after multiple doses within the dose range of 50 mg to 225 mg daily.

Following multiple oral doses, midostaurin displayed time-dependent pharmacokinetics with an initial increase in plasma concentrations during the first week (peak C_{min}) followed by a decline with time to a steady-state after approximately 28 days. While the exact mechanism for the declining concentration of midostaurin is unclear, it may be possibly due to CYP3A4 enzyme auto-induction. The pharmacokinetics of the CGP62221 metabolite showed a similar trend. However, CGP52421 concentrations increased up to 2.5 fold with ASM, SM-AHN and MCL to and up to 9-fold for AML, compared to midostaurin after one month of treatment.

In vitro evaluation of drug interaction potential

Based on *in-vitro* data, midostaurin and its active metabolites, CGP52421 and CGP62221, are considered as inhibitors of CYP1A2 and CYP2E1 and inducers of CYP1A2. Based on *in-vitro* data midostaurin may inhibit BSEP. Simulations using physiologically based pharmacokinetic (PBPK) models predicted that midostaurin given at a dose of 50 mg twice daily at steady-state is unlikely to cause clinically relevant inhibition of OATP1B.

Special populations

Pediatric patients (below 18 years)

Rydapt is not recommended to be used in children and adolescents (see section DOSAGE REGIMEN AND ADMINISTRATION). The pharmacokinetics of midostaurin in pediatric patients were explored in phase 1 dose escalation monotherapy study with 22 patients (12 aged 0-2 years and 10 aged 10-17 years) with AML or MLL-rearranged ALL using a population pharmacokinetic approach. The pharmacokinetics of midostaurin were less than dose proportional with the doses of 30 mg/m^2 and 60 mg/m^2 after single and multiple doses. Due to the limited pharmacokinetic data in paediatric patients, no comparison with midostaurin pharmacokinetics in adults can be made.

Geriatric patients (65 years or above)

Based on population PK model analyses of the effect of age on clearance of midostaurin and its active metabolites, there was no statistically significant finding and the anticipated changes in exposure were not deemed to be clinically relevant. In adult patients with ASM, SM-AHN and MCL or AML, no midostaurin dose adjustment is required based on age.

Gender

Based on population PK model analyses of the effect of gender on clearance of midostaurin and its active metabolites, there was no statistically significant finding and the anticipated changes in exposure were not deemed to be clinically relevant. No midostaurin dose adjustment is required based on gender.

Race/Ethnicity

There are no differences in the pharmacokinetic profile between Caucasian and Black subjects. Based on the phase 1 study in healthy Japanese volunteers, pharmacokinetic profiles of midostaurin and its metabolites (CGP62221 and CGP52421) are similar compared to those observed in other PK studies conducted in Caucasians and Blacks. No midostaurin dose adjustment is required based on ethnicity.

Patients with hepatic impairment

A dedicated hepatic impairment study assessed the systemic exposure of midostaurin in subjects with baseline mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C respectively) and control subjects with normal hepatic function. There was no increase in exposure (AUC) to plasma midostaurin and its metabolites (CGP62221 and CGP52421) in subjects with mild, moderate or severe hepatic impairment compared to subjects with normal hepatic function. No dosage adjustment is necessary for patients with baseline mild, moderate or severe hepatic impairment.

Patients with renal impairment

No dedicated renal impairment study was conducted for midostaurin. Population pharmacokinetic (popPK) analyses were conducted using data from clinical trials in patients with AML (n=180) and ASM, SM-AHN and MCL (n=141). Out of the 321 patients included, 177 patients showed pre-existing mild (n=113), moderate (n=60) or severe (n=4) renal impairment (15 mL/min ≤creatinine clearance [CrCL] <90 mL/min). 144 patients showed normal renal function (CrCL>90 mL/min) at baseline. Based on the population PK analyses, midostaurin clearance was not significantly impacted by renal impairment and therefore, no dosage adjustment is necessary for patients with mild or moderate renal impairment.

CLINICAL STUDIES

Acute Myeloid Leukemia (AML)

The efficacy and safety of RYDAPT in combination with standard chemotherapy versus placebo plus standard chemotherapy and as single agent maintenance therapy was investigated in 717 patients (18 to 60 years of age) in a randomized, double-blind, phase III study. Patients with newly diagnosed FLT3 mutated AML as determined by a clinical trial assay were randomized (1:1) to receive RYDAPT 50 mg twice daily (n=360) or placebo (n=357) sequentially in combination with standard daunorubicin (60 mg/m2 daily on days 1 to 3) / cytarabine (200 mg/m2 daily on days 1 to 7) induction and high dose cytarabine (3 g/m2 every

12 hours on days 1, 3, 5) consolidation, followed by continuous RYDAPT or placebo treatment according to initial assignment for up to 12 additional cycles (28 days/cycle). While the study included patients with various AML related cytogenetic abnormalities, patients with acute promyelocytic leukemia (M3) or therapy related AML were excluded. Patients were stratified by FLT3 mutation status: TKD, ITD with allelic ratio <0.7, and ITD with allelic ratio ≥0.7.

The two treatment groups were generally balanced with respect to the baseline demographics of disease characteristics and details are shown in Table 8.

Table 8 Study: Demographics and baseline characteristics

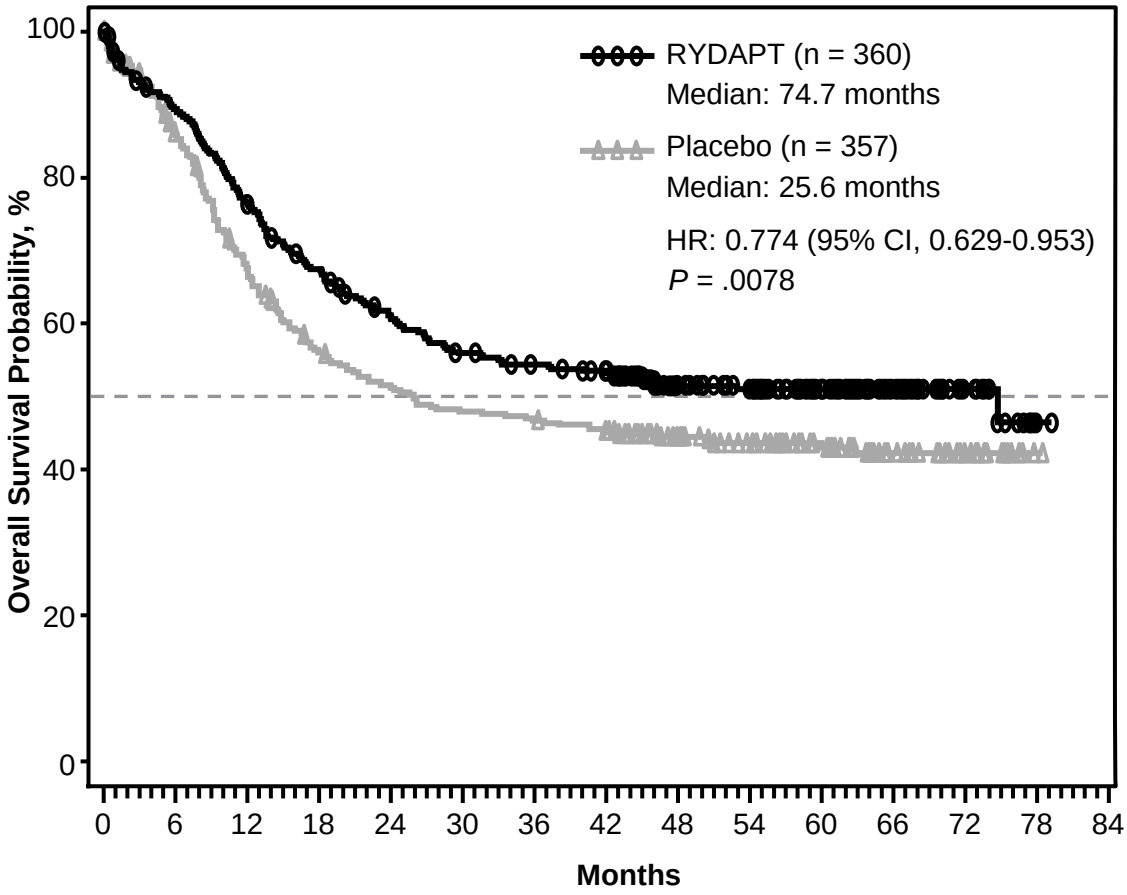
Baseline characteristics	MIDOSTAURIN N=360	PLACEBO N=357
Age (Years)		
Median/Maximum	47.0 / 59	48.0 / 60
Gender -n (%)		
Female	186 (51.7)	212 (59.4)
Male	174 (48.3)	145 (40.6)
ECOG/Zubrod performance status –n (%)		
0 to 2	352 (97.8)	346 (96.97)
3 to 4	8 (2.2)	11 (3.1)
Race -n (%)		
Unknown / Not Reported	195 (54.2)	213 (59.7)
White	147 (40.8)	128 (35.9)
Black or African American	8 (2.2)	9 (2.5)
Other	10 (2.8)	7 (2.0)
FLT3 mutation status -n (%)		
ITD < 0.7	171 (47.5)	170 (47.6)
ITD ≥ 0.7	108 (30.0)	106 (29.7)
TKD	81 (22.5)	81 (22.7)

ITD: Internal Tandem Duplication. TKD: Tyrosine Kinase Domain.
Note: ITD < 0.7, ITD ≥ 0.7 and TKD are the randomization strata.

Patients who proceeded to hematopoietic stem cell transplant (SCT) stopped receiving study treatment on or before the time of stem cell infusion. The overall rate of SCT was 59.4% (214/360) of patient in the RYDAPT plus standard chemotherapy arm versus. 55.2% (197/357) in the placebo plus standard chemotherapy arm. All patients were followed for survival.

The primary endpoint of the study was overall survival (OS), measured from the date of randomization until death by any cause. The primary analysis was conducted after a minimum follow-up of approximately 3.5 years after the randomization of the last patient. The study demonstrated a statistically significant improvement in OS with a 23% risk reduction of death for RYDAPT plus standard chemotherapy over placebo plus standard chemotherapy (see Table 9, figure 1).

Figure 1 **Kaplan-Meier curve for overall survival, non-censored at the time of stem cell transplantation**

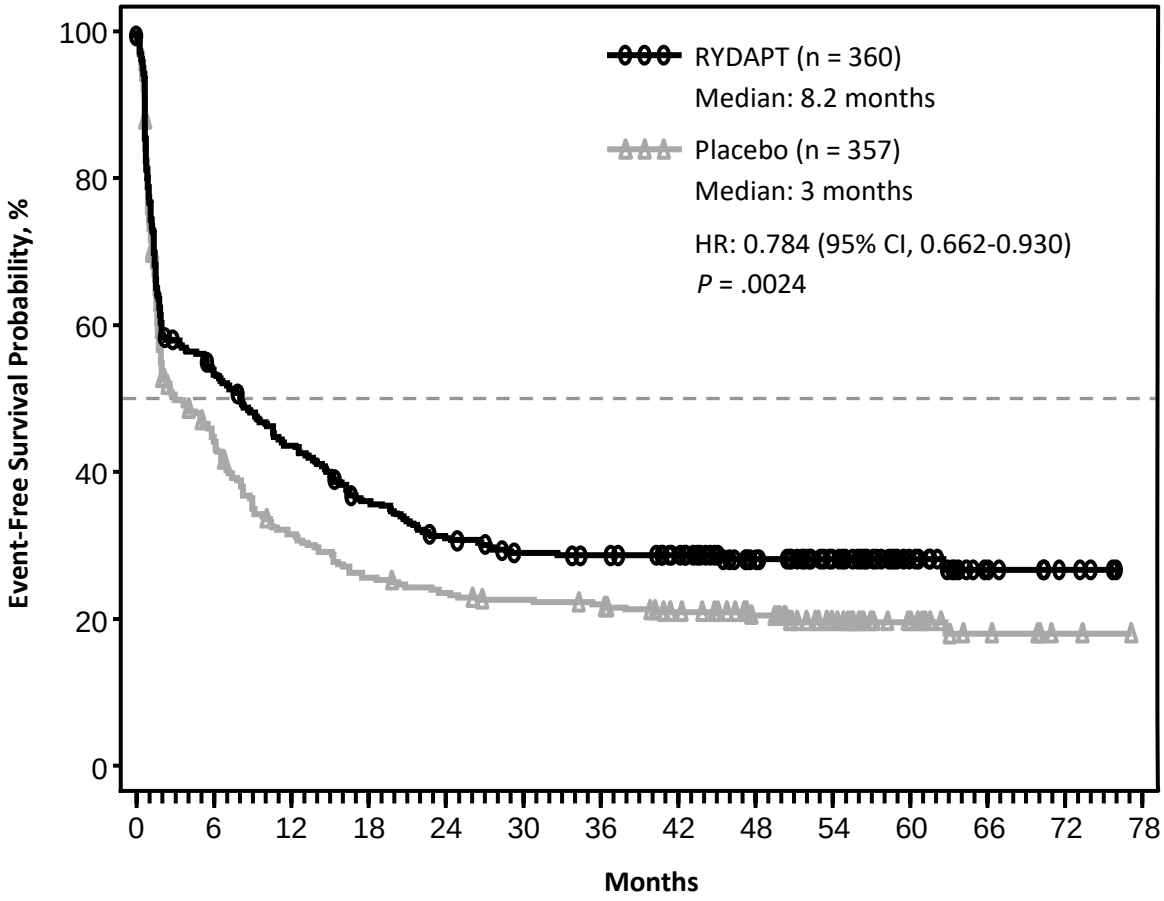


Patients at risk

Months	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72**	**78**	**84**
Midostaurin	360	314	269	234	208	189	181	174	133	120	77	50	22	1	0
Placebo	357	284	221	179	163	152	148	141	110	95	71	45	20	1	0

The key secondary endpoint was event free survival (EFS; an EFS event is defined as a failure to obtain a complete remission (CR) within 60 days of initiation of protocol therapy, or relapse, or death from any cause). The EFS showed a statistically significant improvement for RYDAPT plus standard chemotherapy over placebo plus standard chemotherapy (see Table 9, Figure 2).

Figure 2 Kaplan-Meier curve for event-free survival, non-censored for SCT



Patients at risk

Months	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72**	**78**
Midostaurin	360	190	153	124	106	95	92	83	65	51	27	9	4	0
Placebo	357	153	106	86	78	73	70	60	49	32	18	8	2	0

Sensitivity analyses for both OS and EFS when censored at the time of SCT also supported the clinical benefit with RYDAPT plus standard chemotherapy over placebo. There was a trend favoring RYDAPT for CR rate by day 60 for the midostaurin arm (58.9% versus 53.5%; P = 0.073) that continued when considering all CRs during induction (65.0% versus 58.0%; P = 0.027). In addition, in patients who achieved complete remission in induction, the cumulative incidence of relapse (CIR) at 12 months was 26% in the midostaurin arm vs. 41% in the placebo arm.

Table 9 Efficacy of RYDAPT in AML

Efficacy Parameter	**RYDAPT n=360**	**Placebo n=357**	**HR* (95% CI)**	**P-value¥**
Overall Survival (OS)[1]				
Median OS in months (95% CI)	74.7 (31.5, NE)	25.6 (18.6, 42.9)	0.77 (0.63, 0.95)	0.0078
Event Free Survival (EFS)[2]				
Median EFS in months, considering CRs within 60 days of treatment start (95% CI)	8.2 (5.4-10.7)	3.0 (1.9-5.9)	0.78 (0.66, 0.93)	0.002
Median EFS in months, considering CRs anytime during induction (95% CI)	10.2 (8.1-13.9)	5.6 (2.9-6.7)	0.73 (0.61, 0.87)	0.0001

Efficacy Parameter	RYDAPT n=360	Placebo n=357	HR* (95% CI)	P-value¥
Disease Free Survival (DFS)				
Median DFS in months in patients with CR within 60 days of treatment start (95% CI)	26.7 (19.4, NE)	15.5 (11.3, 23.5)	0.71 (0.55, 0.92)	0.0051
Median DFS in months in patients with CR anytime during induction (95% CI)	28.1 (19.8, NE)	14.1 (10.3, 19.8)	0.66 (0.52, 0.85)	0.0006
Complete Remission (CR)				
within 60 days of treatment start (%)	212 (58.9)	191(53.5)	NE	0.073§
anytime during induction (%)	234 (65.0)	207 (58.0)	NE	0.027§

[1]primary endpoint. [2]key secondary endpoint; NE: Not Estimated,

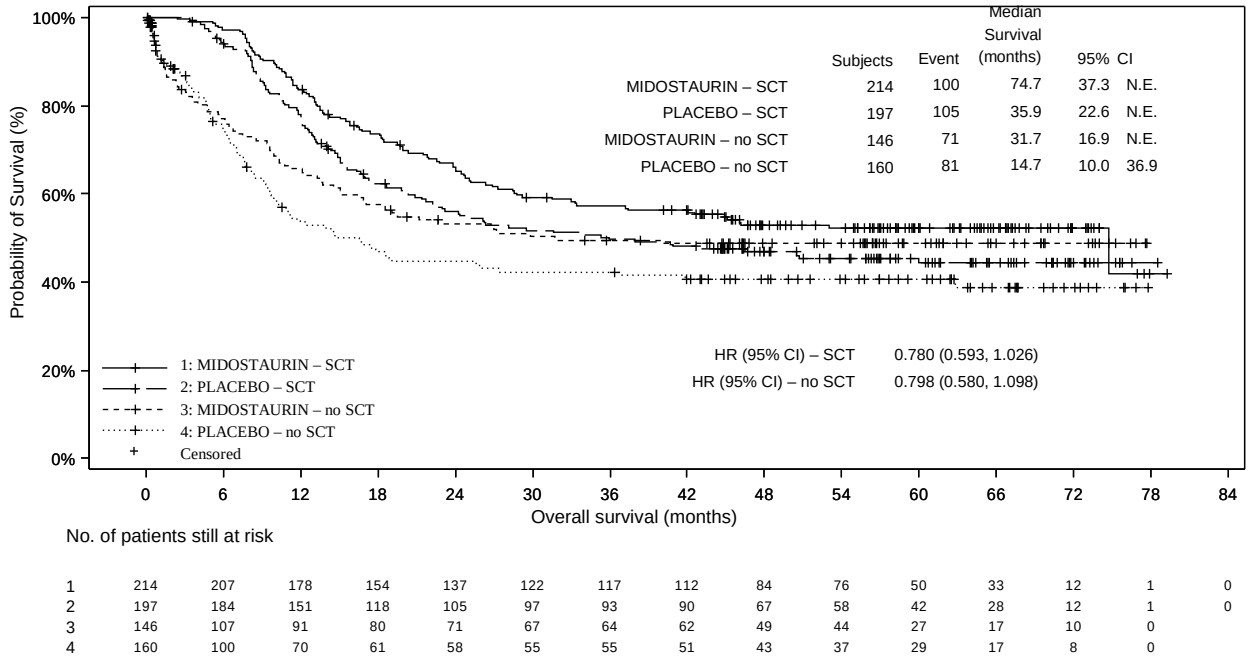
**Hazard ratio (HR) estimated using Cox regression model stratified according to the randomization FLT3 mutation factor.*

¥1-sided p-value calculated using log-rank test stratified according to the randomization FLT3 mutation factor.

§Not Significant (1-sided p-value, CMH test)

Results for OS by SCT status are shown in Figure 3. For EFS, considering complete remissions within 60 days of study treatment start, the HR was 0.602 (95% CI: 0.372, 0.974) for patients with SCT and 0.827 (95% CI: 0.689, 0.993) for patients without SCT, favouring midostaurin.

Figure 3 Kaplan Meier curve for overall survival by SCT status in AML



In a subgroup analysis, no apparent OS benefit was observed in females, however, a treatment benefit was observed in females in all secondary efficacy endpoints (see Table 10).

Table 10 Overview of OS, EFS, CR, DFS and CIR by gender in AML

Endpoint	Overall 95% CI	Males 95% CI	Females 95% CI
OS (HR)	0.774 (0.629, 0.953)	0.533 (0.392, 0.725)	1.007 (0.757, 1.338)
EFS (CR induction) (HR)	0.728 (0.613, 0.866)	0.660 (0.506, 0.861)	0.825 (0.656, 1.037)
CR induction (OR)	0.743* (0.550, 1.005)	0.675* (0.425, 1.072)	0.824* (0.552, 1.230)
DFS (CR induction) (HR)	0.663 (0.516, 0.853)	0.594 (0.408, 0.865)	0.778 (0.554, 1.093)
CIR (CR induction) (HR)	0.676 (0.515, 0.888)	0.662 (0.436, 1.006)	0.742 (0.516, 1.069)
*Odds ratio calculated as (No complete remission in treatment/Complete remission in treatment) / (No complete remission in placebo/complete remission in placebo) HR= Hazard ratio; OR=odds ratio			

Efficacy and safety in patients 60-70 years old were evaluated in a phase II, single- arm, investigator- initiated study of midostaurin in combination with intensive induction, consolidation including allogenic SCT and single-agent maintenance in patients with FLT3-ITD mutated AML. Based on an interim analysis, the EFS rate at 2 years (primary endpoint) was 27.1% (95% CI: 16.6, 44.1) and the median OS was 15.5 months in patients older than 60 years of age (46 out of 145 patients).

Pediatric patients with AML

The safety and efficacy of RYDAPT in pediatric patients (0 to less than 18 years) have not been established.

In a phase 2 study, midostaurin was investigated in combination with chemotherapy in newly diagnosed pediatric patients with FLT3-mutated AML. Among the three FLT3-mutated AML patients enrolled in the study, two patients (10 and 14 years old) experienced Dose Limiting Toxicities (DLTs) following the second induction cycle with midostaurin (at 30 mg/m^2 twice daily) in combination with chemotherapy (containing cytarabine 2 g/m^2/day, day 1 to 5; fludarabine 30 mg/m^2/day, day 1 to 5 and idarubicin 12 mg/m^2/day, day 2, 4 and 6). Both patients showed markedly delayed hematological recoveries (i.e. prolonged grade 4 thrombocytopenia lasting for 44 days in the first patient and 51 days in the second patient and grade 4 neutropenia lasting for 46 days in the second patient). In the first induction cycle both patients received midostaurin in combination with cytarabine, etoposide and idarubicin.

ASM, SM-AHN and MCL

The efficacy of RYDAPT in patients with ASM, SM-AHN and MCL, collectively referred to as Advanced SM, was evaluated in two open-label, single-arm, multicenter studies (142 patients in total).

The pivotal study was a multicenter, single-arm phase II study in 116 patients with ASM, SM-AHN and MCL (Study CPKC412D2201). RYDAPT was administered orally at 100 mg twice daily until disease progression or intolerable toxicity. Of the 116 patients enrolled, 89 were considered eligible for response assessment and constituted the primary efficacy population (PEP). Of these, 73 patients had ASM (57 with an AHNMD), and 16 patients had MCL (6 with

an AHNMD). The median age in the PEP was 64 years with approximately half of the patients to ≥ 65 years). Approximately one-third (36%) received prior anti-neoplastic therapy for ASM, SM-AHN and MCL. At baseline in the PEP, 65% of the patients had >1 measurable C-finding. The KIT D816V mutation was detected in 82% of patients.

The primary endpoint was overall response rate (ORR). Response rates were assessed based on the modified Valent and Cheson criteria and responses were adjudicated by a study steering committee. Secondary endpoints included duration of response, time to response, and overall survival. Responses to RYDAPT are shown in Table 11. Activity was observed regardless of KIT D816V status, number of prior therapies, and presence or absence of an AHNMD. Confirmed responses were observed in both KIT D816V mutation positive patients (ORR=63%) and KIT D816V wild type or unknown patients (ORR=43.8%). However, the median survival for KIT D816V positive patients was longer, i.e. 33.9 months (95% CI: 20.7, 42), than for KIT D816V wild type or unknown patients, i.e. 10 months (95% CI: 6.9, 17.4). Forty-six percent of patients had a decrease in bone marrow infiltration exceeded 50% and 58% had a decrease in serum tryptase levels exceeded 50%. Spleen volume decreased by ≥10% in 68.9% of patients with at least 1 post-baseline assessment (26.7% of patients had a reduction of ≥35%, which correlates with a 50% decrease by palpation).

The median time to response was 0.3 months (range: 0.1 to 3.7 months). The median duration of follow-up was 43 months.

Table 11 Efficacy of RYDAPT in ASM, SM-AHN and MCL: Primary efficacy population

	All N=89	ASM N=16	SM-AHN N=57	MCL N=16
Primary endpoint				
Overall response, n (%)	53 (59.6)	12 (75.0)	33 (57.9)	8 (50.0)
(95% CI)	(48.6, 69.8)	(47.6, 92.7)	(44.1, 70.9)	(24.7, 75.3)
Major response, n (%)	40 (44.9)	10 (62.5)	23 (40.4)	7 (43.8)
Partial response, n (%)	13 (14.6)	2 (12.5)	10 (17.5)	1 (6.3)
Stable disease, n (%)	11 (12.4)	1 (6.3)	7 (12.3)	3 (18.8)
Progressive disease, n (%)	10 (11.2)	1 (6.3)	6 (10.5)	3 (18.8)
Secondary endpoints				
Median duration of response, months (95% CI)	18.6 (9.9, 34.7)	36.8 (5.5, NE)	10.7 (7.4, 22.8)	NR (3.6, NE)
Median overall survival, months (95% CI)	26.8 (17.6, 34.7)	51.1 (28.7, NE)	20.7 (16.3, 33.9)	9.4 (7.5, NE)
Kaplan-Meier estimates at 5 years (95% CI)	26.1 (14.6, 39.2)	34.8 (1.7, 76.2)	19.9 (8.6, 34.5)	33.7 (12.3, 56.8)

NE: Not Estimated, NR: Not Reached

Patients who received non-study anti-neoplastic therapy were considered as having progressed at the time of the new therapy.

Although the study was designed to be assessed with the modified Valent and Cheson criteria, as a *post-hoc* exploratory analysis, efficacy was also assessed per the 2013 International Working Group - Myeloproliferative Neoplasms Research and Treatment - European Competence Network on Mastocytosis (IWG-MRT-ECNM) consensus criteria. Response to Rydapt was determined using a computational algorithm applied without any adjudication. Out

of 116 patients, 113 had a C-finding as defined by IWG response criteria (excluding ascites as a C-finding). All responses were considered and required a 12-week confirmation (see Table 12).

Table 12 Efficacy of midostaurin in ASM, SM-AHN and MCL per IWG-MRT-ECNM consensus criteria using an algorithmic approach

	All patients evaluated	ASM	SM-AHN	MCL	Subtype unknown
	N=113	N=15	N=72	N=21	N=5
Overall response rate, n (%)	32 (28.3)	9 (60.0)	15 (20.8)	7 (33.3)	1 (20.0)
(95% CI)	(20.2, 37.6)	(32.3, 83.7)	(12.2, 32.0)	(14.6, 57.0)	(0.5, 71.6)
Best overall response, n (%)					
Complete remission	1 (0.9)	0	0	1 (4.8)	0
Partial remission	17 (15.0)	5 (33.3)	8 (11.1)	3 (14.3)	1 (20.0)
Clinical improvement	14 (12.4)	4 (26.7)	7 (9.7)	3 (14.3)	0
Duration of response*					
n/N (%)	11/32 (34.4)	4/9 (44.4)	4/15 (26.7)	3/7 (42.9)	0/1 (0.0)
median (95% CI)	NE (27.0, NE)	36.8 (10.3, 36.8)	NE (17.3, NE)	NE (4.1, NE)	NE
Overall survival					
n/N (%)	65/113 (57.5)	4/15 (26.7)	49/72 (68.1)	12/21 (57.1)	0/5 (0.0)
median (95% CI)	29.9 (20.3, 42.0)	51.1 (34.7, NE)	22.1 (16.8, 32.2)	22.6 (8.3, NE)	NE

*Confirmation period for responses: 12 weeks

Analysis excludes ascites as a C-finding.

Patients who received non-study anti-neoplastic therapy were considered as having progressed at the time of the new therapy.

The supportive study was a single arm, multicenter, open-label phase II study of 26 patients with ASM, SM-AHN and MCL (CPKC412A2213). RYDAPT was administered orally at 100 mg twice daily. Lack of a major response (MR) or partial response (PR) by the end of the second cycle resulted in discontinuation from the study treatment. Twenty (76.9%) patients had ASM (17 [85%] with AHNMD) and 6 patients (23.1%) had MCL (2 [33.3%] with AHNMD). The median age was 64.5 years with half of the patients ≥ 65 years. At baseline, 88.5% had > 1 C-finding and 69.2% had received at least one prior anti-neoplastic regimen.

The primary endpoint was ORR evaluated by the Valent criteria during the first two cycles of treatment. Nineteen patients (73.1%; 95% CI = [52.2, 88.4]) achieved a response during the first two cycles of treatment (13 MR; 6 PR). The median duration of follow-up was 73 months, and the median duration of response has not been reached. Median overall survival was 40.0 months (patients were only followed for up one year after treatment discontinuation for survival).

NON-CLINICAL SAFETY DATA

Midostaurin has been evaluated in safety pharmacology, single/repeated dose toxicity, genotoxicity, reproductive and developmental toxicity studies.

Safety pharmacology and single/repeat dose toxicity

Safety pharmacology studies indicate that midostaurin is unlikely to interfere with vital functions of the central nervous systems. *In vitro*, midostaurin did not inhibit hERG channel activity up to the limit of solubility of 12 microM. The two major human metabolites CGP52421 and CGP6221 (also tested up to the limit of solubility) inhibited hERG current by 38.5% at 1.5 microM and 11.3% at 1.21 microM respectively. Midostaurin and the two metabolites are highly protein bound and the free concentrations at therapeutic doses are far below the concentrations associated with no/minimal hERG inhibition *in vitro*. The risk of hERG related-QT prolongation appears to be low. In the repeat dose studies in dogs, a decrease in heart rate and a prolongation of the P-Q interval was seen in individual animals at 10 and 30 mg/kg; there were no morphological changes in the heart.

In the repeat dose studies, the key target organs identified were the gastrointestinal tract (emesis in dogs and monkeys, diarrhea and mucosal alteration), testes (decreased spermatogenesis), bone marrow (hypocellularity) and lymphoid organs (depletion/atrophy). The effect on the bone marrow and lymphoid organs was accompanied by hematological changes of decreased white blood cells, lymphocytes and erythrocytic parameters. An increase in liver enzymes (ALT and AST) was seen consistently in rats, and in dogs and monkeys in long term studies of $\geq$3 months duration. There were no corresponding pathological changes in the liver. Inhibition of spermatogenesis was seen in dogs at doses $\geq$ 3 mg/kg. The no-adverse-effect level after 12 months of treatment was 1 mg/kg in dogs and 3 mg/kg in rats.

Reproductive toxicity

See section PREGNANCY, LACTATION, FEMALES AND MALES OF REPRODUCTIVE POTENTIAL.

Genotoxicity

In vitro and *in vivo* genotoxicity studies covering relevant genotoxicity endpoints showed no evidence of mutagenic or clastogenic activity. No carcinogenicity studies have been performed.

INCOMPATIBILITIES

Not applicable.

STORAGE

See folding box.

RYDAPT should not be used after the date marked “EXP” on the pack.

RYDAPT must be kept out of the reach and sight of children.

INSTRUCTIONS FOR USE AND HANDLING

N/A

SPECIAL PRECAUTIONS FOR DISPOSAL

N/A

Manufacturer:

See folding box.

Presentation:

Alu-Alu blister.

Multipack containing 112 hard capsules (4 packs of 28’s)

Multipack containing 56 hard capsules (2 packs of 28’s)

Not all presentations may be available locally

Country Specific Package Leaflet:

Information issued: Mar 2021.SIN

® = registered trademark

Product Owner:

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Lichtstrasse 35
4056 Basel, Switzerland