## Sponsor

Novartis Pharmaceuticals

## Generic Drug Name

Rydapt / midostaurin

## Trial Indication(s)

Acute myeloid leukemia (AML)

## Protocol Number

CPKC412AFI02

## Protocol Title

Healthcare resource utilization in adults diagnosed with acute myeloid leukemia (AML) with a focus on patients treated with Rydapt (midostaurin) in Helsinki and Uusimaa hospital district

## Clinical Trial Phase

NA

## Phase of Drug Development

NA

## Study Start/End Dates

Study start date: 24/09/2020

Study Completion date: 26/01/2021

## Reason for Termination

NA

## Study Design/Methodology

This was a non-interventional, retrospective registry study, utilizing electronic health record (EHR) data collected in the hospital district of Helsinki and Uusimaa (HUS). Real-world health care resource utilization (HCRU) of AML patients was characterized.

Adult patients (18 years or older) with the inclusion diagnosis, AML (ICD-10 C92.0), between 1.1.2013 – 30.6.2020 were followed from the index date (first ever record of the inclusion diagnosis) until the end of follow-up (30.6.2020), or death. This study did not involve any contacts to patients.

The study inclusion period was changed from 1.1.2013 – 30.6.2020 specified in the protocol to 1.1.2016 – 30.6.2020 due to lack of medication data from pre-2016.

## Centers

Novartis Investigative Site

## Objectives:

### Primary objective(s)

- Describe patients receiving midostaurin at the time of treatment initiation (number of patients, age, sex, AML duration at Midostaurin initiation, comorbidities)

### Secondary objective(s)

The secondary objectives (for patients with midostaurin treatment) were to:

- Describe the treatment duration in induction and consolidation phases of midostaurin treatment
- Describe the number of treatment cycles in induction and consolidation phases of midostaurin treatment
- Describe the dosing of midostaurin in induction and consolidation phases of midostaurin treatment

The secondary objectives (assessing all patients with AML regardless of midostaurin treatment) were to:

- Describe patients at the time of diagnosis (number of patients, age, sex, comorbidities)
- Estimate HCRU and related costs in different disease stages
- Illustrate the cumulative mean cost as a function of time

## Test Product (s), Dose(s), and Mode(s) of Administration

NA

## Statistical Methods

Data was summarized by appropriate summary statistics and/or tabulation. No statistical testing was performed. Confidence intervals for HCRU aggregates were estimated using bootstrapping. Cost accumulation as function of time was assessed by mean cumulative function (mcf). Time to relapse was analyzed in Kaplan-Meier fit.

## Study Population: Key Inclusion/Exclusion Criteria

**Inclusion criteria**

- Patients who are diagnosed with acute myeloid leukemia (ICD-10 C92.0) during 1.1.2016-30.6.2020
- Adult (18 years or older) at the time of first diagnosis
- Health registry data is available and accessible
- Resident in the hospital district HUS at the time of index diagnosis

**Exclusion criteria**

- AML patients with no treatment information

## Participant Flow

The initial data release contained 1404 adult patients with AML diagnosis recorded ever in HUS datalake system. After removing patients outside of HUS region in order to capture the full patient journey which is currently available only for patients within the region, 816 patients were included in the data. Data with good coverage was available only from 1.1.2014 onwards, and therefore the inclusion of patients was restricted to 1.1.2014-30.6.2020, resulting in 352 AML patients.

After applying the final inclusion/exclusion criteria (treated, adult) and limiting the inclusion period to 1.1.2016-30.6.2020 due to limitations in medication data availability, the final cohort size was 81 patients, among which 10 patients received midostaurin during the study period.

## Baseline Characteristics

Characteristics of patients with AML at the time of diagnosis

| Variable | Level | Overall |
|---|---|---|
| N | | 81 |
| Age (mean (SD)) | | 52.68 (14.82) |
| Sex (%) | female | 47 (58.0) |
| | male | 34 (42.0) |
| Follow-up time (median [IQR]) | days | 708 [215, 1135] |

## Primary Outcome Result(s)

The study identified total of 10 AML patients who fulfilled the inclusion criteria and were treated with midostaurin. Patients were described at the time of first midostaurin administration. Patients were on average 45 years old, half being males. They had on median 1.05 years of follow-up available. Mean duration of AML at midostaurin treatment initiation was 47 days. None of the comorbidities in these patients were precent in more than five patients. All recorded diagnosis codes are shown without any a priori restriction of diagnoses, with exact number of patients masked in comorbidities present in <5 patients.

| Variable | Level | Overall |
|---|---|---|
| N | | 10 |
| Age at treatment initiation (mean (SD)) | | 45.27 (17.98) |
| Sex (%) | female | 5 (50.0) |
| | male | 5 (50.0) |
| Follow-up time (median [IQR]) | years | 1.05 [0.46, 1.64] |
| Duration of AML at treatment (mean (SD)) | days | 47 (58) |

## Secondary Outcome Result(s)

**Duration, number of cycles and dosing of midostaurin in different AML phases:**
During the study period, 10 patients received midostaurin for total of 1987 days. These treatments consisted of 35 separate treatment continuums divided into different treatment phases as follows:

*Midostaurin at induction phase:*
Total of seven (out of total ten patients) received midostaurin at induction phase, and there were total of ten different distinct midostaurin continuums recorded. The dosing was 2x50mg daily in all induction related administrations.

The inductions consisted of total 222 days, (22.2 days per administration). One induction related administration continuum was immediately continued to post induction in one of the patients who did not receive consolidation treatment, thus slightly extending the estimated average duration. The average length per patient was 31.7 days per patient.

*Midostaurin at consolidation phase:*
Five patients out of ten received midostaurin at consolidation phase. However, several patients did not receive consolidation treatments per se, but were selected some other (for example hypomethylating) treatment option after induction (see Figure 1). Of additional note, per oral treatment options are not captured in the data.

With consolidation, there were total of 10 separate treatment continuums of midostaurin. Two of these were administered at 2x25mg daily, other eight as 2x50mg daily. These treatments consisted total of 167 days (mean 16.7 days per treatment, 33.4 days per patient). The time-weighted average dose was 43.7 mg twice daily, i.e. higher dose was used more frequently.

**Number of patients at the time of diagnosis (All treated AML patients)**

Characteristics of patients with AML at the time of diagnosis

| Variable | Level | Overall |
|---|---|---|
| N | | 81 |
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| Sex (%) | female | 47 (58.0) |
| | male | 34 (42.0) |
| Follow-up time (median [IQR]) | days | 708 [215, 1135] |

**Main diagnoses and comorbidities of AML patients**

| Diagnosis | Description | N | Percent |
|---|---|---|---|
| N | | 81 | |
| C92 | Myeloid leukaemia | 68 | 84 |
| C95 | Leukaemia of unspecified cell type | 22 | 27.2 |
| D64 | Other anaemias | 20 | 24.7 |
| D70 | Agranulocytosis | 10 | 12.3 |
| D75 | Other diseases of blood and blood-forming organs | 9 | 11.1 |
| D72 | Other disorders of white blood cells | 7 | 8.6 |
| D46 | Myelodysplastic syndromes | 6 | 7.4 |
| D69 | Purpura and other haemorrhagic conditions | 6 | 7.4 |
| R50 | Fever of other and unknown origin | 6 | 7.4 |
| A41 | Other septicaemia | 5 | 6.2 |
| H90 | Conductive and sensorineural hearing loss | 5 | 6.2 |
| I10 | Essential (primary) hypertension | 5 | 6.2 |
| J18 | Pneumonia, organism unspecified | 5 | 6.2 |
| K40 | Inguinal hernia | 5 | 6.2 |
| R10 | Abdominal and pelvic pain | 5 | 6.2 |

**Estimate HCRU and related costs in different disease stages**
The HCRU and associated costs were derived separately for outpatient visits, inpatient stays, procedures, and laboratory measures. The HCRU does not include surgical operations or imaging (data not available in hematological data lake), or costs of medication (precise administration and doses unavailable in structured format).

HCRU was estimated as overall and in different AML disease stages: pre-induction, induction, remission, relapse, and post-stem cell transplantation (allo-SCT). The total sum of corresponding HCRU elements was computed, and the estimates were scaled to “per patient year” -estimates, by dividing the grand total by the contributing patient years and to “per patient” -estimates, by dividing the grand total by the number of patients. The 95% CI for point estimates were evaluated by bootstrapping the HCRU over patients.

The HCRU costs overall and by different disease stages are presented in the following table. Average per patient cost of AML treatment in Helsinki and Uusimaa hospital district was 170,808€, and each month (28d) one AML patient utilized healthcare resources approximately for 6,860€. Although induction stage, as well as pre-induction stage (the time between diagnosis and induction treatment initiation) are relatively short disease stages among AML patients, they generate substantial costs, and the rate of cost generation (per 28 days) was highest in these two disease stages.

Overall, patients spent total of 106,8 days at inpatient ward (95% CI 96,2 to 117,8 days). There were total of 632 unique inpatient stays observed, totaling to 8653 inpatient days, and the mean length of inpatient stay was 13.7 days. During the active induction phase, the mean length was 21.3 days.

**Overall HCRU costs by different AML disease stages**

| | | | Per patient costs (€) | | | Per 28d costs (€) | | |
|---|---|---|---|---|---|---|---|---|
| **Cost type** | **Disease stage** | **Grand total €** | **Average** | **Lower 95% CI** | **Upper 95% CI** | **Average** | **Lower 95% CI** | **Upper 95% CI** |
| Overall costs | TOTAL | 13835409 | 170808 | 153259 | 188811 | 6860 | 5671 | 8364 |
| Overall costs | pre induction | 1018856 | 12578 | 10245 | 15643 | 26939 | 10774 | 81037 |
| Overall costs | induction | 2424312 | 29930 | 27570 | 32635 | 30223 | 25505 | 35058 |
| Overall costs | remission | 4716083 | 58223 | 49200 | 67759 | 5833 | 4285 | 8302 |
| Overall costs | relapse | 1362452 | 16820 | 11048 | 23152 | 7848 | 3916 | 17487 |
| Overall costs | allo-SCT | 4313707 | 53256 | 39884 | 67991 | 4707 | 3169 | 7061 |
| Outpatient | TOTAL | 1477035 | 18235 | 15467 | 21024 | 732 | 584 | 922 |
| Outpatient | pre induction | 37443 | 462 | 236 | 845 | 990 | 305 | 3842 |
| Outpatient | induction | 50430 | 623 | 471 | 847 | 629 | 452 | 882 |
| Outpatient | remission | 669025 | 8260 | 6577 | 10069 | 827 | 568 | 1236 |
| Outpatient | relapse | 122250 | 1509 | 845 | 2350 | 704 | 317 | 1619 |
| Outpatient | allo-SCT | 597887 | 7381 | 5392 | 9496 | 652 | 427 | 995 |
| Inpatient | TOTAL | 8170662 | 100872 | 90903 | 111070 | 4051 | 3370 | 4925 |
| Inpatient | pre induction | 387671 | 4786 | 3476 | 6660 | 10250 | 3936 | 32443 |
| Inpatient | induction | 2014587 | 24871 | 22913 | 27026 | 25115 | 21202 | 29084 |
| Inpatient | remission | 3114343 | 38449 | 32124 | 45298 | 3852 | 2836 | 5430 |
| Inpatient | relapse | 1024639 | 12650 | 8346 | 17404 | 5902 | 2933 | 13136 |
| Inpatient | allo-SCT | 1629422 | 20116 | 13852 | 27323 | 1778 | 1130 | 2720 |
| Procedure | TOTAL | 1652797 | 20405 | 16095 | 24969 | 820 | 617 | 1073 |
| Procedure | pre induction | 19103 | 236 | 156 | 357 | 505 | 183 | 1711 |
| Procedure | induction | 49527 | 611 | 511 | 719 | 617 | 485 | 763 |
| Procedure | remission | 156289 | 1929 | 1566 | 2317 | 193 | 137 | 284 |
| Procedure | relapse | 41689 | 515 | 242 | 870 | 240 | 94 | 573 |
| Procedure | allo-SCT | 1386189 | 17113 | 12847 | 21640 | 1512 | 1011 | 2289 |
| Laboratory | TOTAL | 2534915 | 31295 | 28113 | 34479 | 1257 | 1039 | 1542 |
| Laboratory | pre induction | 574639 | 7094 | 6060 | 8176 | 15193 | 6183 | 45117 |

| | | | Per patient costs (€) | | | Per 28d costs (€) | | |
|---|---|---|---|---|---|---|---|---|
| **Cost type** | **Disease stage** | **Grand total €** | **Cost type** | **Disease stage** | **Grand total €** | **Cost type** | **Disease stage** | **Grand total €** |
| Laboratory | induction | 309768 | 3824 | 3185 | 4500 | 3862 | 3071 | 4753 |
| Laboratory | remission | 776426 | 9586 | 7906 | 11350 | 960 | 689 | 1388 |
| Laboratory | relapse | 173874 | 2147 | 1297 | 3097 | 1002 | 474 | 2277 |
| Laboratory | allo-SCT | 700209 | 8645 | 6394 | 11108 | 764 | 512 | 1144 |

**HCRU overall and by different AML disease stages**

| | | | Resource use per patient | | | Resource use per 28d | | |
|---|---|---|---|---|---|---|---|---|
| **HCRU type** | **disease stage** | **Grand total (n)** | **Average** | **Lower 95% CI** | **Upper 95% CI** | **Average** | **Lower 95% CI** | **Upper 95% CI** |
| Outpatient visits | TOTAL | 11970 | 147,78 | 125,60 | 170,57 | 5,94 | 4,72 | 7,48 |
| Outpatient visits | pre induction | 280 | 3,46 | 1,75 | 6,33 | 7,40 | 2,28 | 28,54 |
| Outpatient visits | induction | 660 | 8,15 | 6,69 | 9,98 | 8,23 | 6,34 | 10,54 |
| Outpatient visits | remission | 5248 | 64,79 | 52,04 | 78,33 | 6,49 | 4,48 | 9,64 |
| Outpatient visits | relapse | 1119 | 13,81 | 6,98 | 23,52 | 6,45 | 2,66 | 15,49 |
| Outpatient visits | allo-SCT | 4663 | 57,57 | 42,06 | 74,14 | 5,09 | 3,32 | 7,75 |
| Inpatient visits | TOTAL | 632 | 7,80 | 6,91 | 8,70 | 0,31 | 0,26 | 0,39 |
| Inpatient visits | pre induction | 114 | 1,41 | 1,21 | 1,67 | 3,01 | 1,24 | 8,93 |
| Inpatient visits | induction | 98 | 1,21 | 1,04 | 1,46 | 1,22 | 0,98 | 1,53 |
| Inpatient visits | remission | 368 | 4,54 | 3,83 | 5,30 | 0,46 | 0,33 | 0,65 |
| Inpatient visits | relapse | 107 | 1,32 | 0,84 | 1,93 | 0,62 | 0,30 | 1,37 |
| Inpatient visits | allo-SCT | 123 | 1,52 | 1,01 | 2,11 | 0,13 | 0,08 | 0,21 |
| Inpatient days | TOTAL | 8653 | 106,83 | 96,16 | 117,82 | 4,29 | 3,56 | 5,24 |
| Inpatient days | pre induction | 424 | 5,23 | 3,80 | 7,23 | 11,21 | 4,30 | 35,39 |
| Inpatient days | induction | 2088 | 25,78 | 23,77 | 28,00 | 26,03 | 21,99 | 30,13 |
| Inpatient days | remission | 3276 | 40,44 | 33,75 | 47,67 | 4,05 | 2,98 | 5,73 |
| Inpatient days | relapse | 1150 | 14,20 | 9,09 | 20,01 | 6,62 | 3,23 | 14,89 |
| Inpatient days | allo-SCT | 1715 | 21,17 | 14,49 | 28,83 | 1,87 | 1,18 | 2,87 |

| | | | Resource use per patient | | | Resource use per 28d | | |
|---|---|---|---|---|---|---|---|---|
| **HCRU type** | **disease stage** | **Grand total (n)** | **Average** | **Lower 95% CI** | **Upper 95% CI** | **Average** | **Lower 95% CI** | **Upper 95% CI** |
| Procedures | TOTAL | 5027 | 62,06 | 52,32 | 72,43 | 2,49 | 1,98 | 3,16 |
| Procedures | pre induction | 162 | 2,00 | 1,28 | 3,07 | 4,28 | 1,55 | 14,54 |
| Procedures | induction | 546 | 6,74 | 5,89 | 7,61 | 6,81 | 5,52 | 8,18 |
| Procedures | remission | 1955 | 24,14 | 19,56 | 29,14 | 2,42 | 1,68 | 3,59 |
| Procedures | relapse | 480 | 5,93 | 2,99 | 9,94 | 2,76 | 1,13 | 6,58 |
| Procedures | allo-SCT | 1884 | 23,26 | 15,99 | 31,62 | 2,06 | 1,29 | 3,20 |
| Laboratory values | TOTAL | 267168 | 3298,37 | 2926,88 | 3668,90 | 132,47 | 108,40 | 163,63 |
| Laboratory values | pre induction | 16733 | 206,58 | 156,93 | 281,51 | 442,42 | 169,54 | 1388,35 |
| Laboratory values | induction | 32279 | 398,51 | 339,95 | 465,80 | 402,41 | 320,76 | 498,07 |
| Laboratory values | remission | 94979 | 1172,58 | 982,11 | 1374,25 | 117,47 | 84,81 | 169,77 |
| Laboratory values | relapse | 31814 | 392,77 | 227,10 | 591,27 | 183,25 | 84,49 | 423,91 |
| Laboratory values | allo-SCT | 91363 | 1127,94 | 838,50 | 1436,44 | 99,68 | 66,81 | 150,47 |

## Safety Results
Not applicable.

## Other Relevant Findings
NA

## Conclusion
The number of AML patients treated with midostaurin in Helsinki and Uusimaa hospital district is low. Midostaurin administration showed significant variation between the patients receiving midostaurin, and the data demonstrated midostaurin usage in treatment phases that are not listed in the SPC. The treatment of AML patients including the ones receiving midostaurin is unified in Finland. Early phases of the treatment, mainly induction phase, have high budget impact. However, after the initial phases, the cost rate gradually decreases. with caution, especially in light of the small number of patients in the RUX group, and differences in baseline patient characteristics between RUX and BAT

## Date of Clinical Study Report
26 January, 2021