# Supplemental material

# Long-Term Efficacy and Safety of Molidustat for Anemia in Chronic Kidney Disease: DIALOGUE Extension Studies

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**Supplemental table 1.** Key inclusion and exclusion criteria for the extension studies

|  |  |
| --- | --- |
| Inclusion criteria | Exclusion criteria |
| * Written informed consent
* Ability tounderstand and follow study-related instructions
* Males; females without childbearing ability
 | * A scheduled kidney transplant or other organ transplant within the next 6 months
* Treatment with immunosuppressive or myelosuppressive therapy, chemotherapeutic agents, systemic steroids (except inhaled steroids), antiretroviral drugs, tyrosine kinase inhibitors or tranilast, acetaminophen paracetamol (single oral doses allowed), probenecid, or phenobarbital, within 7 days prior to baseline
* Severe hepatic insufficiency (defined as ALT, AST >3 times the upper limit of normal, total bilirubin >2 mg/dL, or Child–Pugh B or C) or active hepatitis
* New York Heart Association class III or IV congestive heart failure
* Sustained, poorly controlled arterial hypertension or hypotension at baseline (defined as mean BP≥180/110 mmHg or systolic BP<95 mmHg, respectively)
* Severe rhythm or conduction disorder (e.g., heart rate <50 bpm or >110 bpm, atrial flutter, prolonged QT >500 ms, third-degree atrioventricular block if not treated with a pacemaker)
* Ongoing serious adverse event from the parent study that was determined to be related to the study drug
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ALT,alanine aminotransferase; AST, aspartate aminotransferase; BP, blood pressure; bpm, beats per minute.

**Supplemental table 2**. Additional inclusion criteria specific to each study

|  |  |
| --- | --- |
| DIALOGUE 3: additional inclusion criteria | DIALOGUE 5: additional inclusion criteria |
| * A diagnosis of anemia associated with CKD not on hemodialysis at study entry
* Mean Hb level of 10.0–12.0 g/dL during the evaluation period of the parent study for patients who completed 16 weeks of treatment with molidustat in DIALOGUE 1 or completed 16 weeks of treatment with molidustat or darbepoetin in DIALOGUE 2 without dose suspension lasting >6 consecutive weeks
* Mean Hb level of 10.0–12.0 g/dL for at least two consecutive visits after the Hb-stabilization phase visit 2 (≥4 weeks), and did not have a dose suspension lasting >6 consecutive weeks in the Hb-stabilization phase
 | * A diagnosis of anemia associated with CKD on hemodialysis
* Participation and completion of treatment in DIALOGUE 4 without a dose suspension lasting >6 consecutive weeks; patients must have completed the end of treatment visit (day 113) in the parent study
* Mean Hb level of 9.0–11.5 g/dL, inclusive, during the evaluation period (i.e., the last 4 weeks of the parent study) when the patient completed 16 weeks of treatment with molidustat or epoetin in DIALOGUE 4
 |

CKD, chronic kidney disease; Hb, hemoglobin.

**Supplemental table 3.** Study drug administration

|  |  |  |
| --- | --- | --- |
| DIALOGUE 3 | Molidustat*n* = 118 | Darbepoetin*n* = 42 |
| Treatment duration, daysa |
| *n* | 118 | 42 |
| Mean (SD) | 375.0 (210.0) | 430.5 (211.2) |
| Min, max | 6, 760 | 29, 840 |
| Daily average dose (unitsb)c |
| *n* | 118 | 42 |
| Mean (SD) | 40.2 (30.3) | 2.4 (2.0) |
| Min, max | 8, 150 | 0, 11 |
| Treatment compliance (%) |
| *n* | 116 | – |
| Mean (SD) | 97.2 (6.8) | – |
| Patients without up-titration, *n* (%) | 50 (42) | 18 (43) |
| Patients with up-titration, *n* (%) | 68 (58) | 24 (57) |
| Patients without down-titration, *n* (%) | 40 (34) | 20 (48) |
| Patients with down-titration, *n* (%) | 78 (66) | 22 (52) |
| Patients without dose suspended, *n* (%) | 70 (59) | 39 (93) |
| Patients with dose suspended, *n* (%) | 48 (41) | 3 (7) |
| Patients without any up/down-titration, *n* (%) | 25 (21) | 12 (29) |
| DIALOGUE 5 | Molidustat*n* = 57 | Epoetin*n* = 30 |
| Treatment duration, daysa |  |  |
| *n* | 57 | 30 |
| Mean (SD) | 358.7 (224.8) | 473.0 (226.1) |
| Min, max | 3, 728 | 57, 783 |
| Daily average dose (unitsb)c |  |  |
| *n* | 57 | 30 |
| Mean (SD) | 69.7 (47.8) | 1087.4 (764.3) |
| Min, max | 12, 200 | 71, 3053 |
| Treatment compliance (%) |  |  |
| *n* | 54 | – |
| Mean (SD) | 90.7 (16.4) | – |
| Patients without up-titration, *n* (%) | 13 (23) | 7 (23) |
| Patients with up-titration, *n* (%) | 44 (77) | 23 (77) |
| Patients without down-titration, *n* (%) | 19 (33) | 6 (20) |
| Patients with down-titration, *n* (%) | 38 (67) | 24 (80) |
| Patients without dose suspended, *n* (%) | 42 (74) | 15 (50) |
| Patients with dose suspended, *n* (%) | 15 (26) | 15 (50) |
| Patients without any up/down-titration, *n* (%) | 9 (16) | 3 (10) |

aTreatment duration (days) = date of last non-zero dose – date of first dose in the extension study +1.
bUnit is mg for molidustat, µg for darbepoetin and IU for epoetin.

cDaily average dose = total cumulative dose/treatment duration.

**Supplemental table 4.** Patient disposition in DIALOGUE 3

|  |  |  |  |
| --- | --- | --- | --- |
| Analysis set | Molidustat | Darbepoetin | Total |
|  | DIALOGUE 1 | DIALOGUE 2 | Overall | DIALOGUE 1 | DIALOGUE 2 | Overall | DIALOGUE 1 | DIALOGUE 2 | Overall |
| Number of patients, *n* (%) |  |  |  |  |  |  |
| All enrolled patients | – | – | – | – | – | – | 87 | 77 | 164 |
| Entered Hb-stabilization or main phase  | 69 | 52 | 121 | 18 | 25 | 43 | 87 | 77 | 164 |
| Entered Hb-stabilization phasea | 46 (67) | 3 (6) | 49 (41) | 17 (94) | 1 (4) | 18 (42) | 63 (72) | 4 (5) | 67 (41) |
| Entered main phase directlya | 23 (33) | 49 (94) | 72 (60) | 1 (6) | 24 (96) | 25 (58) | 24 (28) | 73 (95) | 97 (59) |
| Entered main phase from Hb-stabilization phaseb | 29 (63) | 2 (67) | 31 (63) | 15 (88) | 1 (100) | 16 (89) | 44 (70) | 3 (75) | 47 (70) |
| Enrolled in Hb-stabilization phase | 46 (67) | 3 (6) | 49 (41) | 17 (94) | 1 (4) | 18 (42) | 63 (72) | 4 (5) | 67 (41) |
| Nontreatedb | 3 (7) | 0 | 3 (6) | 1 (6) | 0 | 1 (6) | 4 (6) | 0 | 4 (6) |
| Treatedb | 43 (94) | 3 (100.0) | 46 (94) | 16 (94) | 1 (100) | 17 (94) | 59 (94) | 4 (100) | 63 (94) |
| Rolled over to main phaseb | 29 (63) | 2 (67) | 31 (63) | 15 (88) | 1 (100) | 16 (89) | 44 (70) | 3 (75) | 47 (70) |
| Discontinued Hb-stabilization phaseb | 17 (37) | 1 (33) | 18 (37) | 2 (12) | 0 | 2 (11) | 19 (30) | 1 (25) | 20 (30) |
| Reasons for discontinuationc |  |  |  |  |  |  |  |  |  |
| Adverse event | 5 (29) | 1 (100) | 6 (33) | 0 | 0 | 0 | 5 (26) | 1 (100) | 6 (30) |
| Lack of efficacy | 2 (12) | 0 | 2 (11) | 0 | 0 | 0 | 2 (11) | 0 | 2 (10) |
| Physician decision | 2 (12) | 0 | 2 (11) | 0 | 0 | 0 | 2 (11) | 0 | 2 (10) |
| Protocol-driven decision | 4 (24) | 0 | 4 (22) | 1 (50) | 0 | 1 (50) | 5 (26) | 0 | 5 (25) |
| Protocol violation | 2 (12) | 0 | 2 (11) | 0 | 0 | 0 | 2 (11) | 0 | 2 (10) |
| Patient withdrawal | 1 (6) | 0 | 1 (6) | 1 (50) | 0 | 1 (50) | 2 (11) | 0 | 2 (10) |
| Other | 1 (6) | 0 | 1 (6) | 0 | 0 | 0 | 1 (5) | 0 | 1 (5) |
| Enrolled in main phase | 52 (75) | 51 (98) | 103 (85) | 16 (89) | 25 (100) | 41 (95) | 68 (78) | 76 (99) | 144 (88) |
| Nontreatedd | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Treatedd | 52 (100) | 51 (100) | 103 (100) | 16 (100) | 25 (100) | 41 (100) | 68 (100) | 76 (100) | 144 (100) |
| Discontinued main phased | 52 (100) | 51 (100) | 103 (100) | 16 (100) | 25 (100) | 41 (100) | 68 (100) | 76 (100) | 144 (100) |
| Reasons for discontinuationc |  |  |  |  |  |  |  |  |  |
| Adverse event | 9 (17) | 9 (18) | 18 (18) | 1 (6) | 2 (8) | 3 (7) | 10 (15) | 11 (15) | 21 (15) |
| Death | 1 (2) | 3 (6) | 4 (4) | 0 | 0 | 0 | 1 (2) | 3 (4) | 4 (3) |
| Logistical difficulties | 1 (2) | 0 | 1 (1) | 0 | 0 | 0 | 1 (2) | 0 | 1 (0.7) |
| Lost to follow-up | 1 (2) | 0 | 1 (1) | 0 | 0 | 0 | 1 (2) | 0 | 1 (0.7) |
| Physician decision | 1 (2) | 0 | 1 (1) | 0 | 0 | 0 | 1 (2) | 0 | 1 (0.7) |
| Protocol-driven decision | 7 (14) | 5 (10) | 12 (12) | 1 (6) | 6 (24) | 7 (17) | 8 (12) | 11 (15) | 19 (13) |
| Protocol violation | 0 | 1 (2) | 1 (1) | 1 (6) | 0 | 1 (2) | 1 (2) | 1 (1) | 2 (1) |
| Patient withdrawal | 1 (2) | 1 (2) | 2 (2.0) | 1 (6) | 4 (16) | 5 (12) | 2 (3) | 5 (7) | 7 (5) |
| Other | 31 (60) | 32 (63) | 63 (61) | 12 (75) | 13 (52) | 25 (61) | 43 (63) | 45 (59) | 88 (61) |
| Overall follow-up (all treated in either Hb-stabilization or main phase) | 66 (96) | 52 (100) | 118 (98) | 17 (94) | 25 (100) | 42 (98) | 83 (95) | 77 (100) | 160 (98) |
| Completed follow-upe | 54 (82) | 43 (83) | 97 (82) | 13 (77) | 18 (72) | 31 (74) | 67 (81) | 61 (79) | 128 (80) |
| Discontinued follow-upe | 9 (14) | 5 (10) | 14 (12) | 4 (24) | 6 (24) | 10 (24) | 13 (16) | 11 (14) | 24 (15) |
| Reasons for discontinuation |  |  |  |  |  |  |  |  |  |
| Adverse event | 3 (33) | 1 (20) | 4 (29) | 0 | 1 (17) | 1 (10) | 3 (23) | 2 (18) | 5 (21) |
| Death | 0 | 1 (20) | 1 (7) | 1 (25) | 0 | 1 (10) | 1 (8) | 1 (9) | 2 (8) |
| Logistical difficulties | 0 | 1 (20) | 1 (7) | 0 | 1 (17) | 1 (10) | 0 | 2 (18) | 2 (8) |
| Lost to follow-up | 2 (22) | 1 (20) | 3 (21) | 2 (50) | 1 (17) | 3 (30) | 4 (31) | 2 (18) | 6 (25) |
| No follow-up | 2 (22) | 0 | 2 (14) | 0 | 0 | 0 | 2 (15) | 0 | 2 (8) |
| Physician decision | 1 (11) | 0 | 1 (7) | 0 | 0 | 0 | 1 (8) | 0 | 1 (4) |
| Protocol-driven decision | 0 | 0 | 0 | 0 | 1 (17) | 1 (10) | 0 | 1 (9) | 1 (4) |
| Patient withdrawal | 1 (11) | 1 (20) | 2 (14) | 1 (25) | 2 (33) | 3 (30) | 2 (15) | 3 (27) | 5 (21) |

aThe percentage is based on the number of patients who entered the Hb-stabilization or main phase.

bThe percentage is based on the number of patients who entered the Hb-stabilization phase.

cThe percentage is based on the number of patients who discontinued.

dThe percentage is based on the number of patients who entered the main phase.

eThe percentage is based on the number of patients treated.

All enrolled patients: patients who signed the informed consent form.

DIALOGUE 1 and 2 are the parent studies of DIALOGUE 3.

Hb, hemoglobin.

**Supplemental Table 5.** Patient disposition in DIALOGUE 5

|  |  |  |  |
| --- | --- | --- | --- |
| Analysis set | Molidustat | Epoetin | Total |
| Number of patients, *n* (%) |  |  |  |
| All enrolled patients | – | – | 88 |
| Screen failuresa | – | – | 1 (1) |
| Nontreateda | 0 | 0 | 0 |
| Treateda | 57 | 30 | 87 (99) |
| Completed treatmentb | 0 | 0 | 0 |
| Discontinued treatmentb | 57 (100) | 30 (100) | 87 (100) |
| Reasons for discontinuationc |  |  |  |
| Adverse event | 13 (23) | 2 (7) | 15 (17) |
| Death | 5 (9) | 1 (3) | 6 (7) |
| Patient withdrawal | 5 (9) | 1 (3) | 6 (7) |
| Protocol violationc | 8 (14) | 0 | 8 (9) |
| Lost to follow-up | 1 (2) | 0 | 1 (1) |
| New sited | 1 (2) | 3 (10) | 4 (5) |
| Protocol-driven decision | 10 (18) | 7 (23) | 17 (20) |
| Other | 14 (25) | 16 (53) | 30 (35) |
| Completed follow-upb | 41 (72) | 22 (73) | 63 (72) |
| Discontinued follow-upb | 4 (7) | 6 (20) | 10 (12) |
| Reasons for discontinuationd of follow-up |  |  |  |
| Adverse event | 1 (2) | 0 | 1 (1) |
| Patient withdrawal | 0 | 2 (7) | 2 (2) |
| Protocol violation | 1 (2) | 0 | 1 (1) |
| Lost to follow-up | 1 (2) | 2 (7) | 3 (3) |
| New sitee | 1 (2) | 2 (7) | 3 (3) |

aThe percentage is based on the number of patients enrolled.

bThe percentage is based on the number of patients treated.

c One patient was removed from modified intention-to-treat populations due to major protocol deviation.

dThe percentage is based on the number of patients who discontinued.

eNew site refers to the discontinuation of the treatment/study owing to a change of dialysis center.

All enrolled patients: patients who signed the informed consent form.

**Supplemental table 6.** Summary of adverse events

|  |  |  |  |
| --- | --- | --- | --- |
| DIALOGUE 3 | Molidustat  | Darbepoetin | Total |
|  | *n* = 118 | *n* = 42 | *n* = 160 |
| Number of patients (%) with AEs |  |  |  |
| Any AE | 101 (86) | 36 (86) | 137 (86) |
| Any study-drug-related AE | 8 (7) | 2 (5) | 10 (6) |
| Any serious AE | 56 (47) | 22 (52) | 78 (49) |
| Any study-drug-related serious AE | 2 (2) | 1 (2) | 3 (2) |
| Any AE resulting in death | 5 (4) | 1 (2) | 6 (4) |
| Any study-drug-related AE resulting in death | 0 | 0 | 0 |
| Any AE leading to drug withdrawal | 25 (21) | 4 (10) | 29 (18) |
| Any study-drug-related AE leading to drug withdrawal | 5 (4) | 0 | 5 (3) |
| DIALOGUE 5 | Molidustat*n* = 57 | Epoetin*n* = 30 | Total*n* = 87 |
| Number of patients (%) with AEs |  |  |  |
| Any AE | 52 (91) | 28 (93) | 80 (92) |
| Any study-drug-related AE | 11 (19) | 4 (13) | 15 (17) |
| Any serious AE | 29 (51) | 11 (37) | 40 (46) |
| Any study-drug-related serious AE | 3 (5) | 0 | 3 (3) |
| Any AE resulting in death | 5 (9) | 1 (3) | 6 (7) |
| Any study-drug-related AE resulting in death | 0 | 0 | 0 |
| Any AE leading to drug withdrawal | 13 (23) | 2 (7) | 15 (17) |
| Any study-drug-related AE leading to drug withdrawal | 2 (4) | 0 | 2 (2) |

Medical Dictionary for Regulatory Activities version 19.1 was used for coding AEs. A patient with multiple AEs was counted a single time for that system organ class or preferred term. An AE was defined as an event that occurred between the first dose date (regardless of phase) and the end-of-treatment date +3 days in the extension study. Data shown are forthe safety population.

AE, adverse event.

**Supplemental Table 7.** AEs that occurred in ≥10% of patients

|  |  |  |  |
| --- | --- | --- | --- |
| DIALOGUE 3 | Molidustat  | Darbepoetin | Total |
|  | *n* = 118 | *n* = 42 | *n* = 160 |
| Specific AEs reported by ≥10% of patients, *n* (%) |
| Infections and infestations | 53 (44.9) | 17 (40.5) | 70 (43.8) |
| Gastrointestinal disorders  | 42 (35.6) | 18 (42.9) | 60 (37.5) |
| Kidney and urinary disorders | 36 (30.5) | 15 (35.7) | 51 (31.9) |
| Vascular disorders | 34 (28.8) | 17 (40.5) | 51 (31.9) |
| Metabolism and nutrition disorders | 27 (22.9) | 9 (21.4) | 36 (22.5) |
| Cardiac disorders | 24 (20.3) | 7 (16.7) | 31 (19.4) |
| General disorders and administration site conditions | 22 (18.6) | 10 (23.8) | 32 (20.0) |
| Respiratory, thoracic, and mediastinal disorders | 22 (18.6) | 9 (21.4) | 31 (19.4) |
| Musculoskeletal and connective tissue disorders | 20 (16.9) | 11 (26.2) | 31 (19.4) |
| Nervous system disorders | 17 (14.4) | 8 (19.0) | 25 (15.6) |
| Injury, poisoning, and procedural complications | 17 (14.4) | 7 (16.7) | 24 (15.0) |
| Skin and subcutaneous tissue disorders | 17 (14.4) | 3 (7.1) | 20 (12.5) |
| Investigations | 15 (12.7) | 0 | 15 (9.4) |
| DIALOGUE 5 | Molidustat | Epoetin | Total |
|  | *n* = 57 | *n* = 30 | *n* = 87 |
| Specific AEs reported by ≥10% of patients, *n* (%) |
| Gastrointestinal disorders  | 28 (49.1) | 17 (56.7) | 45 (51.7) |
| Infections and infestations | 25 (43.9) | 15 (50.0) | 40 (46.0) |
| Injury, poisoning, and procedural complications | 23 (40.4) | 18 (60.0) | 41 (47.1) |
| Respiratory, thoracic, and mediastinal disorders | 23 (40.4) | 9 (30.0) | 32 (36.8) |
| Metabolism and nutrition disorders | 23 (40.4) | 7 (23.3) | 30 (34.5) |
| Investigations | 18 (31.6) | 13 (43.3) | 31 (35.6) |
| Nervous system disorders | 16 (28.1) | 7 (23.3) | 23 (26.4) |
| Skin and subcutaneous tissue disorders | 15 (26.3) | 7 (23.3) | 22 (25.3) |
| Musculoskeletal and connective tissue disorders | 13 (22.8) | 12 (40.0) | 25 (28.7) |
| General disorders and administration site conditions | 12 (21.1) | 12 (40.0) | 24 (27.6) |
| Cardiac disorders | 12 (21.1) | 8 (26.7) | 20 (23.0) |
| Vascular disorders | 11 (19.3) | 6 (20.0) | 17 (19.5) |
| Psychiatric disorders | 9 (15.8) | 2 (6.7) | 11 (12.6) |

AE, adverse event.