Supplementary Information

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Phase 1 Study to Assess Safety and Pharmacokinetics of
Elexacaftor/Tezacaftor/Ivacaftor in Subjects Without Cystic Fibrosis With Moderate
Hepatic Impairment

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Table S1 Eligibility criteria

| Inclusion criteria: subjects with moderate hepatic impairment |
|-------------------------------------------------------------|
| • Subjects will sign and date an informed consent form       |
| • Subjects must be willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures |
| • Subjects (male or female) must be between the ages of 18 and 65 years, inclusive, and have routine laboratory measurement and physical examination (PE) results, including vital sign measurement and echocardiography, without major or clinically relevant findings, except for those commensurate with the degree of hepatic impairment permitted by the protocol, as judged by the investigator |
| • Subjects must have a body mass index (BMI) of 18.0 to 35.0 kg/m², inclusive. |
| • Subjects must meet the criteria for moderate hepatic impairment defined as a Child-Pugh total score of 7 to 9 points (Child-Pugh Class B, Table 9-1) at the Screening Visit |
| • Subjects taking medications must be receiving a stable dose and/or stable treatment regimen (approved medications are listed in Table S2) |

| Inclusion criteria: matched healthy subjects |
|---------------------------------------------|
| • Subjects will sign and date an informed consent form |
| • Subjects must be willing and able to comply with scheduled visits, treatment plan, study restrictions, laboratory tests, contraceptive guidelines, and other study procedures |
| • Subjects (male or female) must be between the ages of 18 and 65 years, inclusive, and healthy, as defined by no clinically relevant abnormalities identified by a detailed completion of medical history, complete PE, including blood pressure and pulse rate measurement, standard 12-lead electrocardiography, and clinical laboratory tests |
| • Subjects must have a BMI of 18.0 to 35.0 kg/m², inclusive |
| • During screening, subjects will be matched to other subjects with hepatic impairment according to cigarette smoking habit (nonsmoking or smoking up to 10 cigarettes per day), age (± 10 years), sex, and weight (± 10 kg). The screening weight for healthy subjects will be matched to the Day −1 weight for subjects with moderate hepatic impairment |

| Exclusion criteria: subjects with moderate hepatic impairment |
|-------------------------------------------------------------|
| • Subjects must not have a history of any illness or any clinical condition that, in the opinion of the investigator or the subject’s general practitioner, might confound the results of the study or pose an additional risk in administering the study drug to the subject. This may include, but is not limited to, history of relevant drug or food allergies; history of cardiovascular or central nervous system disease; history or presence of clinically significant pathology other than hepatic impairment; history of mental disease; and history of cancer, except for squamous cell skin cancer, basal cell skin cancer, and stage 0 cervical carcinoma in situ (all 3 with no recurrence in the last 5 years) |
| • Subjects must not have fluctuating or rapidly deteriorating hepatic function, in the opinion of the investigator, as indicated by history or by significant variations in or worsening of clinical and/or laboratory signs of hepatic impairment (eg, advanced ascites, infection of ascites, fever, or active gastrointestinal bleeding) within 6 months before the Screening Visit |
• Subjects must not have a change in dose regimen of medically required medication within 14 days before the Screening Visit
• Subjects must not have febrile illness within 5 days before the first study drug dose
• Subjects must not have alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-Glutamyltransferase (GGT), or total bilirubin levels above 5 × upper limit of normal (ULN) at the Screening Visit or Day −1
• Subjects must not have severe portal hypertension (eg, history of esophageal bleeding within the last 6 months, variceal banding procedure in the last 6 months, caput medusa, or spontaneous bacterial peritonitis) or surgical portosystemic shunts, including a transjugular intrahepatic portosystemic shunt
• Subjects must not have biliary obstruction or other causes of hepatic impairment not related to parenchymal disorder and/or disease of the liver
• Subjects must not have a history or presence of severe hepatic encephalopathy (grade >2)
• Subjects must not have a thrombocyte (platelet) level <50 × 10^9/L and/or hemoglobin level <110 g/L at the Screening Visit or Day −1
• Subjects must not have any condition or procedure that could affect drug absorption (eg, gastrectomy, cholecystectomy, or other gastrointestinal tract surgeries, except appendectomy)
• Subjects must not have type 1 diabetes or evidence of poorly controlled type 2 diabetes, as evidenced by a glycated hemoglobin level ≥8.5% at the Screening Visit, or any history of hospitalizations or emergency department visits for hypoglycemia or hyperglycemia in the past year
• Subjects must not have hepatocellular carcinoma, human immunodeficiency virus (HIV), newly diagnosed hepatitis B or C, based on screening laboratory serology, or liver disease caused by drug toxicity. Note: Sites should use all precautions to ensure that prohibited concomitant medications are excluded. Subjects must be stable and must not be taking any medications for chronic viral hepatitis infections (chronic hepatitis B or chronic hepatitis C)
• Subjects must not have significant renal dysfunction (creatinine clearance <50 mL/min), estimated according to the method of Cockcroft and Gault at the Screening Visit or Day −1
• Subjects must not have a medical history of solid organ or bone marrow transplant
• Subjects must not have a standard 12-lead electrocardiogram (ECG; performed in triplicate) demonstrating a median QTcF >450 msec at the Screening Visit
• Subjects must not have used restricted substances or devices or performed restricted activities within the specified duration before the first study drug dose
• Subjects must not have a history of regular alcohol consumption exceeding the following amounts within 6 months before screening (1 drink equals 5 oz/150 mL of wine, 12 oz/360 mL of beer, or 1.5 oz/45 mL of hard liquor):
  • For female subjects: 14 drinks per week
  • For male subjects: 21 drinks per week
• Subjects must not have a positive screening test result for illicit drugs or alcohol at the Screening Visit or at Day −1
• Subjects must not currently smoke >10 cigarettes per day
• Subjects must not have donated blood (approximately 1 pint [500 mL] or more) within 56 days before the first study drug dose
• Female subjects must not be pregnant, nursing, or planning to become pregnant during the study or within 90 days after the last study drug dose
Male subjects must not have a female partner who is pregnant, nursing, or planning to become pregnant during the study or within 90 days after the last study drug dose.

Subjects, or a close relative of the subjects, must not be the investigator, subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site.

Exclusion criteria: matched healthy subjects

- Subjects must not have a history of any illness or any clinical condition that, in the opinion of the investigator or the subject's general practitioner, might confound the results of the study or pose an additional risk in administering the study drug to the subject. This may include, but is not limited to, history of relevant drug or food allergies; history of cardiovascular or central nervous system disease; history or presence of clinically significant pathology; history of mental disease; and history of cancer, except for squamous cell skin cancer, basal cell skin cancer, and stage 0 cervical carcinoma in situ (all 3 with no recurrence in the last 5 years). Any condition requiring chronic or intermittent medication is, by definition, considered significant.
- Subjects must not have febrile illness within 5 days before the first study drug dose.
- Subjects must not have ALT, AST, or total bilirubin levels >1.5 × ULN at the Screening Visit or Day −1, unless otherwise approved by the medical monitor.
- Subjects must not have any condition or procedure that could affect drug absorption (e.g., gastrectomy, cholecystectomy, or other gastrointestinal tract surgery, except appendectomy).
- Subjects must not have a standard 12-lead ECG (performed in triplicate) demonstrating a median QTcF >450 msec at the Screening Visit.
- Subjects must not have used restricted substances or devices or performed restricted activities within the specified duration before the first study drug dose.
- Subjects must not have a history of regular alcohol consumption exceeding the following amounts within 6 months before screening (1 drink equals 5 oz/150 mL of wine, 12 oz/360 mL of beer, or 1.5 oz/45 mL of hard liquor):
  - For female subjects: 14 drinks per week
  - For male subjects: 21 drinks per week
- Subjects must not have a positive screening test result for drugs or alcohol at the Screening Visit or Day −1.
- Subjects must not currently smoke >10 cigarettes per day.
- Subjects must not have a screening test result positive for hepatitis B surface antigen, hepatitis C virus antibody, or HIV 1 or 2 antibodies.
- Subjects must not have donated blood (of approximately 1 pint [500 mL] or more) within 56 days before the first study drug dose.
- Female subjects must not be pregnant, nursing, or planning to become pregnant during the study or within 90 days after the last study drug dose.
- Male subjects must not have a female partner who is pregnant, nursing, or planning to become pregnant during the study or within 90 days after the last study drug dose.
- Subjects, or a close relative of the subjects, must not be the investigator, a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; ECG: electrocardiogram; GGT: γ-Glutamyltransferase; HIV: human immunodeficiency virus; PE: physical examination; ULN: upper limit of normal.
Table S2 Approved concomitant medications in subjects with moderate hepatic impairment

| Medication                                           | Use                                      |
|------------------------------------------------------|------------------------------------------|
| Spironolactone and/or furosemide                     | Treatment of ascites                     |
| Propranolol and/or nitrates                          | Reducing portal pressure                 |
| Proton pump inhibitors such as pantoprazole          | Treatment/prevention of gastrointestinal reflux |
| Oral hypoglycemic medication and/or insulin (metformin, sitagliptin, etc.) | Treatment of type 2 diabetes            |
| Lactulose and/or ornithine aspartate                 | Treatment of encephalopathy             |
| Rifaximin and other non-absorbed antibiotics         |                                          |
| Silymarin, micronutrients, and vitamins              |                                          |

*a Continuation of other medications that are not included on this list could be approved by the sponsor following an assessment of potential safety issues and drug-drug interactions.*
Table S3. Multiple reaction monitoring transitions.

| Analyte       | Precursor ion (m/z) | Product ion (m/z) | Collision energy (eV) | Declustering potential (V) | Approximate retention time (min) |
|---------------|---------------------|-------------------|-----------------------|---------------------------|---------------------------------|
| ELX           | 598.4               | 422.4             | 25                    | 50                        | 1.35                            |
| M23-ELX       | 584.4               | 422.4             | 35                    | 50                        | 1.00                            |
| d5-ELX        | 603.4               | 427.4             | 25                    | 50                        | 1.35                            |
| d5-M23-ELX    | 589.4               | 427.4             | 35                    | 50                        | 1.00                            |

ELX: elexacaftor; M23-elexacaftor.
Table S4. Grading of adverse event severity$^a$

| Classification            | Definition                                                                 |
|---------------------------|---------------------------------------------------------------------------|
| Mild (Grade 1)            | Mild level of discomfort and does not interfere with regular activities   |
| Moderate (Grade 2)        | Moderate level of discomfort and significantly interferes with regular activities |
| Severe (Grade 3)          | Significant level of discomfort and prevents regular activities           |
| Life-threatening (Grade 4) | Any adverse event that places the subject, in the view of the investigator, at immediate risk of death |

$^a$Adverse events were graded according to US Food and Drug Administration guidance [1]; the severity of adverse events that do not appear in this scale were determined according to the definitions listed in this table.
**Table S5.** Mean (CV%) percentage of unbound elexacaftor and M23-elexacaftor in plasma

| Analyte   | Moderate hepatic impairment (n = 11) | Matched healthy subjects (n = 11) | Percent change relative to matched healthy subjects |
|-----------|-------------------------------------|-----------------------------------|---------------------------------------------------|
| ELX       | 0.642 (20.8)                        | 0.511 (8.79)                      | 26                                                |
| M23-ELX   | 0.825 (20.1)                        | 0.645 (11.4)                      | 28                                                |

CV: coefficient of variation; ELX: elexacaftor.
### Table S6. Laboratory values, vital signs, and ECG parameters

| Parameter                                      | Moderate hepatic impairment (n = 11) | Matched healthy subjects (n = 11) |
|------------------------------------------------|-------------------------------------|----------------------------------|
| Chemistry: change from baseline\(^a\) at TE period day 10, mean (SD) |                                     |                                  |
| Albumin, g/L                                   | −0.3 (2.6)                          | −0.1 (2.5)                       |
| Alkaline phosphatase, U/L                      | 9.3 (14.5)                          | 2.9 (7.3)                        |
| Alanine aminotransferase, U/L                  | −0.1 (11.9)                         | 2.5 (15.4)                       |
| Amylase, U/L                                   | −2.1 (25.6)                         | 11.9 (10.2)                      |
| Aspartate aminotransferase, U/L                | −3.5 (11.9)                         | −2.5 (11.7)                      |
| Direct bilirubin, µmol/L                       | 1.1 (1.9)                           | 0.0 (0.5)                        |
| Bilirubin, µmol/L                              | 5.8 (9.4)                           | −0.1 (3.6)                       |
| Calcium, mmol/L                                | 0.03 (0.14)                         | 0.04 (0.14)                      |
| Creatine kinase, U/L                           | −24.9 (42.0)                        | −44.5 (79.2)                     |
| Chloride, mmol/L                               | −2.3 (1.6)                          | −2.5 (2.3)                       |
| Creatinine, µmol/L                             | −3.3 (4.7)                          | −1.9 (6.7)                       |
| Gamma glutamyl transferase, U/L                | 9.7 (25.1)                          | 13.7 (34.6)                      |
| Glucose, mmol/L                                | 0.3 (0.8)                           | −0.1 (0.5)                       |
| Potassium, mmol/L                              | −0.1 (0.4)                          | −0.1 (0.5)                       |
| Lipase, U/L                                    | 2.13 (37.22)                        | 11.67 (13.86)                    |
| Phosphate, mmol/L                              | 0.11 (0.20)                         | 0.15 (0.18)                      |
| Protein, g/L                                   | 0.7 (5.6)                           | 1.3 (3.2)                        |
| Sodium, mmol/L                                 | −1.9 (3.1)                          | −1.2 (1.4)                       |
| Urea nitrogen, mmol/L                          | 0.9 (1.2)                           | 0.7 (1.2)                        |
| Hematology: change from baseline<sup>a</sup> at TE period day 10, mean (SD) |   |   |
|---|---|---|
| Basophils, 10<sup>9</sup>/L | 0.00 (0.01) | 0.00 (0.01) |
| Basophils/leukocytes, % | -0.16 (0.30) | 0.02 (0.21) |
| Eosinophils, 10<sup>9</sup>/L | -0.01 (0.07) | 0.07 (0.09) |
| Eosinophils/leukocytes, % | -0.57 (2.10) | 0.71 (1.39) |
| Hemoglobin, g/L | -2.8 (7.4) | -1.5 (5.9) |
| Lymphocytes, 10<sup>9</sup>/L | 0.19 (0.29) | 0.30 (0.56) |
| Lymphocytes/leukocytes, % | 0.36 (5.88) | 0.30 (9.25) |
| Erythrocyte mean corpuscular volume, fL | -0.4 (2.6) | 0.1 (1.1) |
| Monocytes, 10<sup>9</sup>/L | 0.12 (0.17) | 0.16 (0.13) |
| Monocytes/leukocytes, % | 0.96 (1.63) | 1.25 (1.62) |
| Neutrophils, 10<sup>9</sup>/L | 0.36 (1.19) | 0.29 (1.53) |
| Neutrophils/leukocytes, % | -0.59 (7.13) | -2.28 (11.27) |
| Platelets, 10<sup>9</sup>/L | 12.0 (14.2) | 10.8 (33.2) |
| Erythrocytes, 10<sup>12</sup>/L | -0.11 (0.23) | -0.03 (0.18) |
| Reticulocytes, 10<sup>9</sup>/L | -5.98 (15.68) | 3.63 (16.48) |
| Leukocytes, 10<sup>9</sup>/L | 0.66 (1.33) | 0.83 (1.65) |

| Coagulation: change from baseline<sup>a</sup> at TE period day 10, mean (SD) |   |   |
|---|---|---|
| Activated partial thromboplastin time, sec | -0.2 (3.4) | -1.7 (2.8) |
| Prothrombin international normalized ratio | -0.02 (0.12) | -0.06 (0.07) |
| Prothrombin time, sec | -0.3 (0.8) | -0.4 (0.7) |

| Vital signs: change from baseline<sup>a</sup> at TE period day 10, mean (SD) |   |   |
|---|---|---|
| Parameter                                      | Day 10 (SD) | Day 30 (SD) |
|------------------------------------------------|-------------|-------------|
| Systolic blood pressure, mm Hg                 | −4.2 (9.4)  | 1.2 (8.3)   |
| Diastolic blood pressure, mm Hg                | −1.8 (7.6)  | −0.5 (6.4)  |
| Pulse rate, beats/min                          | 3.2 (3.9)   | 3.6 (6.1)   |
| Temperature, °C                                 | 0.1 (0.2)   | 0.0 (0.2)   |
| Respiratory rate, breaths/min                   | 0.6 (2.9)   | 0.4 (1.6)   |
| ECG parameters: change from baseline at TE period day 10, mean (SD)\(^b\) |             |             |
| ECG mean heart rate, beats/min                 | 1.1 (5.6)   | −2.7 (8.4)  |
| RR interval, aggregate, msec                   | −9.6 (76.6) | 23.0 (77.4) |
| PR interval, aggregate, msec                   | 1.4 (5.9)   | 6.1 (9.6)   |
| QRS duration, aggregate, msec                  | 2.7 (5.7)   | 2.8 (5.7)   |
| QT interval, aggregate, msec                   | −1.0 (14.9) | 3.1 (16.5)  |
| QTcF interval aggregate, msec                  | 0.6 (10.2)  | −1.0 (10.4) |
| Maximum QT/QTcF interval results during the TE period: n (%)\(^c\) |             |             |
| Total, N1                                       | 11          | 11          |
| ≤450 msec                                       |             |             |
| QTcF                                           | 8 (72.7)    | 11 (100.0)  |
| QT                                             | 9 (81.8)    | 10 (90.9)   |
| >450 to ≤480 msec                               |             |             |
| QTcF                                           | 2 (18.2)    | 0           |
| QT                                             | 1 (9.1)     | 1 (9.1)     |
| >480 to ≤500 msec                               |             |             |
| QTcF                                           | 1 (9.1)     | 0           |
| QT                                             | 1 (9.1)     | 0           |
| <500 msec | 0  |
|----------|----|
| QTcF     | 0  |
| QT       | 0  |

ECG, electrocardiogram; PR, PR interval, segment; QRS, the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization; QT, QT interval; QTcF, QT interval corrected by Fridericia’s formula; RR, interval from the onset of 1 QRS complex to the next; TE, treatment-emergent.

a Baseline was defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug.

b The average of triplicate ECG measurements at each visit and time point was used for analysis. Baseline was defined as the most recent non-missing average of ECG triplicate measurements (scheduled or unscheduled) collected before the first dose of study drug.

c The maximum value was defined as the maximum of the post-baseline QT/QTcF measurements in the TE period, including unscheduled assessments. Percentage was calculated as n/N1, where N1 is the number of study participants in the Safety Set with ≥1 non-missing measurement in the TE period.
Fig. S1. Maximum observed concentration ($C_{\text{max}}$) of (A) combined elexacaftor (ELX) and M23-elexacaftor (M23-ELX), (B, D) tezacaftor (TEZ), and (C, E, F) ivacaftor (IVA) in subjects with moderate hepatic impairment versus matched healthy subjects.$^{a,b}$

$^a$ The line inside the box represents the median. The ends of the box are the 25th and 75th percentiles. The whiskers denote the lowest and highest values (excluding values considered to be outliers). Values beyond the whiskers (shown as triangles) are considered outliers.

$^b$ Panels A-C reflect $C_{\text{max}}$ following 10 days of elexacaftor/tezacaftor/ivacaftor. Panels D-E reflect $C_{\text{max}}$ after 10 days of tezacaftor/ivacaftor in a previous study. Panel F reflects $C_{\text{max}}$ after a single dose of ivacaftor in a previous study.
Fig. S2. Mean plasma concentrations of (A) elexacaftor and (B) M23-elexacaftor by nominal time on Day 10.
Fig. S3. Mean plasma concentrations of (A) tezacaftor and (B) ivacaftor by nominal time on Day 10.
References

1. US Food and Drug Administration. Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. https://www.fda.gov/media/73679/download. Accessed July 21, 2022.