Supplementary Information

Clinical Pharmacokinetics

Effects of Hepatic Impairment on the Pharmacokinetics of the Dual GIP and GLP-1 Receptor Agonist Tirzepatide

Shweta Urva, PhD, Tonya Quinlan, BS, John Landry, MMath, Xiaosu Ma, PhD, Jennifer A. Martin, MS, Charles T. Benson, MD

Eli Lilly and Company, Indianapolis, IN, USA

Correspondence and request for reprints:

Shweta Urva, PhD

Lilly Corporate Center

Indianapolis, IN

Telephone: +1 317-276-1164

Email: urva_shweta@lilly.com

ONLINE-ONLY SUPPLEMENTAL APPENDIX

METHODS AND MATERIALS

Inclusion Criteria All participants must meet the following criteria for enrollment (Inclusion Criteria [1] through [6]). Additional subgroupings of inclusion criteria below are specific to the participants' hepatic function (Inclusion Criteria [7] through [12]) and diabetic status (Inclusion Criteria [13] through [16]).

[1] male and female subjects may participants in this study

[1a] Male participants:

- Men, regardless of their fertility status, with non-pregnant women of childbearing potential partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms plus one additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine device) or effective method of contraception (such as diaphragms with spermicide or cervical sponge) for the duration of the study and for at least 3 months after dosing.
    - Men and their partners may choose to use a double-barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted, however, that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.
    - Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.
- Men with pregnant partners should use condoms during intercourse for the duration of the study and until the end of estimated relevant potential exposure in women of childbearing potential.
- Men who are in exclusively same-sex relationships (as their preferred and usual lifestyle) are not required to use contraception.
- Men should refrain from sperm donation for the duration of the study and for at least 3 months after dosing.

[1a] Female participants:

- Women of childbearing potential are excluded from the study.
- Women not of childbearing potential may participate and include those who are:
    - infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as Mullerian agenesis; or

- postmenopausal – defined as either:
  - A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either:
    a) cessation of menses for at least 1 year, or
    b) at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 IU/mL; or
  - A woman 55 or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or
  - A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[2] are between the ages of 18 and 85 years, inclusive
[3] are between the body mass index (BMI) of 19.0 and 40.0 kg/m^2, inclusive, at screening
[4] have venous access sufficient to allow blood sampling as per the protocol
[5] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures
[6] have given written informed consent approved by Lilly and the Institutional Review Board (IRB) governing the site

Additional Inclusion Criteria for Control Participants (Group 1)

[7] healthy males or females as determined by medical history, physical examination, and other screening procedures, with clinically normal hepatic function at screening
[8] have clinical laboratory test results within normal reference range for the population or investigator site, or results with acceptable deviations that are judged to be not clinically significant by the investigator
[9] have normal blood pressure (BP) and pulse rate, as determined by the investigator

Additional Inclusion Criteria for Participants with Mild to Severe Hepatic Impairment (Groups 2 to 4)

[10] are individuals with hepatic impairment classified as Child-Pugh score A, B, or C (mild, moderate, or severe impairment)[1,2], who are considered acceptable for participation in this study by the investigator. Participant must have a diagnosis of chronic hepatic impairment (>6 months) per physician diagnosis and standard of care practice, with no clinically significant changes within 90 days prior to study drug administration. Participants may have mild stable baseline medical conditions for which neither the condition nor treatments received would negatively impact the health of the participant or study conduct.
[11] clinical laboratory test results with deviations that are judged by the investigator to be compatible with the hepatic impairment of the participant, or of no additional clinical significance for this study
[12] have acceptable BP and pulse rate, as determined by the investigator
[13] no significant history of spontaneous or ethanol induced hypoglycemia

Additional Inclusion Criteria for Participants with both T2D and Hepatic Impairment

[14] have T2D controlled with diet or exercise alone or on stable doses of metformin for at least 8 weeks
[15] participants taking stable doses of over-the-counter or prescription medications (e.g., antihypertensive agents, aspirin, lipid-lowering agents) for treatment of concurrent medical conditions are permitted to participate providing they have been stable on their treatment regimen for at least 4 weeks
[16] have a hemoglobin A1c ≥6.0% and ≤11.0% at the screening visit

[17] have clinical laboratory test results within normal range or deemed clinically insignificant by the investigator. Abnormalities of serum glucose, serum lipids, urinary glucose, and urinary protein consistent with T2D are acceptable.

Exclusion Criteria Participants will be excluded from study enrollment if they meet any of the following criteria at screening and/or enrollment. For all participants, Exclusion Criteria [18] through [44] apply; additional subgroupings of exclusion criteria below are specific to the participants' hepatic function (Exclusion Criteria [45] through [56]) and diabetic status (Exclusion Criteria [57] through [60]).

[18] are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.
[19] are Lilly employees, or employees of third-party organizations involved with the study that require exclusion of their employees
[20] are currently enrolled in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
[21] have known allergies to tirzepatide or related compounds
[22] have a history of atopy or clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis)
[23] have previously completed or withdrawn from this study or any other study investigating tirzepatide, and have previously received the investigational product
[24] persons who have a current, functioning organ transplant
[25] have a personal or family history of medullary thyroid carcinoma or have multiple endocrine neoplasia syndrome type 2
[26] febrile illness within 3 days prior to dosing
[27] have a history of second- or third-degree heart block or any abnormality in the 12-lead ECG at screening that, in the opinion of the investigator, increases the risks associated with participating in the study
[28] have estimated creatinine clearance (CLcr) <50 mL/min (using the 4-factor modification of diet in renal disease [MDRD-4]) at screening. Exceptions to this may be allowed on a case-by-case basis after discussion and agreement between the investigator and the sponsor or designated medical representative (no estimated CLcr <30 mL/min will be approved).
[29] have a significant history of or presence of cardiovascular (e.g., myocardial infarction, cerebrovascular accident, etc. within the past 6 months), respiratory, hepatic (applies to Group 1 control participants only), GI, endocrine (except T2D), hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the study medication; or of interfering with the interpretation of data
[30] show evidence of significant active neuropsychiatric disease
[31] have a history of malignancy within 5 years prior to screening
[32] have a history or presence of pancreatitis (history of chronic pancreatitis or idiopathic acute pancreatitis), elevation in serum amylase and/or lipase >1.5 × the upper limit of normal (ULN) or gastrointestinal (GI) disorder (e.g., relevant esophageal reflux or gall bladder disease) or any GI disease which impacts gastric emptying (e.g., gastric bypass surgery,

pyloric stenosis, with the exception of appendectomy) or could be aggravated by GLP-1 analogs or dipeptidyl peptidase-IV inhibitors. Participants with dyslipidemia and participants who had cholecystolithiasis treatment (removal of gall stones) and/or cholecystectomy (removal of gall bladder) in the past, with no further sequelae, may be included in the study at the discretion of the investigator.

[33] have serum AST or ALT >2× ULN or total bilirubin >1.5× ULN (applies to Group 1 control participants only)

[34] have a serum triglyceride ≥5 mmol/L (442.5 mg/dL) at screening (applies to Group 1 control participants only)

[35] show evidence of human immunodeficiency virus (HIV) infection and/or positive HIV antibodies

[36] show evidence of hepatitis C and/or positive hepatitis C antibody (applies to Group 1 control participants only)

[37] show evidence of hepatitis B and/or positive hepatitis B surface antigen (applies to Group 1 control participants only)

[38] are women with a positive pregnancy test or women who are lactating

[39] regularly use known drugs of abuse and/or show positive findings on urinary drug screen that are not otherwise explained by permitted concomitant medications

[40] intend to use:

- over-the-counter medication within 7 days prior to dosing (except for hepatic impairment and T2D participants on stable doses)
- prescription medication within 14 days prior to dosing
- herbal preparations within the 14 days prior to screening

If any of the above situation arises, an otherwise suitable participants may be included at the discretion of the investigator.

[41] have donated more than 450 mL blood, including plasma and platelets, within 1 month prior to Check-in

[42] have an average weekly alcohol intake that exceeds 21 units per week (males up to age 65) and 14 units per week (males over 65 and females), or are unwilling to stop alcohol consumption from 48 hours prior to Check-in on Day -1 and the follow-up visit, and while resident in the CRU (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits)

[43] are currently heavy users of nicotine (>10/cigarettes/day) or cannot comply with the restrictions of the study site during confined periods or abstain for 1 hour prior to dosing and 4 hours following dosing

[44] in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study

Additional Exclusion Criteria for Participants with Mild to Severe Hepatic Impairment (Groups 2 to 4)

[45] are anticipating organ transplant within 6 months

[46] presence of active portal shunt

[47] requires paracentesis more often than 2 times per month

[48] have evidence of spontaneous bacterial peritonitis within 6 months of dosing

[49] have had variceal bleeding within 3 months of Check-in to the CRU

[50] show presence of hepatocellular carcinoma

[51] show evidence of severe hyponatremia (sodium <120 mmol/L)

[52] hepatic encephalopathy of Grade 2 or higher
[53] have hemoglobin <8.5 g/dL
[54] have a platelet count <30×109 cells/L
[55] have total bilirubin >15 mg/dL
[56] have ALT ≥ 6× ULN

Additional Exclusion Criteria for Participants with T2D and Hepatic Impairment

[57] have taken any glucose-lowering medications other than metformin (refer to Inclusion Criterion [13]), including insulin, in the past 3 months before screening
[58] have had more than 1 episode of severe hypoglycemia, as defined by the American Diabetes Association criteria, within 6 months before entry into the study or has a history of hypoglycemia unawareness or poor recognition of hypoglycemic symptoms. Any participant that cannot communicate an understanding of hypoglycemic symptoms and the appropriate treatment of hypoglycemia prior to dosing should also be excluded.
[59] have had a blood transfusion or severe blood loss or have known hemoglobinopathy (alpha-thalassemia), hemolytic anemia, sickle cell anemia, or any other condition known to interfere with hemoglobin A1c methodology
[60] have received chronic (lasting >14 consecutive days) systemic glucocorticoid therapy (excluding topical, intra-articular, and inhaled preparations) in the past year or have received any systemic glucocorticoid therapy within 30 days before screening

Hyperglycemia and Hypoglycemia Reporting Episodes of hyperglycemia (fasting plasma/serum glucose >270 mg/dL [15 mmol/L]) or hypoglycemia (plasma/serum glucose ≤70 mg/dL [3.9 mmol/L]) will be reported by the investigator or designated physician who will be responsible for advising the participant on what further actions to take. Additional monitoring may be requested at the investigator's discretion.

If the fasting plasma/serum glucose during the dosing period exceeds the acceptable level defined as hyperglycemia on 3 or more separate days over any 2-week period between screening and the end of the dosing period, the participant will be evaluated further at the study site. If fasting plasma/serum glucose continues to exceed the acceptable level, treatment with an appropriate antidiabetic agent may be initiated by the investigator. If hyperglycemia occurs during the follow-up period, the participant will remain in the study until completion of the planned follow-up.

Hypoglycemia episodes will be recorded on specific eCRF pages. Hypoglycemia will be treated appropriately by the investigator and additional monitoring of plasma/serum glucose levels may be performed. The following categories of the 2017 American Diabetes Association position statement on glycemic targets[3] based on recommendations of the International Hypoglycaemia Study Group[4] should be applied for reporting in the eCRF and evaluating hypoglycemic events.

Hypoglycemia will be described using the following definitions:

- **Documented Glucose Alert Level (Level 1), Plasma Glucose (PG) ≤70 mg/dL (3.9 mmol/L)**:
    - **Symptomatic hypoglycemia**: an event during which typical symptoms of hypoglycemia are accompanied by PG ≤70 mg/dL (3.9 mmol/L)
    - **Asymptomatic hypoglycemia**: an event not accompanied by typical symptoms of hypoglycemia but with PG ≤70 mg/dL (3.9 mmol/L)
    - **Unspecified hypoglycemia**: an event during which PG ≤70 mg/dL (3.9 mmol/L) but no information relative to symptoms of hypoglycemia was recorded

- **Documented Clinically Significant Hypoglycemia (Level 2) PG <54 mg/dL (3.0 mmol/L)**:
    - **Symptomatic hypoglycemia**: an event during which typical symptoms of hypoglycemia are accompanied by PG <54 mg/dL (3.0 mmol/L)
    - **Asymptomatic hypoglycemia**: an event not accompanied by typical symptoms of hypoglycemia but with PG <54 mg/dL (3.0 mmol/L)
    - **Unspecified hypoglycemia**: an event during which PG <54 mg/dL (3.0 mmol/L) but no information relative to symptoms of hypoglycemia was recorded
- **Severe hypoglycemia (Level 3)**: an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. During these episodes, the participant has an altered mental status and cannot assist in their care, is semiconscious or unconscious, or experienced coma with or without seizures and may require parenteral therapy. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of blood glucose concentration to normal is considered sufficient evidence that the event was induced by a low PG concentration (PG ≤70 mg/dL [3.9 mmol/L])
    - **Severe hypoglycemia requiring medical attention**: a severe hypoglycemic event when participants require therapy by healthcare professionals (e.g., emergency medical technicians, emergency room personnel, etc.)
- **Other Hypoglycemia**:
    - **Nocturnal hypoglycemia**: any hypoglycemic event (documented symptomatic, asymptomatic, probable symptomatic, or severe hypoglycemia) that occurs between bedtime and waking
    - **Relative hypoglycemia**: an event during which typical symptoms of hypoglycemia, that do not require the assistance of another person, are accompanied by PG >70 mg/dL (3.9 mmol/L), but these levels may be quickly approaching the 70 mg/dL (3.9 mmol/L) threshold
    - **Overall (or total) hypoglycemia**: This optional category combines all cases of hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, the event is only counted once in this category
    - **Probable symptomatic hypoglycemia**: An event during which symptoms of hypoglycemia are not accompanied by a PG measurement but that was presumably caused by a blood glucose concentration ≤70 mg/dL (3.9 mmol/L).

The determination of a hypoglycemic event as an episode of severe hypoglycemia as defined above will be made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.

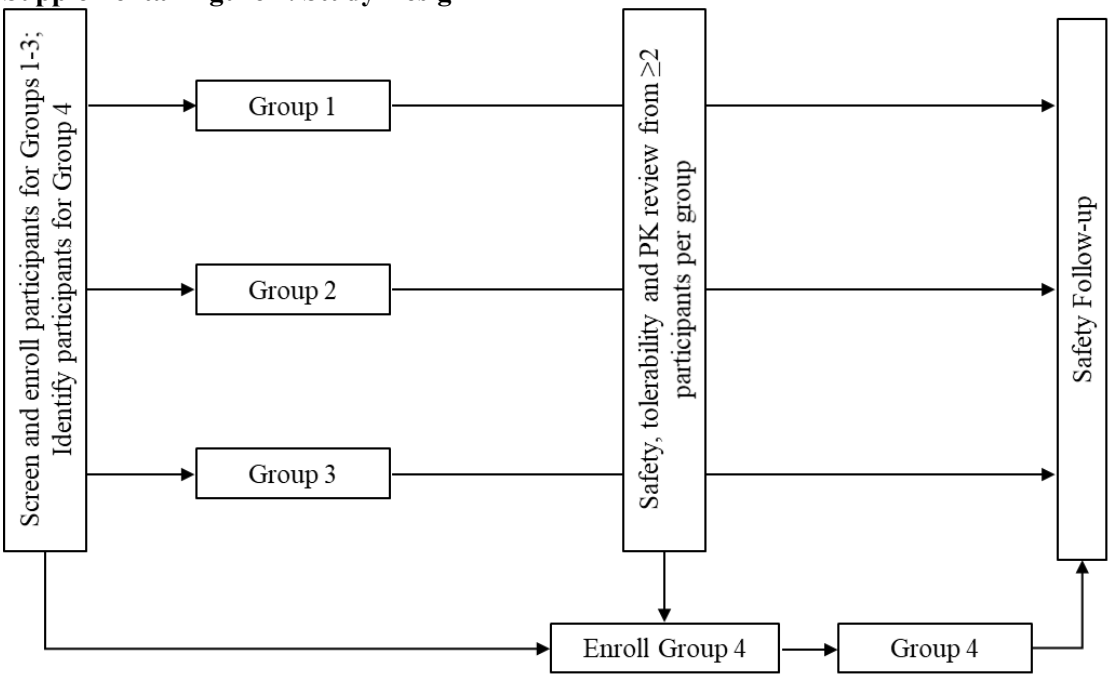
Hypoglycemic events will be recorded in the hypoglycemia module of the eCRF to allow for the collection of comprehensive safety information relating to these events. All episodes of severe hypoglycemia will additionally be reported as serious AEs.

Supplemental Table 1. Participant Groups based on Hepatic Impairment Status

Parameter	1 point	2 points	3 points
Serum Albumin (g/dL)	>3.5	2.8 to 3.5	<2.8
Total Bilirubin (mg/dL)	<2	2 to 3	>3
Prothrombin Time (sec. prolonged) or Prothrombin Time INR	<4	4 to 6	>6
	<1.7	1.7 to 2.3	>2.3
Ascites[a]	Absent	Slight	Moderate
Hepatic Encephalopathy[b]	None	1 or 2 Or current treatment with lactulose or neomycin or other antibiotics	3 or 4 Or continued encephalopathy while receiving treatment with lactulose and/or neomycin or other antibiotics

Child Pugh A (mild): 5 or 6 points; Child Pugh B (moderate): 7 to 9 points; Child Pugh C (severe): 10 to 15 points. Adapted from Child and Turcotte (1964)[1] and Pugh et al. (1973)[2]. [a]Absent: no detectable ascites, slight: no distension; ascites are only detectable by ultrasound examination, moderate: ascites causing moderate symmetrical distension of the abdomen. [b]Grade 0: normal consciousness, personality, neurological examination, electroencephalogram, Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cycles per second waves, Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves, Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves, Grade 4: unrousable coma, no personality/behavior, decerebrate, slow 2 to 3 cycles per second delta activity. Abbreviations: INR = international normalized ratio.

Supplemental Figure 1. Study Design



Note: Group assignments:

- Group 1: normal hepatic function (Control)
- Group 2: mild hepatic impairment (Child-Pugh A)
- Group 3: moderate hepatic impairment (Child-Pugh B)
- Group 4: severe hepatic impairment (Child-Pugh C)

SUPPLEMENTAL REFERENCES:

1. Child CG, Turcotte JG. Surgery and portal hypertension. The liver and portal hypertension. Edited by CG Child. Philadelphia: Saunders;1964:50-64
2. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. Br J Surg. 1973;60:646-654.
3. American Diabetes Association. Glycemic Targets. Sec 6. In Standards of Medical Care in Diabetes—2017. Diabetes Care. 2017;40(Suppl 1): S48-S56. Available at: http://care.diabetesjournals.org/content/40/Supplement_1/S48. Accessed June 04, 2018.
4. International Hypoglycaemia Study Group. Glucose concentrations of less than 3.0 mmol/L (54 mg/dL) should be reported in clinical trials: a joint position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2017;40(1):155-157.