| Clinical Study Protocol | |
|---|---|
| Drug Substance | Dapagliflozin + Saxagliptin |
| Study Code | D1683C00013 |
| Version | 3.0 |
| Date | 22 September 2020 |

# A prospective, multicenter, phase -IV study to assess the safety of fixed dose combination of dapagliflozin and saxagliptin in Indian Type 2 Diabetes Mellitus (T2D) patients.

**Sponsor:**

**AstraZeneca Pharma India Limited,**

**Block N1, 12th Floor, Manyata Embassy Busin s Park**

**Rachenahalli, Outer Ring Road, Bangalore 560045**



This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

## CLINICAL STUDY PROTOCOL SYNOPSIS

**A prospective, multicenter, phase -IV study to assess the safety of fixed dose combination of dapagliflozin and saxagliptin in Indian Type 2 Diabetes Mellitus (T2D) patients.**

Study centers: Approximately 8 Indian centres are planned for participation

Number of Subjects: 200 Indian T2DM (Type 2 Diabetes Mellitus) patients

### 1. Study objectives

#### a. Primary objective

| **Primary Objective:** | **Outcome Measure:** |
|---|---|
| To describe the adverse events profile of dapagliflozin + saxagliptin fixed dose combinations in Indian T2DM patients. | • Adverse Events (AEs) including Serious adverse events (SAEs), AEs leading to discontinuation (DAE) and adverse events of special interest (volume depletion, renal events, major hypoglycaemic events, fractures, urinary/genital tract infections, diabetic ketoacidosis, amputations and hospitalization for heart failure)<br>• Safety laboratory values<br>• Electrocardiogram (ECG)<br>• Vital Signs (pulse and BP)<br>• Physical examination |

#### b. Secondary objectives

| **Secondary Objective:** | **Outcome Measure:** |
|---|---|
| To describe the efficacy of dapagliflozin + saxagliptin fixed dose combination in Indian T2DM patients | • HbA1c change at week 24 compared to baseline<br>• Weight change at week 24 compared to baseline<br>• Systolic Blood Pressure (SBP) change at week 24 compared to baseline<br>• FPG change at week 24 compared to baseline |

## 2. SUBJECT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule. Subjects will be recruited from diabetes management centers under guidance of principal investigator after eligibility check.

### a. Inclusion criteria

For inclusion in the study subjects should fulfil the following criteria:

1. Provision of signed and dated, written informed consent prior to any study specific procedures according to local Indian procedure.

2. Male and female patients aged > 18 and above

3. Documented history of type 2 diabetes mellitus with HbA1c level >7.0% and ≤ 10% at screening visit

4. Patients who are on a stable dose of antidiabetic drugs (including on Metformin dose between 1000-2000mg) in the past 3 months

5. Female subjects must be 1 year post-menopausal, surgically sterile, or using an acceptable method of contraception (an acceptable method of contraception is defined as a barrier method in conjunction with a spermicide) for the duration of the study (from the time they sign consent) to prevent pregnancy. In addition, oral contraceptives, approved contraceptive implant, long-term injectable contraception, intrauterine device, or tubal ligation are allowed. Oral contraception alone is not acceptable; additional barrier methods in conjunction with spermicide must be used.

### b. Exclusion criteria

1. Known allergies or contraindication to the contents of the IP, dapagliflozin or saxagliptin tablets.

2. Active participation in another clinical study with IP and/or investigational device

3. For women only - currently pregnant (confirmed with positive pregnancy test) or breast-feeding.

4. Type 1 diabetes mellitus.

5. Treatment with a SGLT2 inhibitor, GLP-1 agonist or DPP4 inhibitors at Visit 1 or 2

6. Patients with moderate to severe renal impairment (eGFR persistently <45 mL/min/1.73 m2 by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula or end-stage renal disease (ESRD) or 'Unstable or rapidly progressing renal disease

7. Patients with severe hepatic impairment (Child-Pugh class C)

8. History of pancreatitis or pancreatic surgery

9. Patients with a history of any malignancy

10. Patients with any of the following CV/Vascular Diseases within 3 months prior to signing the consent at enrolment, as assessed by the investigator:

- Myocardial infarction.
- Cardiac surgery or revascularization (CABG/PTCA).
- Unstable angina.
- Transient ischemic attack (TIA) or significant cerebrovascular disease.
- Unstable or previously undiagnosed arrhythmia.

11. History of heart failure

12. Severe uncontrolled hypertension defined as systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg at any visit up to randomisation

13. History of diabetic ketoacidosis

14. Any acute/chronic systemic infections

15. Recurrent urogenital infections

16. Patients at risk for volume depletion as judged by the investigator

17. Any condition which, in the judgment of the Investigator, may render the patient unable to complete the study or which may pose a significant risk to the patient or patient suspected or with confirmed poor protocol or medication compliance

**Duration of treatment**

This is a 24 week open label single arm prospective study to characterize safety of Dapa/Saxa, 10 mg/5 mg fixed dose combination in Indian T2DM patients.

**Drug name, dosage and mode of administration**

Patients will be given once daily fixed dose combination of Dapa/Saxa 10 mg/5 mg administered orally at the same time of the day throughout the study. Every attempt should be made to maintain patients on designated therapy for 24 weeks of study duration.

Other Medicinal products:

Patient will continue receiving medicines other than study drug as per investigators discretion. Patient may be eligible to receive additional glucose lowering drug if he meets rescue criteria as details provided in rescue therapy section. Sponsor will not provide any other medicine except investigational product Dapa/Saxa 10 mg/5 mg.

**Statistical methods**

The primary objective of the study is to characterize the safety of fixed dose combination of Dapa/Saxa 10 mg/5 mg in Indian T2DM patients. This is a regulatory requirement to establish that FDCs are safe when used in combination in addition to the data available on individual components. As per the clinical data, based on investigator's assessment incidence of adverse events related to FDC[redacted]

Number and percentages of Incidence of adverse events will be presented, stratified by age/gender/baseline medications. Annualised event rate shall also be presented in addition to the incidence rate during the study. Mean change in HbA1C from baseline to 6 months for patients will be analysed using paired t test / Wilcoxon signed-rank test at 5% level of significance.

## MILESTONES

| | |
|---|---|
| Estimated date of first patient in | December 2020 |
| Estimated date of last patient in | September 2021 |
| Estimated date of last patient last visit | April 2022 |
| Estimated date of data base lock | June 2022 |
| Clinical study report preparation and submission | August 2022 |

# TABLE OF CONTENTS PAGE


| | | |
|---|---|---|
| | TITLE PAGE | 1 |
| | CLINICAL STUDY PROTOCOL SYNOPSIS | 2 |
| | TABLE OF CONTENTS | 6 |
| 1. | INTRODUCTION | 11 |
| 1.1 | Background and rationale for conducting this study | 11 |
| 1.2 | Rationale for study design, doses and control groups | 12 |
| 1.3 | Benefit/risk and ethical assessment | 12 |
| 1.4 | Study Design | 13 |
| 2. | STUDY OBJECTIVES | 14 |
| 2.1 | Primary objective | 14 |
| 2.2 | Secondary objectives | 14 |
| 2.3 | Safety objectives | 14 |
| 3. | SUBJECT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL | 14 |
| 3.1 | Inclusion criteria | 15 |
| 3.2 | Exclusion criteria | 15 |
| 3.3 | Subject enrolment and randomization | 16 |
| 3.4 | Procedures for handling incorrectly enrolled or randomized subjects | 16 |
| 3.5 | Restrictions | 17 |
| 3.6 | Discontinuation of investigational product | 17 |
| 3.7 | Criteria for withdrawal | 18 |
| 3.7.1 | Screen failures | 18 |
| 3.7.2 | Withdrawal of the informed consent | 19 |
| 3.8 | Discontinuation of the study | 19 |
| 4. | STUDY PLAN AND TIMING OF PROCEDURES | 19 |
| 4.1 | Screening/Enrolment period | 21 |
| 4.2 | Treatment period | 21 |
| 4.3 | Follow-up period | 21 |
| 5. | STUDY ASSESSMENTS | 21 |

5.1 Efficacy assessments ..... 21
5.2 Safety assessments ..... 22
5.3 Other assessments ..... 23
6. SAFETY REPORTING AND MEDICAL MANAGEMENT ..... 27
6.1 Definition of adverse events ..... 27
6.2 Definitions of serious adverse event ..... 27
6.3 Recording of adverse events ..... 27
6.3.1 Time period for collection of adverse events ..... 27
6.3.2 Follow-up of unresolved adverse events ..... 28
6.3.3 Variables ..... 28
6.3.4 Causality collection ..... 29
6.3.5 Adverse events based on signs and symptoms ..... 29
6.3.6 Adverse events based on examinations and tests ..... 29
6.4 Reporting of serious adverse events ..... 30
6.5 Overdose ..... 30
6.6 Pregnancy ..... 30
6.6.1 Maternal exposure ..... 31
6.7 Medication Error ..... 31
7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS ..... 32
7.1 Identity of investigational product(s) ..... 32
7.2 Dose and treatment regimens ..... 33
7.3 Labelling ..... 33
7.4 Storage ..... 33
7.5 Compliance ..... 33
7.6 Accountability ..... 33
7.7 Concomitant and other treatments ..... 33
7.7.1 Other concomitant treatment ..... 34
8. STATISTICAL ANALYSES BY ASTRAZENECA ..... 34
9. STUDY AND DATA MANAGEMENT BY ASTRAZENECA ..... 35
9.1 Training of study site staff ..... 35
9.2 Monitoring of the study ..... 35
9.2.1 Source data ..... 36
9.2.2 Study agreements ..... 36
9.2.3 Archiving of study documents ..... 36
9.3 Study timetable and end of study ..... 36

9.4 Data management by AstraZeneca ..... 36
10. ETHICAL AND REGULATORY REQUIREMENTS ..... 37
10.1 Ethical conduct of the study ..... 37
10.2 Subject data protection ..... 37
10.3 Ethics and regulatory review ..... 37
10.4 Informed consent ..... 38
10.5 Changes to the Clinical Study Protocol and Informed Consent Form ..... 38
10.6 Audits and inspections ..... 39
11. LIST OF REFERENCES ..... 40
12. SIGNATURES ..... 48

## LIST OF TABLES

Table 1 Study Plan detailing the procedures ..... 19
Table 2 Laboratory Safety Variables ..... 22

## LIST OF FIGURE

Figure 1 *Study flow chart* ..... 13

## LIST OF APPENDICES

Appendix A Additional Safety Information ..... 41
Appendix B Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law ..... 43

# LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

| **Abbreviation or special term** | **Explanation** |
|---|---|
| AE | Adverse Event |
| ALP | Alkaline phosphatase |
| AST | Aspartate aminotransferase |
| BMI | Body Mass Index |
| CABG/PTCA | coronary artery bypass grafting/percutaneous transluminal coronary angioplasty |
| CK | Creatine kinase |
| CRF | Case Report Form (electronic/paper) |
| CSA | Clinical Study Agreement |
| CSR | Clinical Study Report |
| DAE | Discontinuation of Investigational Product due to Adverse Event |
| DKA | Diabetic ketoacidosis |
| EC | Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC) |
| ECG | Electrocardiogram |
| eGFR | Estimated Glomerular Filtration |
| ESRD | End Stage Renal Disease |
| FBG | Fasting Blood Glucose |
| FDC | Fixed Dose Combination |
| FPG | Fasting Plasma Glucose |
| GCP | Good Clinical Practice |
| Hb | Hemoglobin |
| HbA1c | Glycated haemoglobin |
| ICH | International Conference on Harmonisation |
| International Coordinating investigator | If a study is conducted in several countries the International Coordinating Investigator is the Investigator coordinating the investigators and/or activities internationally. |

| **Abbreviation or special term** | **Explanation** |
|---|---|
| IP | Investigational Product |
| IVRS | Interactive Voice Response System |
| IWRS | Interactive Web Response System |
| LIMS | Laboratory Information Management System |
| LSLV | Last Subject Last Visit |
| NYHA | New York Heart Association |
| OAE | Other Significant Adverse Event |
| PI | Principal Investigator |
| PPG | Post prandial Glucose |
| SAE | Serious Adverse Event |
| SBP | Systolic Blood Pressure |
| SGLT | Sodium Glucose Co transporter |
| SU | Sulphonylurea |
| T2DM | Type 2 Diabetes Mellitus |
| TIA | Transient Ischemic Attack |
| UPT | Urine Pregnancy Test |
| UTI | Urinary Tract Infection |

# 1. INTRODUCTION

## 1.1 Background and rationale for conducting this study

Diabetes is now an endemic to India with an estimated 72.9 million Indians living with this condition and currently at second position after China in world.(1) Metformin is used as 1st line oral anti- diabetic drug in most cases. Sulfonylureas (SU) are used as frequent first add-on after failure of metformin monotherapy.(2) Approximately 67% patients fail to achieve <7% HbA1c goal.(3) This emphasise need for newer treatment options. Sodium Glucose Co-transporter 2 (SGLT2) inhibitors are a newer class of therapy which has a lower incidence of hypoglycaemia and in addition helps in weight and BP reduction. Saxagliptin is a DPP (Dipeptidyl Peptidase)-4 inhibitor. The said FDC are approved worldwide basis available data on study done with individual components. Local Health Authority in India has mandated to submit clinical data on FDC post marketing authorization even if individual components are approved for use. This study is addressing this unmet need to generate local data on FDC in Indian T2DM patients.

Dapagliflozin (marketed under the trade name FORXIGA®) is a reversibly-competitive, highly selective and orally active inhibitor of SGLT2, the major transporter responsible for renal glucose reabsorption. Dapagliflozin's mechanism of action is different from, and complementary to, the mechanisms of action of currently available diabetic medicines, resulting in the direct and insulin-independent elimination of glucose by the kidney.(4) Further, as SGLT2 is almost exclusively expressed in the kidney, the highly selective nature of dapagliflozin minimizes the risk of off target (ie, non-kidney) effects. As such, dapagliflozin offers an important additional strategy for improving glycaemic control in patients with T2DM.

Saxagliptin is a highly potent, selective, reversible, and competitive DPP-4 inhibitor. By inhibiting DPP-4, saxagliptin potentiates active endogenous GLP-1 concentrations, augmenting the physiological mechanism of insulin secretion and suppressing glucagon release, thereby reducing PPG and FPG levels in patients with T2D. Saxagliptin is approved by the US and EU for the treatment of T2D and in Phase III trials, has effectively reduced HbA1c in patients with inadequately controlled T2D on a stable dose of metformin, SUs, or thiazolidinedione, and has favorable safety and tolerability profiles.(5)

QTERN®(dapagliflozin/saxagliptin) combines dapagliflozin and saxagliptin in a fixed-dose combination tablet designed to be administered once daily. The combination of these drugs, with complementary mechanism of actions, and with clinically important effects on HbA1c, FBG, PPG and weight loss, is expected to form a clinically relevant paradigm for achieving and maintaining glycaemic control in patients who have difficulty with maintaining glycaemic control on diet/lifestyle, metformin alone, or in combination with other oral antidiabetic drugs or insulin. QTERN is indicated as an adjunct to diet and exercise in patients whose glycemic control is inadequate with dapagliflozin or who are already treated with dapagliflozin and saxagliptin.(6)

An FDC product combining dapagliflozin and saxagliptin has the potential for providing patients with T2DM with a new treatment option that may improve compliance by reducing tablet burden than the individual tablets administered separately.(7)

## 1.2 Rationale for study design, doses and control groups

This study is designed to generate local Indian safety evidence for Dapa/Saxa 10 mg/5 mg FDC as per local health regulatory request. Both dapagliflozin and saxagliptin are approved in India for clinical use as individual therapy for managing T2DM patients. This study is to provide safety data when both molecules are administered as FDC formulation. This is a single arm study and no control group is planned.

## 1.3 Benefit/risk and ethical assessment

### Risk category

Considering saxagliptin and dapagliflozin's mechanism of action, the previous clinical experience with both molecules, the study's design features (including the inclusion, exclusion, and is continuation criteria), and the planned safety procedures, participation in this study presents a minimal and thus acceptable risk to the individual subjects that will be included. Dapagliflozin and saxagliptin both have global and Indian market approval and have been administered to thousands of T2DM patients.

### Potential Risk

The safety and efficacy of the 10 mg dapagliflozin/5 mg saxagliptin fixed-dose combination was evaluated in three phase 3, randomised, double-blind, active/placebo-controlled clinical trials in 1169 adult subjects with type 2 diabetes mellitus. One trial with saxagliptin and dapagliflozin added concomitantly to metformin was conducted for 24 weeks. Two add-on therapy trials, which added either dapagliflozin to saxagliptin plus metformin or saxagliptin to dapagliflozin plus metformin, were also conducted for 24 weeks followed by a 28week extension treatment period. The safety profile of the combined use of saxagliptin and dapagliflozin in these trials for up to 52 weeks was comparable to the safety profiles for the mono-components.

Patients at risk for volume depletion due to co-existing conditions or concomitant medications, such as loop diuretics should have careful monitoring of their volume status, as judged by the investigator.

In addition, all subjects will continue taking similar dose of their antidiabetic medications.

No study procedure will put subjects at a risk beyond those ordinarily encountered during the performance of routine medical examinations or routine tests.

### Potential benefits to subjects

All subjects will receive active antihyperglycemic therapy of dapagliflozin /saxagliptin as fixed dose combination; global studies have established the the risk-benefit profile for the individual components, but the safety for the fixed dose combination needs to be confirmed in an Indian phase IV study. In this study, the doses of Dapa/Saxa 10 mg/5 mg FDC was chosen to provide

efficacy in reducing hyperglycemia while mitigating the potential for AEs, based on previous clinical experience. In addition, dapagliflozin decrease body weight (or prevent weight gain) as well as lower blood pressure (BP) especially in subjects with elevated baseline BP.

Subjects are also expected to receive benefit in the form of increased medical care/attention when participating in study procedures, which includes at least 4 clinic visits with at least 4 physical examinations over the 24-week study.

**Informed consent**

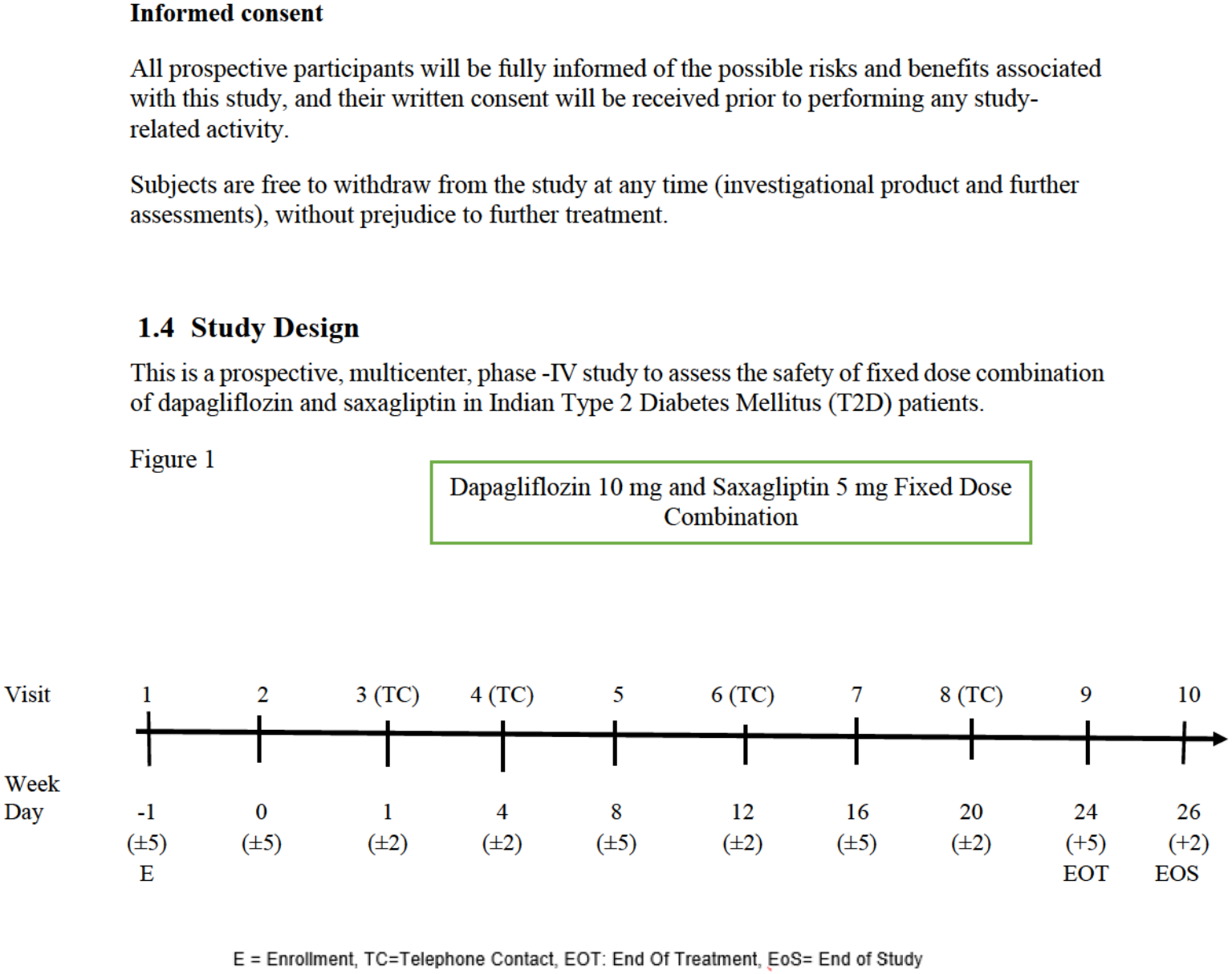
All prospective participants will be fully informed of the possible risks and benefits associated with this study, and their written consent will be received prior to performing any study-related activity.

Subjects are free to withdraw from the study at any time (investigational product and further assessments), without prejudice to further treatment.

## 1.4 Study Design

This is a prospective, multicenter, phase -IV study to assess the safety of fixed dose combination of dapagliflozin and saxagliptin in Indian Type 2 Diabetes Mellitus (T2D) patients.

Figure 1




E = Enrollment, TC=Telephone Contact, EOT: End Of Treatment, EoS= End of Study

# 2 STUDY OBJECTIVES

## 2.1 Primary objective

| **Primary Objective:** | **Outcome Measure:** |
|---|---|
| To describe the adverse events profile of dapagliflozin + saxagliptin fixed dose combinations in Indian T2DM patients at 24 weeks. | • Adverse Events (AEs) including Serious adverse events (SAEs), AEs leading to discontinuation (DAE) and adverse events of special interest (volume depletion, renal events, major hypoglycaemic events, fractures, urinary/genital tract infections diabetic ketoacidosis, amputations and hospitalization for heart failure)<br>• Safety laboratory values<br>• Electrocardiogram (ECG)<br>• Vital Signs (pulse and BP)<br>• Physical examination |

## 2.2 Secondary objectives

| **Secondary Objective:** | **Outcome Measure :** |
|---|---|
| To describe the efficacy of dapagliflozin + saxagliptin fixed dose combination in Indian T2DM patients at 24 weeks | • HbA1c change at week 24 compared to baseline<br>• Weight change at week 24 compared to baseline<br>• Systolic Blood Pressure (SBP) change at week 24 compared to baseline<br>• FPG change at week 24 compared to baseline |

## 2.3 Safety objectives

See section 2.1

# 3 SUBJECT SELECTION, ENROLMENT, RANDOMISATION, RESTRICTIONS, DISCONTINUATION AND WITHDRAWAL

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule. Subjects will be recruited from diabetes management centers under guidance of principal investigator after eligibility check.

## 3.1 Inclusion criteria

For inclusion in the study subjects should fulfil the following criteria:

1. Provision of signed and dated, written informed consent prior to any study specific procedures according to local Indian procedure.

2. Male and female patients aged > 18 and above

3. Documented history of type 2 diabetes mellitus with HbA1c level >7.0% and ≤ 10% at screening visit

4. Patients who are on a stable dose of antidiabetic drugs (including on Metformin dose between 1000-2000mg) in the past 3 months

5. Female subjects must be 1 year post-menopausal, surgically sterile, or using an acceptable method of contraception (an acceptable method of contraception is defined as a barrier method in conjunction with a spermicide) for the duration of the study (from the time they sign consent) to prevent pregnancy. In addition, oral contraceptives, approved contraceptive implant, long-term injectable contraception, intrauterine device, or tubal ligation are allowed. Oral contraception alone is not acceptable; additional barrier methods in conjunction with spermicide must be used.

## 3.2 Exclusion criteria

1. Known allergies or contraindication to the contents of the IP, dapagliflozin or saxagliptin tablets.

2. Active participation in another clinical study with IP and/or investigational device
3. For women only - currently pregnant (confirmed with positive pregnancy test) or breast-feeding.

4. Type 1 diabetes mellitus.

5. Treatment with a SGLT2 inhibitor, GLP-1 agonist or DPP4 inhibitors at Visit 1 or 2

6. Patients with moderate to severe renal impairment (eGFR persistently <45 mL/min/1.73 m2 by CKD-EPI formula, or end-stage renal disease (ESRD) or 'Unstable or rapidly progressing renal disease

7. Patients with severe hepatic impairment (Child-Pugh class C)

8. History of pancreatitis or pancreatic surgery

9. Patients with a history of any malignancy

10. Patients with any of the following CV/Vascular Diseases within 3 months prior to signing the consent at enrolment, as assessed by the investigator:

- Myocardial infarction.
- Cardiac surgery or revascularization (CABG/PTCA).
- Unstable angina.
- Transient ischemic attack (TIA) or significant cerebrovascular disease.
- Unstable or previously undiagnosed arrhythmia.

11. History of heart failure

12. Severe uncontrolled hypertension defined as systolic blood pressure ≥180 mm Hg and/or diastolic blood pressure ≥110 mm Hg at any visit up to randomisation

13. History of diabetic ketoacidosis

14. Any acute/chronic systemic infections

15. Recurrent urogenital infections

16. Patients at risk for volume depletion as judged by the investigator

17. Any condition which, in the judgment of the Investigator, may render the patient unable to complete the study or which may pose a significant risk to the patient or patient suspected or with confirmed poor protocol or medication compliance

## 3.3 Subject enrolment and randomization

This is a single arm open label study. Each eligible patient recruited in study will be provided with unique identification number.

Investigator(s) should keep a record, the subject screening log, of subjects who entered pre-study screening.

The Investigator(s) will:

1. Obtain signed informed consent from the potential subject before any study specific procedures are performed.

2. Assign potential subject a unique enrolment number.

3. Determine subject eligibility. See Section 3.1 and 3.2.

If a subject withdraws from participation in the study, then his/her enrolment code cannot be reused.

## 3.4 Procedures for handling incorrectly enrolled or randomized subjects

Subjects who fail to meet the eligibility criteria should not, under any circumstances, be enrolled or receive study medication. There can be no exceptions to this rule. Subjects who are enrolled, but subsequently found not to meet all the eligibility criteria must not be initiated on treatment, and must be withdrawn from the study.

Where a subject does not meet all the eligibility criteria but is incorrectly started on treatment, the Investigator should inform the AstraZeneca study physician immediately, and a discussion should occur between the AstraZeneca study physician and the investigator regarding whether to continue or discontinue the subject from treatment. The AstraZeneca study physician must ensure all decisions are appropriately documented.

## 3.5 Restrictions

- Subjects must be in a fasting state at least 8 hours prior to study visit (however, drinking water is allowed). Permitted medications may be taken with water only.

- Subjects must make every attempt to adhere to the dietary and physical activity changes and goals as discussed with the Investigator(s).

- Women of child-bearing potential must immediately contact the Investigator if they suspect they might be pregnant and if they have changed, or plan to change their birth control method.

- If a subject arrives for a visit without having followed the above instructions, the entire visit should be rescheduled (within the allowed time-window, if possible).

## 3.6 Discontinuation of investigational product

Every attempt will be made to retain subject on study medication. Subjects who discontinue study medication during the treatment period will be performed the End of treatment visit (Visit no: 9) and will be contacted for 2 weeks later and asked for the presence of any AEs.

Subjects are free to discontinue investigational product at any time, without prejudice to further treatment and follow up.

**General discontinuation criteria:**

1.Voluntary discontinuation by the subject who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment
2. Risk to subjects as judged by the investigator and/or AstraZeneca
3. Severe non-compliance to protocol as judged by the investigator and/or AstraZeneca
4. Incorrectly enrolled subjects (See Section 5.3)

5. AEs, ie, any clinical AE, laboratory abnormality or intercurrent illness which, in the opinion of the investigator, indicates that continued participation in the study is not in the best interest of the subject
6. Major and/or frequent hypoglycemic events; If more than one event of severe hypoglycemia, defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behaviour, with a capillary or plasma glucose value <3 mmol/L (<54 mg/dL), and prompt recovery after glucose or glucagon administration occurs, or if the investigators decides that current treatment poses the subject at risk of either repeated hypoglycemic events or severe hypoglycemia.
7. Consider temporary interrupting dapagliflozin if DKA is suspected. The patient should be promptly evaluated. If DKA is confirmed, investigational product(s) should be discontinued permanently.
8. Acute renal insufficiency or worsened chronic renal insufficiency based on repeat eGFR values (eGFR<45 mL/minute/1.73m2). The re-test should be scheduled within 4 days, whenever possible.If an unexpected, acute decline in kidney function is observed, the patient should be promptly evaluated. Volume depletion, hypotension, inter-current medical problems and concomitant drugs may cause increases in blood creatinine. Urinary tract infection and urinary obstruction should be considered. Several drugs may cause a decline in kidney function, especially non-steroidal anti-inflammatory drugs (NSAID) and certain antibiotics such as trimethoprim. If any drug is suspected of causing or contributing to worsening kidney function, their use should be re-considered.
9. Pregnancy confirmed by a positive pregnancy test or otherwise verified. An AZ representative should be notified if a patient becomes pregnant during the course of the study.

**Procedures for discontinuation of a subject from investigational product**

A subject that discontinues treatment will always be asked about the reason(s) for discontinuation and the presence of any AEs. The Principal Investigator/sub-investigator will perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the subject. They will also immediately inform AstraZeneca of the withdrawal.

If a subject is withdrawn from study, see Section 3.7

## 3.7 Criteria for withdrawal from study

### 3.7.1 Screen failures

Screening failures are subjects who do not fulfil the eligibility criteria for the study, and therefore must not be initiated on study treatment. These subjects should have the reason for study withdrawal recorded as ‘Screen failure’ (the potential subject who does not meet one or more criteria required for participation in a trial).

### 3.7.2 Withdrawal of the informed consent

Subjects are free to withdraw from the study at any time (investigational product and further assessments), without prejudice to further treatment.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). AEs will be followed up (See Section 6.4); subject diaries, glucometer and study drug should be returned by the subject.

If a subject withdraws from participation in the study, then his/her enrolment code cannot be reused. Withdrawn subjects will not be replaced.

## 3.8 Discontinuation of the study

The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that meet individual stopping criteria or are otherwise considered significant

Regardless of the reason for termination, all data available for the subject at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests.

# 4 STUDY PLAN AND TIMING OF PROCEDURES

This is a 24-week open label prospective study. After eligibility check as per criteria mentioned in section 3.1 and 3.2 patients, will be recruited in the study and procedures as mentioned in below table will be performed at various scheduled visits.

Table 1

| Assessments | Visit 1 | Visit 2 | Visit 3# | Visit 4# | Visit 5 | Visit 6# | Visit 7 | Visit 8# | Visit 9 (EOT) | Visit 10 (EoS) |
|---|---|---|---|---|---|---|---|---|---|---|
| | Enrolment* (-1 wk) | (0 Wk) | (1 Wk) | (4 wk) | (8 wk) | (12 wk) | (16 wk) | (20 wk) | (24 wk) | (26 wk) |
| Window period (Days) | (±5) | (±5) | (±2) | (±2) | (±5) | (±2) | (±5) | (±2) | (+5) | (+2) |
| Informed Consent | X | | | | | | | | | |
| Physical Exam | X | X | | | X | | X | | X | X |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Vital Signs | X | X | | | X | | X | | X | X |
| Eligibility check | X | X | | | | | | | | |
| HbA1c | X | X | | | X | | X | | X | X |
| Fasting Plasma Glucose (FPG)** | | X | | | X | | X | | X | X |
| Weight & Height | | X | | | X | | X | | X | X |
| Waist circumference | | X | | | X | | X | | X | X |
| BMI (Body Mass Index) | | X | | | X | | X | | X | X |
| Blood Pressure | | X | | | X | | X | | X | X |
| Safety labs | X | X | | | X | | X | | X | X |
| ECG | | X | | | | | X | | X | X |
| AE assessment | | X | X | X | X | X | X | X | X | X |
| Urinalysis | X | X | | | X | | X | | X | X |
| UPT (WOCBP) | X | X | | | X | | X | | X | X |
| IP dispensation | | X | | | X | | | | | |
| IP accountability | | X | X | X | X | X | X | | X | X |

*enrolment and Visit 2 can coincide to enter patient into the study, #telephonic visit

** Subjects must be in a fasting state at least 8 hours prior to study visit.

## 4.1 Screening/Enrolment period

*Procedures will be performed according to the Study Plan.*

Eligible patients will be enrolled into the study and unique identification number will be provided to each patient.

## 4.2 Treatment period

*Descriptions of the procedures for this period are included in the Study Plan.*

## 4.3 Follow-up period

*Descriptions of the procedures for this period are included in the Study Plan.*

# 5 STUDY ASSESSMENTS

*Electronic* Case Report Forms (eCRF) will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRF as specified in the Clinical Study Protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, e*CRFs include:* timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

## 5.1 Efficacy assessments

### 5.1.1 Glycosylated Haemoglobin -HbA1c

HbA1c is a well-established measure of glycemic efficacy and considered to be an acceptable secondary endpoint the assessment for the determination of glycemic efficacy. HbA1c will be analysed by a central laboratory according to the procedures described in the Laboratory Manual which will be distributed to each study site during site initiation.

.

### 5.1.2 Fasting Plasma Glucose (FPG)

FPG is a well-established measure of glycemic efficacy and considered to be an acceptable secondary endpoint.

### 5.1.3 Weight and height

The subject's weight will be recorded in kilogram (kg) to one decimal place, on a fasting stomach with light clothing and no shoes. The subject's height will be recorded in centimetres, with no shoes. All readings should be recorded as accurately as possible and the same scale should be used for all assessments for a given subject.

## 5.2 Safety assessments

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

### 5.2.1 Laboratory safety assessments

Blood samples shall be collected and processed as per the local affiliated laboratory criteria.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs and other safety variables will only be reported as AEs if they are clinically significant, fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product, or require the subject to receive specific corrective therapy. If a deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign/symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Any new or aggravated clinically relevant abnormal medical finding at a physical examination or ECG evaluation as compared with the baseline assessment will be reported as an AE.

Clinically relevant deterioration in non-protocol-mandated measurements will be reported as AE(s).

Wherever possible the reporting investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low haemoglobin value).

The following laboratory variables will be measured:

**Table 2 Laboratory Safety Variables**

| **Haematology/Haemostasis (whole blood)** | **Clinical Chemistry (serum or plasma)** |
|---|---|
| B- Hematocrit | S/P-Creatinine |
| B-Leukocyte count | S/P-Bilirubin, total |
| B-Leukocyte differential count (absolute count) | S/P-Alkaline phosphatise (ALP) |
| B-Platelet count | S/P-Aspartate transaminase (AST) |
| B - Haemoglobin (Hb) | S/P-Alanine transaminase (ALT) |
| **Urinalysis** (dipstick) | S/P-Albumin |
| U-Hb/Erythrocytes/Blood | S/P-Potassium |
| U-Protein/Albumin | S/P-Calcium, total |
| U-Glucose | S/P-Sodium |
| | S/P-Creatine kinase (CK) |

*The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.3*

**NB.** In case a subject shows an AST **or** ALT ≥3xULN **or** total bilirubin ≥2xULN please refer to Appendix B 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions.

### 5.2.2 Physical examination

A brief physical examination should include the cardiovascular system, lungs, abdomen, and extremities, and any organ system pertinent to the subject's signs, symptoms, or AEs. The subject should always be evaluated for the presence of oedema.

### 5.2.3 ECG

**Resting 12-lead ECG**

A 12-lead ECG will be taken after the subject has been lying down resting. The ECG will be evaluated by the investigator and entered as 'Normal' or 'Abnormal' in the eCRF. If the ECG is evaluated as "Abnormal" the investigator should document the specific abnormality.

### 5.2.4 Vital signs

Vital signs will be measured and recorded during each on site visit through the study duration.

#### 5.2.4.1 Pulse and blood pressure

Pulse and BP readings should be taken while the subject is in a comfortable seated position with the arm supported at the level of the heart. All readings should be recorded. A standard mercury sphygmomanometer with a standardised cuff adapted to the size of the subject's arm is recommended.

## 5.3 Other assessments

Self-monitored blood glucose readings and hypoglycemic events will be collected in a subject diary and reviewed by the investigator at each visit.

### 5.3.1 Hypoglycemic events

Subject self-monitoring of FBG is performed in order to reduce the risks associated with prolonged hyperglycemia and to confirm symptoms of hypoglycemia. Subjects will be asked to perform self-monitoring of FBG using glucometers provided by AstraZeneca. The subjects will receive instructions for the use of the glucometer according to the manufacturer's instructions.

FBG should be self-monitored once every week between Visit 2 and 10 The results should be recorded in the subject diary, which will be collected and reviewed by the study personnel at each visit starting with Visit 3; record will be stored in the investigator study file.
The memory of the glucometer should be reviewed and compared with the readings in the subject's diary. The glucose values should be reviewed by the study personnel to identify any unusually high or low values, and to confirm that self-monitoring was performed by the subject.
If fingerstick glucose values are discordant with central laboratory results or with clinical symptoms, the subject's glucometer should be tested and the glucometer instructions should be re-reviewed with the subject.
If self-monitored FBG is above 240 mg/dL then subject should repeat the FBG on the same day. If the second FBG value is above 240 mg/dL, the subject should contact the study centre and be scheduled for a central laboratory FBG measurement within one week.

If central laboratory values show similar values, the subject should be discontinued (if there is no obvious explanation, i.e. infections) and treated according to local practice.
A separate section in the eCRF will be used to document all reported episodes of hypoglycaemia. The subjects will be asked to check their blood glucose if they develop symptoms suggestive of hypoglycemia and to record specific symptoms in the subject diary. The Investigator is responsible for questioning the subject about all symptoms reported in the diary and for determining if they meet the clinical definition of hypoglycemia. Only symptoms and/or blood glucose values that meet the definition of hypoglycamia should be reported on the hypoglycemia eCRF pages.

A hypoglycemic event can be either:

- Symptoms of hypoglycemia with a low blood glucose reading (<63 mg/dL)
- A low blood glucose reading (<63 mg/dL [<3.5 mmol/L])
- Symptoms of hypoglycemia without a blood glucose reading

Hypoglycemic episodes or discontinuation due to hypoglycemia should not be reported on the AE eCRF page unless the event fulfils protocol criteria for a SAE (see Section 6.4). In this case, an SAE must be reported in addition to the hypoglycemia eCRF pages for hypoglycemia.

Symptoms suggestive of hypoglycemia with an associated capillary or plasma glucose value ≥63 mg/dL (≥3.5 mmol/L), should be recorded as an AE rather than as a hypoglycemic event. If the physician does not consider the glucose measurement to be accurate, however, the event should be documented as a hypoglycemic event in the hypoglycemia eCRF.

For the evaluation of hypoglycemic events, this study will use the definitions provided in the Committee for propritery medicinal product (CPMP) guidance on clinical investigation of medicinal products in the treatment of diabetes
mellitus, as described below.

- Major hypoglycemic events, defined as symptomatic events requiring external assistance due to severe impairment in consciousness or behaviour, with a capillary or plasma glucose value <54 mg/dL (<3.0 mmol/L) if available, and prompt recovery after glucose or glucagon administration.

- Minor hypoglycemic event, defined as either a symptomatic episode with a capillary or plasma glucose measurement <63 mg/dL (<3.5 mmol/L) regardless of need for external assistance or an asymptomatic capillary or plasma glucose measurement below 63 mg/dL (3.5 mmol/L), that does not qualify as a major episode
- Events suggestive of hypoglycemia, defined as a symptomatic event without a confirmatory blood glucose measurement.

Data to be collected for each hypoglycemic event:

- Date and time of episode (start and stop)
- Whether the subject was sleeping at the time of the event
- Whether symptoms were present, and list of symptoms
- Possible contributing factors
- Whether a fingerstick value was obtained, and if so, the plasma glucose value
- Whether intervention was needed for recovery
- How the episode was treated
- Whether recovery was prompt after treatment
- Time of last anti-diabetic agents administration
- Time of last meal and its contents

The subject diary will be reviewed and the hypoglycemic event data will be transcribed into the eCRFs at each clinical visit. A new diary for the next period will be handed over to the subject if needed. If a major hypoglycemic event or more than one minor event has occurred since the previous visit, the subject should contact the investigator.

### 5.3.2 Urinary and Genital Infections

The following is presented to assist in the classification and management of infections of the urinary and genital tracts in studies with dapagliflozin. It is not intended to supplant investigators' clinical judgement.

**Urinary Tract Infections**

If based on the suggestive signs or symptoms (dysuria, urgency or frequency of urination, suprapubic or perineal discomfort, flank, back, or abdominal pain, costovertebral angle tenderness, nausea, vomiting, fever, chills, or sepsis) the investigator believes that a urinary tract infection may be present, urine cultures (in a local laboratory) should be obtained to confirm a presumptive diagnosis of cystitis, urinary tract infection, pyelonephritis, or prostatitis. Mid-stream clean catch urine collections are recommended. Clinical judgement and local standards of care should apply to decisions concerning therapy. Any treatment needs to be documented in the eCRF.

Between scheduled visits, subjects may experience novel signs or symptoms that are potentially indicative of urinary or a genital tract infection. The subject should contact the investigator by telephone. An unscheduled visit will be planned as soon as possible, preferably within 24 h. The investigator will take the subject's recent history, a midstream urine sample will be obtained for urine analyses and a mandated urine culture, and it is also recommended that a genital swab is done, if indicated. Analyses and culture(s) are to be performed at the local laboratory. The

investigator will follow local guidelines to recommend treatment for urinary tract infection or genital tract infection.

Investigational product should be temporary stopped in subjects with clinical evidence of upper urinary tract infection (eg, pyelonephritis) or presumed urosepsis until the course of treatment of the infection has been completed and clinical recovery has occurred. It is recommended that a follow-up urine culture is obtained within 7 days of clinical recovery from a documented UTI. Whether additional therapy is prescribed because of culture results should be determined by Investigator judgement.

**Genital Tract Infections**

The diagnosis of vaginitis, vulvovaginitis, vulvitis or balanitis can be made based on physical examinations, culture of secretions or a therapeutic response to treatment of fungal or other vaginal pathogens. A urine culture is not required for diagnosis of genital infections if the diagnosis is confirmed by physical examination, culture of secretions, or a therapeutic response to treatment of fungal or other vaginal pathogens. Any treatment needs to be documented in the eCRF.

### 5.3.3 Volume Depletion

Patients at risk of volume depletion due to co-existing conditions or concomitant medications should have careful monitoring of their volume status as judged by the Investigator. Events of volume depletion include dehydration, hypovolemia, or hypotension.

### 5.3.4 Diabetic ketoacidosis

Patients treated with study medication who present with signs and symptoms consistent with ketoacidosis, including nausea, vomiting, abdominal pain, malaise and shortness of breath, should be assessed for ketoacidosis, even if blood glucose levels are < 14 mmol/l (250 mg/dl). If ketoacidosis is suspected, discontinuation or temporary interruption of study drug should be considered and the patient should be promptly evaluated.

### 5.3.5 Renal Events

Renal events are defined by doubling of serum creatinine, dialysis and renal transplantation

### 5.3.6 Hospitalization for Heart Failure

Patients who present with symptoms of heart failure and get hospitalized for more than 24 hours need to evaluated further to understand the reason for new or worsening of heart failure symptoms.

HF is defined as an event that meets all of the following criteria:

- Admitted to the hospital with a primary diagnosis of HF
- Length-of-stay in hospital extends for at least 24 hours
- Exhibits documented new or worsening symptoms due to HF on presentation, including at least one of the following:
  - Dyspnea (dyspnea with exertion, dyspnea at rest, orthopnea, paroxysmal nocturnal dyspnea); decreased exercise tolerance; fatigue; other symptoms of worsened end-organ perfusion or volume overload
- Physical examination finding considered to be due to HF, including new or worsened:
  - Peripheral edema
  - Increasing abdominal distension or ascites (in absence of primary hepatic disease)
  - Pulmonary rales/crackles/crepitations
  - Increased jugular venous pressure and/or hepatojugular reflux
  - S3 gallop
  - Clinically significant or rapid weight gain thought to be related to fluid retention
- Laboratory evidence of new or worsening HF, if obtained within 24 hours of presentation, including:
  - Increased BNP/N-terminal pro-BNP (NT-proBNP) concentrations consistent with decompensation of HF (such as BNP > 500 pg/mL or NT-proBNP > 2,000 pg/mL),
  - Radiological evidence of pulmonary congestion
  - Non-invasive or invasive diagnostic evidence of clinically significant elevated left- or right-sided ventricular filling pressure or low cardiac output.
    OR
  - Invasive diagnostic evidence with right heart catherization showing a pulmonary capillary wedge pressure (pulmonary artery occlusion pressure) ≥18 mm Hg, central venous pressure ≥ 12 mm Hg, or a cardiac index < 2.2 L/min/m2

- Receives initiation or intensification of treatment specifically for HF, including at least 1 of the following:
  - Augmentation in oral diuretic therapy
  - Intravenous diuretic, inotrope, or vasodilator therapy
  - Mechanical or surgical intervention, including:
    - Mechanical circulatory support (e.g., intra-aortic balloon pump, ventricular assist device)
    - Mechanical fluid removal (e.g., ultrafiltration, hemofiltration, dialysis)

# 6 SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

## 6.1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a subject or clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no study treatment has been administered.

## 6.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix A to the Clinical Study Protocol.

## 6.3 Recording of adverse events

### 6.3.1 Time period for collection of adverse events

Adverse Events will be collected throughout the treatment period and including the follow-up period of one week after end of study. SAEs will be recorded from the time of informed consent.

### 6.3.2 Follow-up of unresolved adverse events

Any AEs that are unresolved at EOS visit are followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

### 6.3.3 Variables

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Select the appropriate as required: maximum intensity or intensity or changes in intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)
- Action taken with regard to investigational product
- AE caused subject's withdrawal from study *(*yes or no*)*
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE

- AE is serious due to
- Date of hospitalisation
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication
- Description of AE.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Section 6.2.

### 6.3.4 Causality collection

The Investigator will assess causal relationship between Investigational Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix A to the Clinical Study Protocol.

### 6.3.5 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study site staff: or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

### 6.3.6 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the CSR. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE

## 6.4 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

## 6.5 Overdose

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

If an overdose is suspected, monitoring of vital functions as well as treatment should be performed as appropriate.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 6.4. For other overdoses, reporting must occur within 30 days.

## 6.6 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study subject has received any study drug

### 6.6.1 Maternal exposure

If a subject becomes pregnant during the course of the study investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see Section 6.4) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

## 6.7 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the subject or has the potential to cause harm to the subject.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or subject.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the subject received the drug
- did not occur, but circumstances were recognize that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the subject
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature

Examples of events that **do not** require reporting as medication errors in clinical studies:

- Subject accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Subject failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If any medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error (see Section 6.4) and within 30 days for all other medication errors.

# 7 INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

## 7.1 Identity of investigational product(s)

| Investigational product | Dosage form and strength | Manufacturer |
|---|---|---|
| dapagliflozin/saxagliptin | film-coated tablets, 10 mg/5 mg | AstraZeneca |

## 7.2 Dose and treatment regimens

The IP should be taken once daily at approximately the same time of the day during the study period. The IP should not be altered (eg, crushed, put in another vehicle) and should not be given by nasogastric tube or other routes.

## 7.3 Labelling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling.

## 7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. A description of the appropriate storage conditions is specified on the investigational product pack label.

## 7.5 Compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the eCRF. Subjects will be asked to return all unused investigational product and empty packages and bottles to the clinic at each visit. The subject will be asked about compliance at each study visit; compliance will also be assessed based on returned tablet counts. Tablet counts will be recorded in the eCRF. Subjects judged to be non-compliant (defined as taking less than 80% or more than 120% of the prescribed dose of investigational product) may continue in the study, but should be counselled on the importance of taking their study medication as prescribed.

## 7.6 Accountability

Study drug will not be distributed to the study site until the contract is concluded between the study site and AstraZeneca/Delegate. The Investigator/ Site is responsible for managing the study drug from receipt by the institution until the return of all unused study drug to AstraZeneca/delegate. AstraZeneca will provide the study documents 'Procedures for drug

accountability' and 'Procedures for drug storage' which describes the specific requirements. The investigator(s) is responsible for ensuring that the subject has returned all unused study drug.

## 7.7 Concomitant and other treatments

Changes in concomitant medication should be avoided during study participation, with the exception of situations defined in this protocol, but medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the investigators, who must decide if the subject should remain in study or need to be dismissed from study due to subject's safety or interference with study objectives.
The administration of all medication must be recorded in the appropriate sections of the electronic case report form (eCRF) with trade names, dosages, dates of starting and ending of medication and reason for therapy. If the patients glycemic status remains uncontrolled (HbA1c ≥ 9 %, FBG ≥ 240 mg/dl (confirmed on readings taken on 2 consecutive days)

After having completed or discontinued the study, investigational product will be discontinued from sponsor but subjects will receive usual care and antidiabetic agents according to the investigator's judgement and according to local medical practice.

**Prohibited Therapies**

- Weight loss medication, including but not limited to mazindol, sibutramine, phentermine, orlistat, rimonabant, benzphetamine, diethylproprion, methamphetamine, and/or hendimetrazine
- Antiviral drugs (delavirdine, indinavir, nelfinavir, ritonavir, saquinavir)
- Treatment with systemic glucocorticoids equivalent to oral prednisolone ≥10 mg (betametasone ≥1.2 mg, dexamethasone ≥1.5 mg, hydrocortisone ≥40 mg) per day (two temporary periods of higher daily doses for no longer than 7 days each are allowed).
- Anti-diabetic agents except for the study medication, a basal anti-diabetic agents medication and rescue therapies (Anti-diabetic agents planned to be stopped for wash-out are allowed to be used until the beginning of wash-out period. After completion of the treatment period, alternative anti-diabetic treatment will be initiated according to standard medical practice.)

### 7.7.1 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

# 8 STATISTICAL ANALYSES BY ASTRAZENECA

This is an India regulatory requirement study. Objective is to establish that FDC of Dapagliflozin 10mg / Saxagliptin 5 mg is a safe treatment option in Indian T2DM patients. This study is planned as prospective study on 200 patients in single arm open label study. CCI [redacted]

Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, SD, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate.

The safety analysis population will include all patients who sign the ICF and receive at least one dose of study medication.

The safety analysis population is also applicable to the efficacy analysis, and any efficacy measurements collected before the study medication discontinuation will be included. Last on treatment observation will be carried forward to impute the missing data at week 24.

Any AE occurring within 2 weeks of discontinuation of investigational product (ie, the last dose of study medication) will be included in the AE summaries. Any events in this period that occur after a patient has received further therapy for (following discontinuation of study drug) will be flagged in the data listings. Adverse event rates shall be stratified by age/gender/baseline medications. Annualised event rate shall also be presented in addition to the incidence rate during the study. Mean change in HbA1C from baseline to 6 months for patients will be analysed using paired t test / Wilcoxon signed-rank test at 5% level of significance.

The study is designed in accordance with the Health Authority requirements in India. It is intended to provide information regarding the safety profile for patients in India, and will contribute additional information to the overall safety profile of Dapa-Saxa FDC. Due to the small sample size, this study should not be directly compared to the data from any other country.

# 9 STUDY AND DATA MANAGEMENT BY ASTRAZENECA

## 9.1 Training of study site staff

Before the first subject is entered into the study, an AstraZeneca representative/delegate will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and *electronic data capture* system(s) utilised.

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

## 9.2 Monitoring of the study

During the study, an AstraZeneca representative/delegate will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the Clinical Study Protocol, that data are being accurately and timely recorded in the eCRF, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed
- Perform source data verification (a comparison of the data in the eCRF with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts)
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the centre needs information and advice about the study conduct.

### 9.2.1 Source data

Refer to the Clinical Study Agreement for location of source data.

### 9.2.2 Study agreements

The Principal Investigator at each/the centre should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

### 9.2.3 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement (CSA).

## 9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last subject undergoing the study'.

The study may be terminated at individual centres if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with Dapagliflozin / saxagliptin fixed dose combination.

## 9.4 Data management by delegate

Data management will be performed by external partner, according to the Data Management Plan.

The data collected through third party sources will be obtained and reconciled against study data.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the WHO Drug Dictionary.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. The Data Management Plan will also clarify the roles and responsibilities of the various functions and personnel involved in the data management process.

When all data have been coded, validated, and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

**Serious Adverse Event (SAE) Reconciliation**

SAE reconciliation reports are produced and reconciled with the Patient Safety database and/or the investigational site.

# 10 ETHICAL AND REGULATORY REQUIREMENTS

## 10.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, applicable

regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

## 10.2 Subject data protection

The Informed Consent Form will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

## 10.3 Ethics and regulatory review

An Ethics Committee must approve the final Clinical Study Protocol, including the final version of the Informed Consent Form and any other written information and/or materials to be provided to the subjects. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study site staff.

The opinion of the Ethics Committee should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any subject into the study.

The Ethics Committee should approve all advertising used to recruit subjects for the study.

AstraZeneca should approve any modifications to the Informed Consent Form that are needed to meet local requirements.

Before enrolment of any subject into the study, the final Clinical Study Protocol, including the final version of the Informed Consent Form, is approved by the national regulatory authority.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

## 10.4 Informed consent

The Principal Investigator(s) at each centre will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided

- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed Informed Consent Form(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed Informed Consent Form is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the informed consent form that is approved by an Ethics Committee.

## 10.5 Changes to the Clinical Study Protocol and Informed Consent Form

If there are any substantial changes to the Clinical Study Protocol, then these changes will be documented in a new version of the study protocol.

The new version of the Clinical Study Protocol is to be approved by the relevant Ethics Committee and also the national regulatory authority approval, before implementation. Local requirements are to be followed for new versions of Clinical Study Protocols.

AstraZeneca will distribute any new versions of the Clinical Study Protocol to each Principal Investigator(s). For distribution to Ethics Committee see Section 10.3.

If a change to a Clinical Study Protocol requires a change to a centre's Informed Consent Form, AstraZeneca and the centre's Ethics Committee are to approve the revised Informed Consent Form before the revised form is used.

## 10.6 Audits and inspections

Authorised representatives of AstraZeneca or delegate, a regulatory authority, or an Ethics Committee may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the Clinical Study Protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonisation (ICH), and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the centre.

# 11 LIST OF REFERENCES

1. International Diabetes Federation. IDF Diabetes Atlas, 8th edn. Brussels, Belgium: International Diabetes Federation, 2017.
2. Ramachandran A, Das A, Joshi S, Yajnik C, Shah S, Kumar KP. Current status of diabetes in India and need for novel therapeutic agents. J Assoc Physicians India. 2010;58:7-9.
3. Joshi SR, Bhansali A, Bajaj S, Banzal SS, Dharmalingam M, Gupta S, et al. Results from a dietary survey in an Indian T2DM population: a STARCH study. BMJ Open. 2014;4(10).
4. Plosker GL. Dapagliflozin: a review of its use in patients with type 2 diabetes. Drugs. 2014;74(18):2191-209.
5. Deanna S. Kania et al, Saxagliptin: A Clinical Review in the Treatment of Type 2 Diabetes Mellitus. Clinical Therapeutics/Volume 33, Number 8, 2011.
6. QTERN [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2019
7. Blonde L, San Juan ZT. Fixed-dose combinations for treatment of type 2 diabetes mellitus. Adv Ther. 2012;29(1):1–13.

# Appendix A Additional Safety Information

## Further Guidance on the Definition of a Serious Adverse Event (SAE)

### Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

### Hospitalisation

Outsubject treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

### Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation

Development of drug dependency or drug abuse

### A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility

# Appendix B Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

## 1. Introduction

This Appendix describes the process to be followed in order to identify and appropriately report cases of Hy's Law. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

## 2. Definitions

### Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

### Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

## 3. Identification of Potential Hy's Law Cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN

- AST ≥ 3xULN
- TBL ≥ 2xULN

When a subject meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the subject meets PHL criteria (see Section 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the subject meets PHL criteria (see Section 2 Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

**4. Follow-up**

**4.1 Potential Hy's Law Criteria not met**

If the subject does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

### 4.2 Potential Hy's Law Criteria met

If the subject does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Section 6. Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment)

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. For studies using a central laboratory add: This includes deciding which the tests available in the Hy's law lab kit should be used

- Complete the three Liver CRF Modules as information becomes available

- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

### 5. Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

**6. Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment**

This section is applicable to subjects with liver metastases who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the subjects' condition[#] compared with the last visit where PHL criteria were met[#]
  - If there is no significant change no action is required
  - If there is a significant change notify the AstraZeneca representative, who will inform the central Study Team, then follow the subsequent process described in 4.2 Potential Hy's Law Criteria met of this Appendix

[#] A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of

whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

## 7. Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a subject meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g. chronic or progressing malignant disease, severe infection or liver disease, or did the subject meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in section 6. Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

If No: follow the process described in 4.2 Potential Hy's Law Criteria met of this Appendix

If Yes:

Determine if there has been a significant change in the subject's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required
- If there is a significant change follow the process described in Section 4.2 of this Appendix

[#] A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator; this may be in consultation with the Study Physician if there is any uncertainty.

# 12 SIGNATURES

## ASTRAZENECA SIGNATURE(S)

**A prospective, multicenter, phase -IV study to assess the safety of fixed dose combination of dapagliflozin and saxagliptin in Indian Type 2 Diabetes Mellitus (T2D) patients.**

*This Study Protocol has been subjected to an internal AstraZeneca review*

I agree to the terms of this Study protocol.

**AstraZeneca representative**

PPD

# SIGNATURES

## ASTRAZENECA SIGNATURE(S)

---

**A prospective, multicenter, phase -IV study to assess the safety of fixed dose combination of dapagliflozin and saxagliptin in Indian Type 2 Diabetes Mellitus (T2D) patients.**

---

*This Study Protocol has been subjected to an internal AstraZeneca review*

I agree to the terms of this Study protocol.

**AstraZeneca representative**

PPD

# SIGNATURES

## ASTRAZENECA SIGNATURE(S)

**A prospective, multicenter, phase -IV study to assess the safety of fixed dose combination of dapagliflozin and saxagliptin in Indian Type 2 Diabetes Mellitus (T2D) patients.**

*This Study Protocol has been subjected to an internal AstraZeneca review*

I agree to the terms of this Study protocol.

**AstraZeneca representative**

PPD

# SIGNATURES

## ASTRAZENECA SIGNATURE(S)

**A prospective, multicenter, phase -IV study to assess the safety of fixed dose combination of dapagliflozin and saxagliptin in Indian Type 2 Diabetes Mellitus (T2D) patients.**

*This Study Protocol has been subjected to an internal AstraZeneca review*

I agree to the terms of this Study protocol.

**AstraZeneca representative**

PPD