Risk and Adverse Events Overview

Sotagliflozin – known risks and mitigation strategies

- **Diabetic Ketoacidosis (DKA) (3%)**
  - Make participant aware of DKA and provide further information on how to prevent, recognise, and treat DKA along with educational prompts.
  - Ensure participant is educated about precipitating factors for DKA (e.g. acute medical illness, vomiting, insulin pump failure, excessive carbohydrate restriction, excessive alcohol) and when to discontinue therapy if these events occur.
  - Provide participant with contact details of the local research team and relevant emergency contacts for advice should any of these situations occur.
  - Provide blood ketone meter if they don't already have them.
  - Provide participant with medical alert such as STOP-DKA wallet card or local guidelines.
  - Ask participant to check their blood ketone levels:
    - 3 days before and after starting trial drug/placebo 4 times a day as well as 2 hours after changing each insulin giving set for those on insulin pump therapy.
    - At least once weekly throughout the trial, ideally at the same time of day each week.
    - If capillary/CGM glucose is >11.1mmol/L for >2 hours or if feeling sick/unwell irrespective of glucose levels.
    - With changes in diet, activity, insulin dose or events known to precipitate ketoacidosis.
    - At any other time at their discretion or that of the local investigator.
  - Review insulin, glucose and ketone management at every visit after screening.

Sotagliflozin – known risks and mitigation strategies

- **Hypoglycaemia (3%)**
  - Individuals with an HbA1c <58mmol/mol at screening will have a 10% insulin dose reduction prior to taking their first dose of sotagliflozin/placebo. No reduction in insulin dose will be made for those with HbA1c ≥58mmol/mol at screening.
  - Advise participants to monitor blood glucose levels regularly and to adjust insulin doses every 24-48 hours to achieve recommend blood glucose targets.
  - Recommend participants to set up CGM high alarm of 15 mmol/L (13 mmol/L if on insulin pump) and a low alarm of 3.9 mmol/L (the latter may be adjusted based on clinician and participant judgement/preferences).
  - Ask participant to check their blood glucose levels:
    - 3 days before and after starting trial drug/placebo 4 times a day as well as 2 hours after changing each insulin giving set for those on insulin pump therapy.
    - At least once weekly throughout the trial, ideally at the same time of day each week.
    - If feeling sick/unwell.
  - Review insulin, glucose and ketone management at every visit after screening.

- **Genital/Urinary Tract Infections (5%)** – Advice on risk of urogenital infection given at the randomisation visit as per standard initiation of SGLT2 inhibitors (i.e. educating about symptoms and encouraging good hygiene practices).

Sotagliflozin – known risks and mitigation strategies

- **Volume Depletion (2%)** – Advice given regarding “sick day rules” as per the STOP-DKA protocol (appendix 6).

- **Blood creatinine increase/glomerular filtration decrease and renal-related events (1-2%) –** Careful attention to fluid status and signs and symptoms of dehydration with renal function checked at visits 3, 5 and 7 and renal-related events at every visit.

Please note:

Participants should be managed in accordance with the recently developed position statements of the Association of British Clinical Diabetologists[1] and the International Consensus approach[2]. All participants should be carefully monitored throughout the trial and insulin dose adjustments made under the supervision of the research team.

1 Dashora U, et al., Association of British Clinical Diabetologists (ABCD) position statement on the use of sodium-glucose cotransporter-2 inhibitors in type 1 diabetes (updated 2019). *Br J Diabetes*. 2019:66-72.

2 Danne T, et al., International Consensus on Risk Management of Diabetic Ketoacidosis in Patients With Type 1 Diabetes Treated With Sodium-Glucose Cotransporter (SGLT) Inhibitors. *Diabetes Care*. 2019;42:1147-1154.

Sotagliflozin – known interactions

- Insulin: may increase the risk of hypoglycaemia.
- UGT enzyme inducers e.g. phenytoin, ritonavir, rifampicin: may decrease efficacy of sotagliflozin.
- Digoxin: increase in AUC0-mf and Cmax of digoxin. If digoxin toxicity is clinically suspected appropriate clinical action will be taken. This is likely to include checking digoxin levels.
- Sotagliflozin may increase exposure of rosuvastatin, fexofenadine, paclitaxel, bosentan, methotrexate, furosemide, benzylpenicillin. It should be evaluated if additional safety monitoring is needed.
- CYP2C9, CYP2B6 and CYP1A2: substrates of these enzymes should be monitored for decreases in their efficacy.

Adverse Event Definitions (Part 1 of 3)

Adverse Event (AE) - Any untoward medical occurrence in a consented participant which is not necessarily caused by or related to a medicinal product.

Adverse Reaction (AR) - An untoward and unintended response in a participant to an IMP which is related to any dose administered to that participant.

The phrase "response to an IMP" means that a causal relationship between a trial drug and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial drug qualify as adverse reactions. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative aetiology that would explain the event.

Adverse Event Definitions (Part 2 of 3)

Serious Adverse Event (AE) – A serious adverse event is any untoward medical occurrence that:

- Results in death.
- Is life-threatening.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity.
- Consists of a congenital anomaly or birth defect.

Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Adverse Event Definitions (Part 3 of 3)

Serious Adverse Reaction (SAR) – An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.

Suspected Unexpected Serious Adverse Reaction (SUSAR) - A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information in the investigator's brochure (IB).

Please note: to avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

Operational Definitions for (S)AEs

- Worsening of glycaemic control, including hypoglycaemia and DKA are defined outcomes:
  - Participant not hospitalised: not classed as an AE.
  - Participant hospitalised: SAE.

- Clinically significant volume depletion or incurrent illness requiring temporary cessation of study drug: AE.

- All other hospitalisations or deaths: SAE.

- Abnormal laboratory findings:
  - Not requiring medical intervention and not medically significant: not classed as an AE.
  - Requires medical intervention or medically significant: AE.

- Worsening of a pre-existing condition:
  - Not clinically significant: not classed as an AE.
  - Clinically significant: AE. Requires medical intervention or medically significant: AE.

- Pre-specified elective hospitalisations for treatment planned prior to randomisation: not classed as an AE.
  - However, any AEs occurring during such hospitalisations should be recorded.

Identifying Adverse Events

- The CI, PI or delegate must ask about the occurrence of AEs and hospitalisations at every visit during the trial, in person and/or over the telephone/video call.

- Review medical records for the occurrence of AEs and hospitalisations at every visit, in person and/or over the telephone/video call.

Recording Adverse Events

- Details of AEs must be recorded in the participant's medical record for source data verification.
- All AEs must be recorded on the AE Log in the eCRF.
- AEs must be assessed for severity and causality (see later slides for guidance) by the PI or delegate.
- AEs must be recorded from the time a participant consents to join the trial until the participant's last trial visit.
- Any SUSAR, that the investigator becomes aware of, must be reported to the Sponsor irrespective of how long after IMP administration the reaction has occurred.
- Unresolved AEs/SAEs at end of trial must be followed up until 30 days after participant's last visit.
- SUSARS will be followed until resolution, where a participant agrees to this.

Reporting SAEs

- SAEs must be submitted to the Sponsor Pharmacovigilance Section via the online Tayside Pharmacovigilance (PV) System within 24 hours of becoming aware of the SAE.
- Site PIs will also notify the CI when submitting an SAE.
- If further information is required, this must be provided as soon as available.
- PV system website:

https://pharmacovigilance.hicservices.dundee.ac.uk/

Guidance on Assessment of Adverse Event Severity

- **Mild:** An event that is easily tolerated by the trial participant, causing minimal discomfort, and not interfering with everyday activities.

- **Moderate:** An event that is sufficiently discomforting to interfere with normal everyday activities and may warrant intervention.

- **Severe:** An event that prevents normal everyday activities or significantly affects clinical status and usually warrants intervention.

Guidance on Assessment of Adverse Event Causality

- **Unrelated:** Where the AE is not considered to be related to the trial drug.

- **Possibly:** Although a relationship to the trial drug cannot be completely ruled out, the nature of the event, the underlying disease, concomitant medication, or temporal relationship make other explanations more likely. Information on drug withdrawal may be lacking or unclear.

- **Probably:** The temporal relationship and absence of a more likely explanation suggest the event could be related to the trial drug. Information on drug withdrawal may be available and if so the observed response to trial drug withdrawal is considered clinically reasonable.

- **Definitely:** The known effects of the trial drug or its therapeutic class, or based on challenge testing, suggest that the trial drug is the most likely cause. Information on drug withdrawal is usually available and the observed response to trial drug withdrawal is considered clinically reasonable and has a plausible temporal relationship to trial drug exposure.