Supplementary data

Basic analytical procedure

For primary and secondary endpoints, both the full analysis set and per protocol set will be analyzed. The analyses will be conducted with a two-sided significance level of 5%. A biomedical statistical expert created a statistical analysis plan (SAP) separately, and specified the details of the statistical methods, including handling data. The SAP was prepared before the database lock.

When an amendment of the SAP is needed, the data handling committee will carefully consider the effect of the amendment on the study itself, the results of the study, ethical concerns, and scientific validity of the effect. If the data handling committee judges that the SAP amendment is valid, the procedure, the content, and the result of the discussion are recorded.

Analysis of study subjects' background information

Summary statistics will be calculated for the background information of study subjects per group. Frequencies and percentages of categories are shown for nominal variables. Summary statistics (number of cases, mean, standard deviation, minimum, median, and maximum values) were calculated for continuous variables. For comparisons between the groups, the chi-square test will be used for nominal variables. If the proportion of cells with an expected frequency of less than 5 is 20% or more, Fisher's exact test will be used. For comparisons between groups for continuous variables, a two-sample t-test or the Wilcoxon rank sum test was used.

Dissemination

All parties involved in the RISING-STAR study will endeavor to protect the personal information of study subjects. The RISING-STAR study is being conducted in accordance with the Personal Information Protection Law and other legislation/laws and regulations. The unique information (initial, carte number) of study subjects is stored securely in the research institutions, and information that allows a person outside the research institution to identify the study subjects (name, address, telephone number, etc.) is not included in the case report forms (CRFs) or the registration database.

A central registration number is used when the data center enquires regarding data from a study subject at a research institution. Investigators use correspondence tables to identify their research subjects (anonymization), which they managed. Investigators store the correspondence tables securely and keep them properly for at least 5 years from the day of completion of the study. The person responsible for personal information management at each research institution shall be the responsible investigator unless otherwise specified.

The principal investigator, responsible investigators, sub-investigators, and the heads of the research institutions agree to store the study-related information properly until at least 5 years from the completion date of the study. The responsible person in charge of data management also stores the study-related information such as CRF as source documents and electronic information, such as data sets, are stored in the same way.

After the storage period, the data will be discarded. Anonymized data collected for the analysis are stored for future secondary studies such as meta-analysis. If the anonymized data is to be used for other studies, approval from the ethics review board is required before study implementation.

Samples for special blood tests were measured in laboratories utilized by each research institution. After the requisite data is obtained, the samples are disposed of in accordance with standard procedural guidelines.

The study explored whether the reduction of the basal insulin dose combined with an SGLT2 inhibitor in patients with type 1 diabetes mellitus can reduce the frequency of hypoglycemia with an overall acceptable safety profile.

The treatment intervention in the RISING-STAR study is based on the Basal/TDD ratio at the time of consent. Therefore, study subjects cannot always receive their desired treatment. However, all study subjects will receive regular medication, measure ketone body and blood glucose levels and titrate both basal and bolus insulin after the fourth day of the intervention. As a result, the study subjects may receive better medical care than if they did not participate in the RISING-STAR study.

To reduce the burden on study subjects, changes in medications during the study were not restricted. Special blood tests are conducted using residual samples to reduce the burden caused by multiple blood draws. Therefore, special compensation is generally not provided even when health damages are considered to be caused by the drug(s) used in the study. For reporting purposes, all incidences during the study will be treated similarly to health damage or medical accidents caused by regular medication. The compensation in such a case is based on the Adverse Drug Reaction Relief System of the Pharmaceutical and Medical Devices Agency, Product Liability Law, or product liability insurance. The principal investigator contracted the insurance for a clinical study corresponding to any incidences. The current research is carried out in accordance with the Clinical Trial Act and other laws and regulations. Burdens and predicted risks are minimized as much as possible from the perspective of protecting human subjects. In particular, we believe that

the risk of adverse effects can be minimized by discontinuing the study treatment as soon as a symptom emerges and providing treatments using appropriate procedures. Based on the overall evaluation and considering conceivable benefits from the study participation, the RISING-STAR study protocol is considered appropriate to implement and adequate in terms of ethical considerations.