

**Multicenter, Randomized, Open-label Study of Diabetes  
Treatment Support System (BAP0527 and Blood Glucose Meter)  
in Patients with Type 2 Diabetes Mellitus**

**ISN/Protocol 0527-CL-0002**

**Amendment 1 [Non-substantial]**

**October 24, 2023**

IND not applicable

IND Grantor not applicable

EU CT Number not applicable

EU-PAS not applicable

Pediatric Investigational Plan not applicable

Sponsor

**Astellas Pharma Inc.**

2-5-1, Nihonbashi-Honcho, Chuo-ku, Tokyo 103-8411, Japan

Revised on October 24, 2023 (Amendment 1) [Non-substantial]

---

The information contained in this document is supplied as a background for clinical investigations. This document contains confidential information, which is the intellectual property of Astellas. By accepting or reviewing this document, you agree to hold this information in confidence and not copy or disclose it to others or use it for unauthorized purposes except (1) as otherwise agreed to in writing; (2) where required by applicable law; (3) where disclosure is directly related to the care and safety of the research participant; and (4) where disclosure of such information is made to a member of the investigator's team who agrees to hold this information in confidence.

## Table of Contents

|                                                                                          |           |
|------------------------------------------------------------------------------------------|-----------|
| <b>CONTACT DETAILS OF SPONSOR'S KEY PERSONNEL</b>                                        | <b>8</b>  |
| <b>LIST OF ABBREVIATIONS</b>                                                             | <b>9</b>  |
| <b>DEFINITION OF TERMS</b>                                                               | <b>11</b> |
| <b>PROTOCOL AMENDMENT SUMMARY OF CHANGES</b>                                             | <b>12</b> |
| Overview of Changes                                                                      | 12        |
| <b>1      PROTOCOL SUMMARY</b>                                                           | <b>13</b> |
| 1.1      Synopsis                                                                        | 13        |
| 1.2      Study Schema                                                                    | 19        |
| 1.3      Schedule of Assessments                                                         | 20        |
| <b>2      INTRODUCTION</b>                                                               | <b>23</b> |
| 2.1      Study Rationale                                                                 | 23        |
| 2.2      Background                                                                      | 24        |
| 2.3      Risk/Benefit Assessment                                                         | 25        |
| 2.3.1      Risk Assessment                                                               | 25        |
| 2.3.1.1      Expected Device-Related Adverse Events                                      | 25        |
| 2.3.1.2      Risks Relating to Study Participation                                       | 26        |
| 2.3.1.3      Possibility of Interactions with Concomitant Drugs Considered Risk Analysis | 26        |
| 2.3.1.4      Actions Taken to Manage or Reduce Risk                                      | 26        |
| 2.3.2      Benefit Assessment (Expected Clinical Benefits)                               | 27        |
| 2.3.3      Overall Risk-Benefit Conclusion (Rationale for Benefit-Risk Ratio)            | 27        |
| <b>3      OBJECTIVES, ENDPOINTS AND ESTIMANDS</b>                                        | <b>28</b> |
| 3.1      Estimands                                                                       | 29        |
| <b>4      STUDY DESIGN</b>                                                               | <b>30</b> |
| 4.1      Overall Study Design                                                            | 30        |
| 4.2      Scientific Rationale for Study Design                                           | 31        |
| 4.2.1      Participant Input into Study Design                                           | 32        |
| 4.3      Dose Rationale                                                                  | 32        |
| 4.4      Start and End of Study Definitions                                              | 32        |
| <b>5      STUDY POPULATION</b>                                                           | <b>32</b> |
| 5.1      Inclusion Criteria                                                              | 32        |

- CONFIDENTIAL -

|          |                                                                         |           |
|----------|-------------------------------------------------------------------------|-----------|
| 5.2      | Exclusion Criteria .....                                                | 34        |
| 5.3      | Lifestyle Considerations .....                                          | 35        |
| 5.4      | Screen Failures .....                                                   | 35        |
| 5.4.1    | Rescreening .....                                                       | 36        |
| <b>6</b> | <b>STUDY INTERVENTION AND CONCOMITANT THERAPY .....</b>                 | <b>36</b> |
| 6.1      | Study Intervention(s) Administered .....                                | 36        |
| 6.1.1    | Overview of BAP0527 and the Blood Glucose Meter .....                   | 37        |
| 6.1.2    | Control of Investigational Devices and Devices for Study Use .....      | 37        |
| 6.1.2.1  | BAP0527 .....                                                           | 37        |
| 6.1.2.2  | Blood Glucose Meters .....                                              | 38        |
| 6.1.2.3  | Other Medical Devices and Other Equipment .....                         | 39        |
| 6.1.3    | Method for Ensuring Traceability During and After the Study .....       | 39        |
| 6.1.3.1  | BAP0527 .....                                                           | 39        |
| 6.1.3.2  | Blood Glucose Meters .....                                              | 39        |
| 6.1.4    | Training .....                                                          | 40        |
| 6.1.4.1  | BAP0527 .....                                                           | 40        |
| 6.1.4.2  | Blood Glucose Meters .....                                              | 40        |
| 6.1.5    | The BAP0527 Call Center .....                                           | 41        |
| 6.2      | Preparation/Handling/Storage/Accountability .....                       | 41        |
| 6.2.1    | Packaging and Labeling .....                                            | 41        |
| 6.2.2    | Handling, Storage and Accountability .....                              | 42        |
| 6.3      | Assignment to Study Intervention .....                                  | 42        |
| 6.4      | Study Intervention Compliance .....                                     | 42        |
| 6.5      | Continued Access to Study Intervention After the End of the Study ..... | 43        |
| 6.6      | Prior and Concomitant Therapy .....                                     | 43        |
| 6.6.1    | Prohibited Concomitant Medications .....                                | 44        |
| 6.6.2    | Prohibited Concomitant Therapies .....                                  | 44        |
| 6.6.3    | Restricted Concomitant Medications .....                                | 44        |
| 6.6.4    | Restricted Concomitant Therapies .....                                  | 44        |
| <b>7</b> | <b>STUDY PROCEDURES AND ASSESSMENTS .....</b>                           | <b>44</b> |
| 7.1      | Efficacy Assessments .....                                              | 45        |
| 7.1.1    | Laboratory Assessments .....                                            | 45        |
| 7.1.2    | Vital Signs .....                                                       | 45        |
| 7.1.3    | Physical Examination .....                                              | 45        |

- CONFIDENTIAL -

|          |                                                                                                                                                                     |           |
|----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 7.1.4    | Participants with Changes of Antidiabetics .....                                                                                                                    | 45        |
| 7.1.5    | EuroQol 5 Dimension 5-level (EQ-5D-5L) .....                                                                                                                        | 45        |
| 7.1.6    | Diabetes Treatment Satisfaction Questionnaire (DTSQ) .....                                                                                                          | 46        |
| 7.1.7    | Percentage of Accesses to BAP0527 and Percentage of Data Inputs into<br>BAP0527 .....                                                                               | 46        |
| 7.2      | Safety Assessments .....                                                                                                                                            | 46        |
| 7.2.1    | Laboratory Assessments .....                                                                                                                                        | 46        |
| 7.2.2    | Vital Signs .....                                                                                                                                                   | 47        |
| 7.2.3    | Physical Examination .....                                                                                                                                          | 47        |
| 7.2.4    | Order of Assessments .....                                                                                                                                          | 47        |
| 7.3      | Adverse Events, Deficiencies and Other Safety Aspects .....                                                                                                         | 47        |
| 7.3.1    | Time Period and Frequency for Collecting Adverse Events, Serious<br>Adverse Events, Deficiencies and/or Deficiencies That May Cause Serious<br>Adverse Events ..... | 47        |
| 7.3.2    | Method of Detecting Adverse Events, Serious Adverse Events,<br>Deficiencies and/or Deficiencies That May Cause Serious Adverse Events .....                         | 48        |
| 7.3.3    | Follow-up of Adverse Events, Serious Adverse Events, Deficiencies and/or<br>Deficiencies That May Cause Serious Adverse Events .....                                | 49        |
| 7.3.4    | Regulatory Reporting Requirements for Serious Adverse Events and<br>Deficiencies That May Cause Serious Adverse Events .....                                        | 49        |
| 7.3.5    | Disease-related Events and/or Disease-related Outcomes Not Qualifying as<br>Adverse Events or Serious Adverse Events .....                                          | 50        |
| 7.3.6    | Regulatory Requirements Relating to Deficiencies in Medical Devices .....                                                                                           | 50        |
| 7.4      | Pharmacokinetics .....                                                                                                                                              | 50        |
| 7.5      | Electronic Clinical Outcome Assessment .....                                                                                                                        | 50        |
| 7.6      | Total Amount of Blood .....                                                                                                                                         | 50        |
| 7.7      | Other Assessment .....                                                                                                                                              | 50        |
| 7.7.1    | Participant Backgrounds .....                                                                                                                                       | 50        |
| 7.7.2    | Medical History and Concurrent Diseases .....                                                                                                                       | 51        |
| 7.7.3    | 14-item Health Literacy Scale (HLS-14) .....                                                                                                                        | 51        |
| 7.7.4    | Status of Directions About the Use of Sphygmomanometers and Scales for<br>Weight Measurement .....                                                                  | 51        |
| <b>8</b> | <b>PARTICIPANT DISCONTINUATION .....</b>                                                                                                                            | <b>51</b> |
| 8.1      | Discontinuation of Individual Participant(s) from Study Intervention .....                                                                                          | 51        |
| 8.2      | Discontinuation of Individual Participant(s) from Study .....                                                                                                       | 52        |
| 8.3      | Lost to Follow-up .....                                                                                                                                             | 52        |

- CONFIDENTIAL -

|           |                                                                                                                                |           |
|-----------|--------------------------------------------------------------------------------------------------------------------------------|-----------|
| <b>9</b>  | <b>STATISTICAL CONSIDERATIONS .....</b>                                                                                        | <b>52</b> |
| 9.1       | Statistical Hypotheses .....                                                                                                   | 52        |
| 9.2       | Analysis Sets .....                                                                                                            | 53        |
| 9.3       | Statistical Analyses .....                                                                                                     | 53        |
| 9.3.1     | General Considerations .....                                                                                                   | 53        |
| 9.3.2     | Primary Endpoint(s) Analysis .....                                                                                             | 53        |
| 9.3.2.1   | Primary Analysis .....                                                                                                         | 53        |
| 9.3.2.2   | Sensitivity Analysis .....                                                                                                     | 54        |
| 9.3.3     | Secondary Endpoint(s) Analysis .....                                                                                           | 54        |
| 9.3.4     | Exploratory Endpoint(s) Analysis .....                                                                                         | 55        |
| 9.3.5     | Safety Analyses .....                                                                                                          | 55        |
| 9.3.5.1   | Adverse Events and Deficiencies .....                                                                                          | 55        |
| 9.3.5.2   | Laboratory Assessments .....                                                                                                   | 56        |
| 9.3.5.3   | Vital Signs .....                                                                                                              | 56        |
| 9.3.6     | Subgroup Analyses .....                                                                                                        | 56        |
| 9.3.7     | Assessment of Variation Between Study Sites .....                                                                              | 56        |
| 9.4       | Interim Analysis .....                                                                                                         | 56        |
| 9.5       | Sample Size Determination .....                                                                                                | 56        |
| 9.6       | Additional Conventions .....                                                                                                   | 57        |
| <b>10</b> | <b>SUPPORTING DOCUMENTATION AND OPERATIONAL<br/>CONSIDERATIONS .....</b>                                                       | <b>58</b> |
| 10.1      | Appendix 1 Ethical, Regulatory and Study Oversight Considerations .....                                                        | 58        |
| 10.1.1    | Regulatory and Ethical Considerations .....                                                                                    | 58        |
| 10.1.2    | Financial Disclosure .....                                                                                                     | 58        |
| 10.1.3    | Informed Consent of Participants .....                                                                                         | 58        |
| 10.1.3.1  | Informed Consent Process .....                                                                                                 | 58        |
| 10.1.3.2  | Supply of New and Important Information Influencing the<br>Participant's Consent and Revision of the Written Information ..... | 59        |
| 10.1.4    | Data Protection .....                                                                                                          | 60        |
| 10.1.5    | Dissemination of Clinical Study Data .....                                                                                     | 61        |
| 10.1.5.1  | Disclosure of Study Information and Results .....                                                                              | 61        |
| 10.1.5.2  | Access to Study Data .....                                                                                                     | 62        |
| 10.1.6    | Data Quality Assurance .....                                                                                                   | 62        |
| 10.1.7    | Source Documents .....                                                                                                         | 63        |
| 10.1.8    | Study and Site Closure .....                                                                                                   | 65        |

- CONFIDENTIAL -

|           |                                                                                                                                    |           |
|-----------|------------------------------------------------------------------------------------------------------------------------------------|-----------|
| 10.1.9    | Publication Policy .....                                                                                                           | 65        |
| 10.1.10   | Insurance of Participants and Others .....                                                                                         | 66        |
| 10.1.11   | Quality Assurance (QA) .....                                                                                                       | 66        |
| 10.1.12   | Other Study Organization and Planned Study Period/Duration .....                                                                   | 66        |
| 10.2      | Appendix 2 Contraception Requirements .....                                                                                        | 67        |
| 10.3      | Appendix 3 Adverse Events and Deficiencies: Definitions and Procedures for<br>Recording, Evaluating, Follow-up and Reporting ..... | 69        |
| 10.3.1    | Definition of Adverse Events .....                                                                                                 | 69        |
| 10.3.1.1  | Abnormal Laboratory Findings .....                                                                                                 | 70        |
| 10.3.2    | Definition of Serious Adverse Events .....                                                                                         | 70        |
| 10.3.3    | Definition of Deficiencies .....                                                                                                   | 71        |
| 10.3.4    | Assessment of Causality .....                                                                                                      | 72        |
| 10.3.5    | Assessment of Severity .....                                                                                                       | 74        |
| 10.3.6    | Recording and Follow-up of AEs, SAEs, Deficiencies and/or Deficiencies<br>That May Cause SAEs .....                                | 74        |
| 10.3.7    | Reporting Procedures for SAEs or Deficiencies That May Cause SAEs .....                                                            | 75        |
| 10.3.7.1  | Detection of Adverse Events, Serious Adverse Events or Deficiencies<br>via the BAP0527 Call Center .....                           | 75        |
| 10.3.8    | Supply of New Information Affecting the Conduct of the Study .....                                                                 | 76        |
| 10.3.9    | Urgent Safety Measures .....                                                                                                       | 77        |
| 10.3.9.1  | Deviations from the Protocol and Other Actions Taken to Avoid Life-<br>threatening Risks to Participants .....                     | 77        |
| 10.3.10   | Reporting Urgent Safety Measures .....                                                                                             | 77        |
| 10.4      | Appendix 4 Liver Safety Monitoring and Assessment .....                                                                            | 78        |
| 10.5      | Appendix 5 List of Excluded Concomitant Medications .....                                                                          | 79        |
| 10.6      | Appendix 6 Clinical Laboratory Assessments .....                                                                                   | 81        |
| 10.7      | Appendix 7 Clinical Study Continuity .....                                                                                         | 83        |
| 10.8      | Appendix 8 Decentralized Clinical Trial (DCT) .....                                                                                | 86        |
| 10.9      | Appendix 9 EuroQol 5 Dimension 5-level (EQ-5D-5L) .....                                                                            | 87        |
| 10.10     | Appendix 10 Diabetes Treatment Satisfaction Questionnaire (DTSQ) .....                                                             | 88        |
| 10.11     | Appendix 11 14-Item Health Literacy Scale (HLS-14) .....                                                                           | 89        |
| <b>11</b> | <b>REFERENCES .....</b>                                                                                                            | <b>90</b> |
| <b>12</b> | <b>INVESTIGATOR'S SIGNATURE .....</b>                                                                                              | <b>91</b> |
| <b>13</b> | <b>SPONSOR'S SIGNATURE .....</b>                                                                                                   | <b>92</b> |

**List of In-text Tables**

|         |                                                                                                |    |
|---------|------------------------------------------------------------------------------------------------|----|
| Table 1 | Schedule of Assessments.....                                                                   | 20 |
| Table 2 | Study Objectives and Endpoints .....                                                           | 28 |
| Table 3 | Treatment Groups and Study Interventions.....                                                  | 36 |
| Table 4 | Details and Roles of Suppliers of the Investigational Device and Devices for<br>Study Use..... | 41 |
| Table 5 | Grading Scale Defining the Severity of an Adverse Event .....                                  | 74 |
| Table 6 | Clinical Laboratory Tests .....                                                                | 81 |

**List of In-text Figures**

|          |                    |    |
|----------|--------------------|----|
| Figure 1 | Study Schema ..... | 19 |
|----------|--------------------|----|

- CONFIDENTIAL -

**CONTACT DETAILS OF SPONSOR'S KEY PERSONNEL**

|                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-----------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>24-hour Contact for Serious Adverse Events or Deficiencies That May Cause Serious Adverse Events</b><br><br>See Section 10.3.7 | <b>Please fax or email the JUTOKUNA YUUGAIJISHOU OYOBI FUGUAI HOUKOKUSHO to:</b><br>Astellas Pharma Inc. Japan<br>Pharmacovigilance<br><b>Fax number: +81-(0)3-3243-5747</b><br><b>Email: rk-safety-jp@astellas.com</b>                                                                                                                                                                                                                                                                                                                        |
| Medical Monitor                                                                                                                   | <div data-bbox="586 533 802 606">PPD</div> <div data-bbox="786 575 842 606">MD</div> <div data-bbox="586 611 797 642">CMIC Co., Ltd.</div> <div data-bbox="834 642 919 674">PPD</div> <div data-bbox="631 716 740 747">PPD</div> <div data-bbox="805 722 1097 753">(Astellas Pharma Inc.)</div> <div data-bbox="631 753 716 785">PPD</div> <div data-bbox="764 758 894 789">MD, PhD</div> <div data-bbox="643 789 727 821">PPD</div> <div data-bbox="789 795 1073 827">, Astellas Pharma Inc.</div> <div data-bbox="821 827 906 858">PPD</div> |

- CONFIDENTIAL -

**LIST OF ABBREVIATIONS**

| <b>Abbreviations</b> | <b>Description of abbreviations</b>                                                                 |
|----------------------|-----------------------------------------------------------------------------------------------------|
| ADL                  | activities of daily living                                                                          |
| AE                   | adverse event                                                                                       |
| AI                   | artificial intelligence                                                                             |
| ALP                  | alkaline phosphatase                                                                                |
| ALT                  | alanine aminotransferase                                                                            |
| API                  | Astellas Pharma Inc.                                                                                |
| AST                  | aspartate aminotransferase                                                                          |
| BMI                  | body mass index                                                                                     |
| CBC                  | complete blood count                                                                                |
| CFR                  | Code of Federal Regulations                                                                         |
| CIOMS                | Council for International Organizations of Medical Sciences                                         |
| CRF                  | case report form                                                                                    |
| CRO                  | contract research organization                                                                      |
| CSR                  | clinical study report                                                                               |
| CTR                  | Clinical Trial Regulations (EU)                                                                     |
| DBP                  | diastolic blood pressure                                                                            |
| DCF                  | data clarification form                                                                             |
| DCT                  | decentralized clinical trial                                                                        |
| DTSQ                 | Diabetes Treatment Satisfaction Questionnaire                                                       |
| ECG                  | electrocardiogram                                                                                   |
| eCOA                 | electronic clinical outcome assessment                                                              |
| eCRF                 | electronic case report form                                                                         |
| EDF                  | early discontinuation in follow-up period                                                           |
| EDT                  | early discontinuation in treatment period                                                           |
| eGFR                 | estimated glomerular filtration rate                                                                |
| EOS                  | end of study                                                                                        |
| EOT                  | end of treatment: end of use of this product/end of study intervention                              |
| EQ-5D-5L             | EuroQol 5 Dimension 5-level                                                                         |
| FAS                  | full analysis set                                                                                   |
| FSH                  | follicle stimulating hormone                                                                        |
| GCP                  | good clinical practice for clinical studies of medical devices                                      |
| HbA1c                | hemoglobin A1c                                                                                      |
| HIPAA                | Health Insurance Portability and Accountability Act                                                 |
| HLS-14               | 14-item health literacy scale                                                                       |
| HRT                  | hormone replacement therapy                                                                         |
| IB                   | Investigator's Brochure                                                                             |
| ICF                  | informed consent form                                                                               |
| ICH                  | International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use |
| IEC                  | Independent Ethics Committee                                                                        |
| IND                  | Investigational New Drug                                                                            |
| IRB                  | Institutional Review Board                                                                          |
| IRT                  | interactive response technology                                                                     |
| ISN                  | international study number                                                                          |
| ISO                  | International Organization for Standardization                                                      |

- CONFIDENTIAL -

| Abbreviations | Description of abbreviations                                                                                                  |
|---------------|-------------------------------------------------------------------------------------------------------------------------------|
| IUD           | intrauterine device                                                                                                           |
| LAR           | legally authorized representative                                                                                             |
| MAR           | missing at random                                                                                                             |
| MMRM          | mixed effect model for repeated measures                                                                                      |
| QA            | quality assurance                                                                                                             |
| QC            | quality control                                                                                                               |
| QMS           | quality management system: criteria for manufacturing control and quality control of medical devices and in vitro diagnostics |
| QOL           | quality of life                                                                                                               |
| QTL           | quality tolerance limit                                                                                                       |
| RSI           | reference safety information                                                                                                  |
| (S)AE         | serious adverse event or adverse event                                                                                        |
| SAE           | serious adverse event                                                                                                         |
| SAF           | safety analysis set                                                                                                           |
| SAP           | statistical analysis plan                                                                                                     |
| SBP           | systolic blood pressure                                                                                                       |
| SMBG          | self-measured blood glucose                                                                                                   |
| SOP           | standard operating procedure                                                                                                  |
| SUSAR         | suspected unexpected serious adverse reactions                                                                                |
| TBL           | total bilirubin                                                                                                               |
| TEAE          | treatment-emergent adverse event                                                                                              |
| USM           | urgent safety measure                                                                                                         |
| WOCBP         | woman of childbearing potential                                                                                               |

- CONFIDENTIAL -

**DEFINITION OF TERMS**

| Technical term     | Definition of technical term                                                                                                                                                                                                                                                         |
|--------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| BMI                | Body Mass Index (kg/m <sup>2</sup> )<br>BMI = Body mass (kg)/height (m <sup>2</sup> )                                                                                                                                                                                                |
| eGFR               | Estimated glomerular filtration rate (mL/min/1.73m <sup>2</sup> )<br>Males: eGFR = $194 \times \text{serum creatinine (mg/dL)}^{-1.094} \times \text{age}^{-0.287}$<br>Females: eGFR = $194 \times \text{serum creatinine (mg/dL)}^{-1.094} \times \text{age}^{-0.287} \times 0.739$ |
| Follow-up period   | The period after the treatment period, from the end of assessment at visit 9 to the end of assessment at visit 12                                                                                                                                                                    |
| Study end date     | The date when assessment of all participants has ended (the date when all periods of the study, including final assessment, are complete)                                                                                                                                            |
| Screening period   | The period after registration, from visit 1 to randomization at visit 2                                                                                                                                                                                                              |
| Treatment period   | The period after the screening period, from randomization at visit 2 to the end of assessment at visit 9                                                                                                                                                                             |
| Registration date  | The date of obtaining informed consent                                                                                                                                                                                                                                               |
| This product       | The diabetes mellitus treatment support system (BAP0527 and blood glucose meter)                                                                                                                                                                                                     |
| Randomization date | The date when a participant is assigned to the BAP0527 group or usual treatment group                                                                                                                                                                                                |

**PROTOCOL AMENDMENT SUMMARY OF CHANGES**

| <b>Revision history</b>       |                  |
|-------------------------------|------------------|
| <b>Document</b>               | <b>Date</b>      |
| Amendment 1 [Non-substantial] | October 24, 2023 |
| Initial version               | October 2, 2023  |

**Amendment 1 [Non-substantial]: October 24, 2023**

This revision has been determined to be [Non-substantial] because it does not have a significant impact on the safety or physical or mental wellbeing of participants or the scientific value of this study, based on the criteria specified in Directive 2001/20/EC Article 10 (a) of the European Parliament and the Council of the European Union and EU regulations on clinical trials.

**Overall Rationale for Revision:**

Minor revisions were made to clarify the procedure of this study.

**Overview of Changes****Non-substantial changes**

| <b>Chapter number</b> | <b>Contents of change</b>                                                                                                                                        | <b>Brief rationale</b>                                                 |
|-----------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| 1.3, 10.6             | “Blood biochemistry: eGFR” and “Urinalysis: albumin” were added to the footnotes of Table 1 and Appendix 6 as items for which central lab measurement performed. | To clarify the procedure.                                              |
| 5.4                   | “Deficiency” was deleted from the scope of CRF collection data if the participant was ineligible for screening.                                                  | To clarify the procedure.                                              |
| 1.1, 2.1, 5.1         | Phrasing was amended.                                                                                                                                            | To make the expressions in the text and the notation style consistent. |

- CONFIDENTIAL -

# 1 PROTOCOL SUMMARY

## 1.1 Synopsis

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                 |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Title of Study:</b><br>Multicenter, Randomized, Open-label Study of Diabetes Treatment Support System (BAP0527 and Blood Glucose Meter) in Patients with Type 2 Diabetes Mellitus                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                 |
| <b>Regulatory Agency Identifier Number(s):</b><br>Not applicable.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                 |
| <b>Planned Total Number of Study Sites and Location(s):</b><br>Approximately 25 to 35 sites (Japan)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                 |
| <b>Rationale:</b><br><p>Welldoc Inc. (Maryland, U.S.) has developed BlueStar® as a digital health product for supporting management of disease treatment in adult patients with diabetes mellitus, and has obtained 510(k) authorization from the FDA for it as a medical device. BAP0527 is an application based on BlueStar, with its specification tailored to Japan, with the user language translated to Japanese and with alterations to aspects such as its algorithms to take into account the Japanese medical environment and guidelines, and aspects of the Japanese cultural background such as diet. The performance studies for BAP0527 include software verification and validation. Verification and validation of BlueStar, which BAP0527 is based on, has already been performed, and have demonstrated that it functions safely and efficaciously in the intended usage environment. Software verification has shown that the application operates as intended on different mobile platforms and web browsers. Validation has shown that the application functions as intended when operated in test scenarios anticipating actual use. Since the user language and some functions in the specification tailored to Japan have been altered from BlueStar for BAP0527, separate verification and validation have been performed, and have shown that it functions safely and efficaciously in the intended usage environment.</p> <p>Measurement of blood glucose levels is important for BAP0527 to be fully functional, but in Japan, the adoption of SMBG in patients with type 2 diabetes mellitus is limited. Accordingly, in Japan, the product for development has taken the form of a diabetes mellitus treatment support system (BAP0527 and the blood glucose meter, referred to below as “this product”) combining BAP0527 with a dedicated blood glucose meter (Accu-Chek® Guide Me from Roche DC Japan K. K., Tokyo [certification number: 303AABZX00007000]).</p> <p>Clinical studies using this product have not yet been performed. This study is conducted to assess the efficacy and safety of using this product in combination with usual treatment in patients with type 2 diabetes mellitus, based on the change in HbA1c levels.</p> |                                                                                                                                                                                                                                                                                                                                                 |
| <b>Study Objectives, Endpoints and Estimands:</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                 |
| <b>Objective</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <b>Endpoints</b>                                                                                                                                                                                                                                                                                                                                |
| <b>Primary</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                 |
| <ul style="list-style-type: none"> <li>To assess efficacy based on the change in HbA1c level.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <ul style="list-style-type: none"> <li>Change from baseline in HbA1c level at Week 24 (central lab measurement)</li> </ul>                                                                                                                                                                                                                      |
| <b>Secondary</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                 |
| <ul style="list-style-type: none"> <li>To assess efficacy based on blood glucose-related indices.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | <ul style="list-style-type: none"> <li>Change from baseline in HbA1c level at each assessment time point (except Week 24) (central lab measurement)</li> <li>Percentage of participants with a baseline HbA1c level <math>\geq 8.0\%</math> who achieved an HbA1c level <math>&lt; 8.0\%</math> at Week 24 (central lab measurement)</li> </ul> |

- CONFIDENTIAL -

|                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
|----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                                                                          | <ul style="list-style-type: none"> <li>Change from baseline in fasting blood glucose level and fasting insulin level at Week 24 (central lab measurement)</li> <li>Percentage of participants with a decreased dose of antidiabetics or reduced number of antidiabetics by Week 24, relative to antidiabetic use at baseline</li> <li>Percentage of participants with an increased dose of antidiabetics or newly started hypoglycemics by Week 24, relative to antidiabetic use at baseline</li> </ul>                                                                                                                                                                                                                                                                                                                   |
| <ul style="list-style-type: none"> <li>To assess the persistence of the effect based on the change in HbA1c level in the follow-up period.</li> </ul>    | <ul style="list-style-type: none"> <li>Change from baseline in HbA1c level at each assessment time point in the follow-up period (central lab measurement)</li> <li>Change from Week 24 in HbA1c level at each assessment time point in the follow-up period (central lab measurement)</li> <li>Percentage of participants with a decreased dose of antidiabetics or reduced number of antidiabetics by Week 12 of the follow-up period, relative to antidiabetic use at Week 24</li> <li>Percentage of participants with an increased dose of antidiabetics or newly started hypoglycemics by Week 12 of the follow-up period, relative to antidiabetic use at Week 24</li> </ul>                                                                                                                                        |
| <ul style="list-style-type: none"> <li>To assess safety.</li> </ul>                                                                                      | <ul style="list-style-type: none"> <li>AEs, deficiencies, laboratory test values (hematology, blood biochemistry, urinalysis), vital signs</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Exploratory</b>                                                                                                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <ul style="list-style-type: none"> <li>To assess efficacy based on the change in HbA1c level in participants with no change in hypoglycemics.</li> </ul> | <ul style="list-style-type: none"> <li>Change from baseline in HbA1c level at Week 24 (central lab measurement)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <ul style="list-style-type: none"> <li>To assess the effect on other efficacy endpoints.</li> </ul>                                                      | <ul style="list-style-type: none"> <li>Percentage of participants who achieved an HbA1c level &lt;7.0% at Week 24 (central lab measurement)</li> <li>Percentage of participants with a baseline HbA1c level <math>\geq 8.0\%</math> who achieved an HbA1c level &lt;8.0% at each assessment time point (except Week 24) (central lab measurement)</li> <li>Change from baseline in fasting blood glucose level and fasting insulin level at each assessment time point (except Week 24) (central lab measurement)</li> <li>Change from baseline in tests related to complications of diabetes mellitus (vital signs, lipid levels) at each assessment time point</li> <li>Percentages of each EQ-5D-5L level at each assessment time point</li> <li>Change from baseline in DTSQ at each assessment time point</li> </ul> |

- CONFIDENTIAL -

|                                                                                                                                         |                                                                                                                                                                                                                                                          |
|-----------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>To assess the effect on the number of unscheduled visits during the treatment period.</li> </ul> | <ul style="list-style-type: none"> <li>The number of unscheduled visits up to Week 24</li> </ul>                                                                                                                                                         |
| <ul style="list-style-type: none"> <li>To assess the relationship between the state of use of this product and effects.</li> </ul>      | <ul style="list-style-type: none"> <li>The BAP0527 access rate and blood glucose level data input rate</li> <li>The relationship between the BAP0527 access rate and blood glucose level data input rate and the effect improving HbA1c level</li> </ul> |

DTSQ: diabetes treatment satisfaction questionnaire; EQ-5D-5L: EuroQol 5 dimension 5-level; HbA1c: hemoglobin A1c

**Primary Estimand**  
Not applicable.

**Study Population:**  
Patients with type 2 diabetes mellitus

**Number of Participants:**  
Approximately 240 participants will be randomized so that, in both groups combined, approximately 220 assessable participants complete the study.

**Study Design Overview:**  
This study is a Japanese multicenter, randomized, open-label study of this product with a usual treatment group as a comparator group. The blood glucose meter that will be used in combination with BAP0527 is Accu-Chek Guide Me from Roche DC Japan K. K. (certification number: 303AABZX00007000). For the inclusion/exclusion criteria of this study, refer to “5.1 Inclusion Criteria” and “5.2 Exclusion Criteria.” After a screening period of up to 4 weeks, participants will be randomized in a 1:1 ratio to the group using this product in combination with usual treatment (below, “the BAP0527 group”) and the usual treatment group. To address bias, the HbA1c level (central lab measurement: <8.5%, ≥8.5%) and BMI level (<25 kg/m<sup>2</sup>, ≥25 kg/m<sup>2</sup>) at screening have been selected as assignment factors. During the 24-week treatment period, participants in the BAP0527 group will use this product in addition to usual treatment. After the end of the treatment period, use of this product will not be allowed. After the end of the treatment period, usual treatment will be administered in a 12-week follow-up period in both the BAP0527 group and the usual treatment group. From visit 2 to the end of the follow-up period, changing medication to hypoglycemics other than insulin preparations will be allowed if it is considered particularly necessary (for example, if there is a tendency towards markedly increased HbA1c levels or if there are reasons for concern about safety such as hypoglycemia). The use of insulin preparations will be prohibited. After the end of the study, participants will transition to usual healthcare. The objective of this study is to assess the efficacy and safety of the use of this product in combination with usual treatment in patients with type 2 diabetes mellitus aged ≥18 years not receiving treatment with insulin preparations.

**Inclusion Criteria:**

Participants who meet all of the following criteria will be eligible for inclusion in this study.

1. Participants who are at least 18 years old at the time of signing the ICF
2. Participants who have had a diagnosis of type 2 diabetes mellitus for at least 12 weeks (84 days) before visit 1
3. Participants being treated with only diet and exercise therapy, or participants being treated with hypoglycemics other than insulin preparations in addition to diet and exercise therapy, who have continued the same treatment for at least 12 weeks (84 days) as of visit 1
4. Participants who the investigator judges have potential for improvement from self-management of diabetes mellitus, including diet therapy and exercise therapy, and who are willing to improve their self-management of diabetes mellitus, while complying with the rules for participants relating to the use of BAP0527 and the blood glucose self-management device, as of visit 1
5. Participants who the investigator judges are able to perform outpatient management while participating in this study, as of visit 1
6. Participants judged by the investigator to have no problems inputting information into BAP0527 or using the blood glucose meter, from the perspective of cognitive function, visual acuity or device operating ability, as of visit 1
7. Participants having and using a smartphone device meeting the following operating system requirements as of visit 1
  - For iOS: Version 13 or later
  - For Android: Version 10 or later
8. Participants with an HbA1c level  $\geq 8.0\%$  and  $\leq 10.0\%$  (central lab measurement) as of visit 1
9. Participants who also meet inclusion criteria 3 to 7 at visit 2
10. Female participant:
  - is not pregnant (see “10.2 Appendix 2 Contraception Requirements”) and at least 1 of the following conditions apply:
    - a. Not a WOCBP (see “10.2 Appendix 2 Contraception Requirements”)
    - b. WOCBP who has a negative urine or serum pregnancy test between the time of providing informed consent and visit 2 and agrees to follow the contraceptive guidance (see “10.2 Appendix 2 Contraception Requirements”) from the time of informed consent through the end of the follow-up period
  - Consenting not to breastfeed from the time of providing informed consent until the end of the follow-up period
11. The participant has provided informed consent as described in “10.1.3 Informed Consent of Participants” which includes compliance with the requirements and restrictions listed in the ICF and protocol.
12. Participant agrees not to participate in another interventional study while participating in the present study.

**Exclusion Criteria:**

Participant will be excluded from participation in the study if any of the following apply:

1. Participants diagnosed with a type of diabetes mellitus other than type 2 diabetes mellitus, such as type 1 diabetes mellitus or secondary diabetes mellitus
2. Participants with a history of, or currently receiving treatment for, diabetic ketoacidosis

- CONFIDENTIAL -

3. Participants with retinopathy proliferative (however, if treatment such as photocoagulation has been performed and the investigator judges that symptoms are stable, the participant may be enrolled)
4. Participants diagnosed with clinically problematic cardiovascular or cerebrovascular disease such as myocardial infarction, poorly controlled angina pectoris/coronary artery disease, clinically problematic ventricular arrhythmia, cardiac failure (class III or IV according to the New York Heart Association classification) in the period of 12 weeks (84 days) before visit 1 (including the date of visit 1)
5. Participants with chronic disease requiring continuous use (such as oral use or injection) of adrenocortical steroids or immunosuppressants for their systemic action
6. Participants with concurrent malignant tumor (with a relapse-free period of less than 5 years)
7. Participants with concurrent serious infection
8. Participants with concurrent serious hepatic disorder
9. Participants with drug addiction, alcohol dependence or unstable psychiatric disease
10. Participants using insulin preparations
11. Participants who plan to be hospitalized or receive surgery during the period of participation in this study
12. Participants who have already been assigned in this study
13. Participants who receive any study treatment (including a follow-up period) in the period of 12 weeks (84 days) before visit 1 (including the date of visit 1) or who participate in any study treatment, when 5 half-lives of this treatment have not elapsed as of 12 weeks (84 days) before visit 1
14. Participants who have used a mobile application operating on a smartphone device for managing, or assisting in the management of, diabetes mellitus in the 12 weeks (84 days) before visit 1 (including the date of visit 1), when the investigator judges that the possibility of this history of use affecting efficacy evaluation in this study cannot be ruled out
15. Participants with a difference of more than 1.0% in the maximum and minimum HbA1c levels (measured at the hospital) measured in the 12 weeks (84 days) before visit 1 (including the date of visit 1)
16. Participants with SBP >180 mmHg or DBP >110 mmHg at rest in a sitting position at either visit 1, visit 2 or both, or participants with SBP >160 mmHg or DBP >100 mmHg at rest in a sitting position at both visit 1 and visit 2
17. Participants with concurrent diabetic nephropathy of stage 3 or higher (eGFR <30 mL/min/1.73m<sup>2</sup> or urine albumin ≥300 mg/gCre [each centrally measured values at visit 1])
18. Participants who have and use a smartphone device on which BAP0527 may not be displayed appropriately, or who plan to buy a new smartphone device on which BAP0527 may not be displayed appropriately between the time of providing informed consent and the end of the treatment period
19. Participants who are employees of Astellas Group, Welldoc Inc., Roche DC Japan K.K. or a study site, or the CRO involved in the study
20. Participant has any condition, which, in the investigator's opinion, makes the participant unsuitable for study participation.

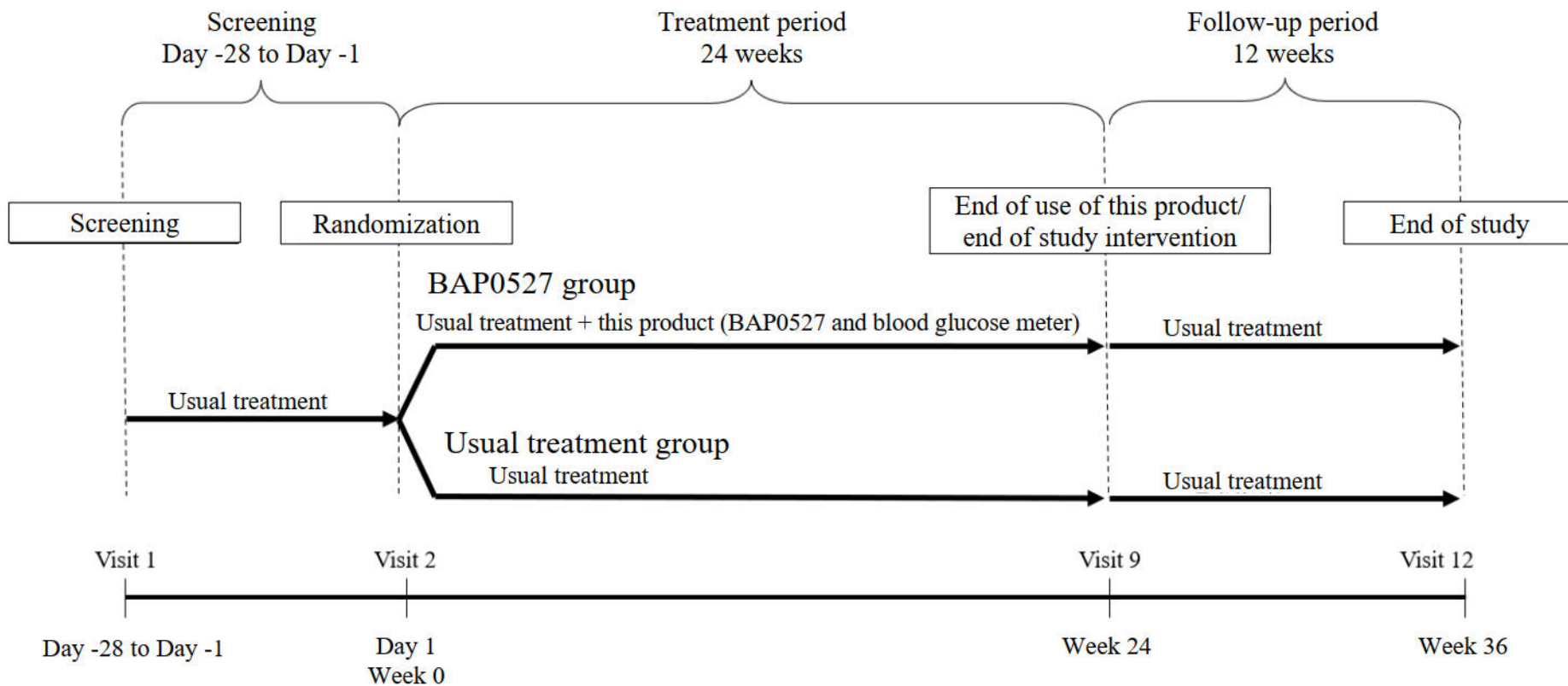
- CONFIDENTIAL -

| Treatment Groups and Study Periods:                                                                                                               |                                                                                                    |                                                              |                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------|--------------------------------------------------------------|-----------------------|
|                                                                                                                                                   | BAP0527 group                                                                                      |                                                              | Usual treatment group |
|                                                                                                                                                   | BAP0527                                                                                            | Blood glucose meter                                          |                       |
| <b>Intervention Name</b>                                                                                                                          | BAP0527                                                                                            | Accu-Chek Guide Me (certification number: 303AABZX00007000)  | Not applicable        |
| <b>Intervention Description</b>                                                                                                                   | Use of this product                                                                                | Use of this product                                          | Not applicable        |
| <b>Type</b>                                                                                                                                       | Medical device for study (application for patients + web application for healthcare professionals) | Medical device                                               | Not applicable        |
| <b>Use</b>                                                                                                                                        | Investigational device                                                                             | Device used in the clinical study                            | Not applicable        |
| <b>Supplier</b>                                                                                                                                   | Welldoc Inc.                                                                                       | Roche DC Japan K. K.                                         | Not applicable        |
| <b>Packaging and Labeling</b>                                                                                                                     | Labels are displayed inside the application according to government requirements.                  | The packaging and labeling of the marketed product are used. | Not applicable        |
| The expected study period for each participant, including the screening period, treatment period and follow-up period, is approximately 40 weeks. |                                                                                                    |                                                              |                       |

- CONFIDENTIAL -

## 1.2 Study Schema

Figure 1 Study Schema



- CONFIDENTIAL -

**1.3 Schedule of Assessments****Table 1 Schedule of Assessments**

| Item                                                                                                                                                 | Screening | Treatment period                                                                   |         |                      |                      |         |                      |                      |                  | Follow-up period        |                         |                       |
|------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|------------------------------------------------------------------------------------|---------|----------------------|----------------------|---------|----------------------|----------------------|------------------|-------------------------|-------------------------|-----------------------|
| Visit                                                                                                                                                | Visit 1   | Visit 2                                                                            | Visit 3 | Visit 4 <sup>p</sup> | Visit 5 <sup>p</sup> | Visit 6 | Visit 7 <sup>p</sup> | Visit 8 <sup>p</sup> | Visit 9          | Visit 10 <sup>p,q</sup> | Visit 11 <sup>p,q</sup> | Visit 12 <sup>q</sup> |
| Visit (Week)                                                                                                                                         | -         | 0                                                                                  | 2       | 4                    | 8                    | 12      | 16                   | 20                   | 24               | 28                      | 32                      | 36                    |
| Visit (Day)                                                                                                                                          | -28 to -1 | 1                                                                                  | 15      | 29                   | 57                   | 85      | 113                  | 141                  | 169<br>(EOT/EDT) | 197                     | 225                     | 253<br>(EOS/EDF)      |
| Allowable time window (days)                                                                                                                         | -         | -                                                                                  | ± 3     | ± 7                  | ± 7                  | ± 7     | ± 7                  | ± 7                  | ± 7              | ± 7                     | ± 7                     | ± 7                   |
| Informed consent <sup>a</sup>                                                                                                                        | X         |                                                                                    |         |                      |                      |         |                      |                      |                  |                         |                         |                       |
| Inclusion/exclusion criteria                                                                                                                         | X         | X                                                                                  |         |                      |                      |         |                      |                      |                  |                         |                         |                       |
| Medical History and<br>Concurrent Diseases                                                                                                           | X         | X                                                                                  |         |                      |                      |         |                      |                      |                  |                         |                         |                       |
| Participant Backgrounds                                                                                                                              | X         |                                                                                    |         |                      |                      |         |                      |                      |                  |                         |                         |                       |
| HLS-14                                                                                                                                               |           | X                                                                                  |         |                      |                      |         |                      |                      |                  |                         |                         |                       |
| Randomization                                                                                                                                        |           | X                                                                                  |         |                      |                      |         |                      |                      |                  |                         |                         |                       |
| Installation/uninstallation of<br>BAP0527, dispensing/return<br>of blood glucose meters <sup>b,c</sup>                                               |           | X                                                                                  |         |                      |                      |         |                      |                      | X                |                         |                         |                       |
| Use of this product <sup>b</sup>                                                                                                                     |           |  |         |                      |                      |         |                      |                      |                  |                         |                         |                       |
| Viewing of the web<br>application for healthcare<br>professionals <sup>b,d</sup>                                                                     |           |  |         |                      |                      |         |                      |                      |                  |                         |                         |                       |
| Setting target values for<br>diabetes mellitus treatment<br>(HbA1c level, amount of<br>carbohydrates, body weight,<br>blood pressure) <sup>b,e</sup> |           | X                                                                                  |         |                      |                      |         |                      |                      |                  |                         |                         |                       |
| Checks on and directions<br>about the participant's use of<br>this product <sup>b,f</sup>                                                            |           |                                                                                    | X       | X                    | X                    | X       | X                    | X                    | X                |                         |                         |                       |
| Looking back at the<br>participant's lifestyle between<br>visits by the investigator and<br>the participant using<br>BAP0527 data <sup>b</sup>       |           |                                                                                    | X       | X                    | X                    | X       | X                    | X                    | X                |                         |                         |                       |

- CONFIDENTIAL -

| Item                                                                                                                    | Screening | Treatment period |         |                      |                      |         |                      |                      |                  | Follow-up period        |                         |                       |
|-------------------------------------------------------------------------------------------------------------------------|-----------|------------------|---------|----------------------|----------------------|---------|----------------------|----------------------|------------------|-------------------------|-------------------------|-----------------------|
| Visit                                                                                                                   | Visit 1   | Visit 2          | Visit 3 | Visit 4 <sup>p</sup> | Visit 5 <sup>p</sup> | Visit 6 | Visit 7 <sup>p</sup> | Visit 8 <sup>p</sup> | Visit 9          | Visit 10 <sup>p,q</sup> | Visit 11 <sup>p,q</sup> | Visit 12 <sup>q</sup> |
| Visit (Week)                                                                                                            | -         | 0                | 2       | 4                    | 8                    | 12      | 16                   | 20                   | 24               | 28                      | 32                      | 36                    |
| Visit (Day)                                                                                                             | -28 to -1 | 1                | 15      | 29                   | 57                   | 85      | 113                  | 141                  | 169<br>(EOT/EDT) | 197                     | 225                     | 253<br>(EOS/EDF)      |
| Allowable time window (days)                                                                                            | -         | -                | ± 3     | ± 7                  | ± 7                  | ± 7     | ± 7                  | ± 7                  | ± 7              | ± 7                     | ± 7                     | ± 7                   |
| Reviewing set target values<br>(HbA1c level, amount of<br>carbohydrates, body weight,<br>blood pressure) <sup>b,g</sup> |           |                  | X       | X                    | X                    | X       | X                    | X                    |                  |                         |                         |                       |
| Checks on and directions<br>about the use of<br>sphygmomanometers and<br>scales                                         |           |                  | X       | X                    | X                    | X       | X                    | X                    | X                | X                       | X                       | X                     |
| Physical findings <sup>h</sup>                                                                                          | X         | X                | X       | X                    | X                    | X       | X                    | X                    | X                | X                       | X                       | X                     |
| Height/body weight <sup>i</sup>                                                                                         | X         | X                | X       | X                    | X                    | X       | X                    | X                    | X                | X                       | X                       | X                     |
| Vital Signs <sup>j</sup>                                                                                                | X         | X                | X       | X                    | X                    | X       | X                    | X                    | X                | X                       | X                       | X                     |
| HbA1c level                                                                                                             | X         | X                |         | X                    | X                    | X       | X                    | X                    | X                | X                       | X                       | X                     |
| Fasting blood glucose, fasting<br>insulin                                                                               |           | X                |         | X                    | X                    | X       | X                    | X                    | X                | X                       | X                       | X                     |
| Hematology <sup>k</sup>                                                                                                 | X         | X                |         | X                    | X                    | X       | X                    | X                    | X                | X                       | X                       | X                     |
| Blood biochemistry <sup>l</sup>                                                                                         | X         | X                |         | X                    | X                    | X       | X                    | X                    | X                | X                       | X                       | X                     |
| Urinalysis <sup>m</sup>                                                                                                 | X         | X                |         | X                    | X                    | X       | X                    | X                    | X                | X                       | X                       | X                     |
| Urine pregnancy tests<br>(WOCBP) <sup>n</sup>                                                                           | X         | X                |         | X                    | X                    | X       | X                    | X                    | X                | X                       | X                       | X                     |
| EQ-5D-5L, DTSQ <sup>o</sup>                                                                                             |           | X                |         | X                    | X                    | X       | X                    | X                    | X                | X                       | X                       | X                     |
| Concomitant<br>medications/concomitant<br>therapies                                                                     | X         | X                | X       | X                    | X                    | X       | X                    | X                    | X                | X                       | X                       | X                     |
| Assessment of AEs                                                                                                       | X         | X                | X       | X                    | X                    | X       | X                    | X                    | X                | X                       | X                       | X                     |
| Assessment of deficiencies <sup>b</sup>                                                                                 |           | X                | X       | X                    | X                    | X       | X                    | X                    | X                |                         |                         |                       |

DTSQ: diabetes treatment satisfaction questionnaire; EDF: early discontinuation in follow-up period; EDT: early discontinuation in treatment period; EOS: end of study; EOT: end of treatment; EQ-5D-5L: euroqol 5 dimension 5-level; HbA1c: hemoglobin A1c; HLS-14: 14-item health literacy scale; WOCBP: woman of childbearing potential

a: Consent will be obtained before the screening is performed. Consent may be obtained before visit 1.

b: This applies only to the BAP0527 group.

- CONFIDENTIAL -

c: When the application is installed, consent for the usage contract will be obtained from the participant.

d: During the study period, the investigator will prepare treatment plans as necessary with reference to the web application for healthcare professionals, including the smart report produced based on the information input by participants.

e: The investigator will set target values for HbA1c level, amount of carbohydrates, body weight and blood pressure for each participant. The participant will input the target value into the application.

f: At visit 3, the investigator will check the participant's use of the investigational device and provide directions and explanations about the usage method for this product as necessary. Additional directions will also be given at subsequent visits as necessary.

g: At visit 3, the set target values will be reviewed through consultation with the investigator. The set target values in the application will be changed as necessary. The set target values will also be reviewed on subsequent visits as necessary.

h: Subjective symptoms and objective findings will be checked via an interview.

i: Height will be measured only at visit 1.

j: Vital signs will include blood pressure at rest in a sitting position, pulse rate and body temperature.

k: Hematology will include hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, platelet count, red blood cell count, white blood cell count and white blood cell count differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes).

l: Blood biochemistry will include sodium, potassium, chloride, blood urea nitrogen, creatinine, eGFR, calcium, phosphorus, magnesium, albumin, total protein, ALP, lactate dehydrogenase, creatine phosphokinase, TBL, ALT, AST, total cholesterol, triglycerides, HDL cholesterol and LDL cholesterol.

m: Urinalysis will include specific gravity, pH, bilirubin, occult blood, glucose, ketones, leukocyte esterase, nitrite, protein, urobilinogen and albumin.

n: A dipstick will be used for the urine pregnancy test.

o: DTSQ will be performed after interview at each visit. In addition, in the BAP0527 group, DTSQ will be performed after setting target values for diabetes mellitus treatment, checks on and directions about the participant's use of this product, looking back at the participant's lifestyle between visits by the investigator and the participant using BAP0527 data, and reviewing set target values.

p: Visits 4, 5, 7, 8, 10 and 11 may be held as online examinations at the option of the participant, but only at sites that have agreed in advance with the sponsor about conducting the DCT. At the online examination, the following procedures will be performed: checks on and directions about the participant's use of this product, looking back at the participant's lifestyle between visits by the investigator and the participant using BAP0527 data, reviewing set target values (HbA1c level, amount of carbohydrates, body weight, blood pressure), and assessment of concomitant medications/concomitant therapies and AEs/deficiencies. The visiting nurse will measure body weight and vital signs, perform EQ-5D-5L and DTSQ, retrieve samples for specified tests and perform a urine pregnancy test.

q: Visits 10, 11 and 12 will be made by participants who have completed the treatment period.

## 2 INTRODUCTION

### 2.1 Study Rationale

Diabetes mellitus is a chronic disease that still presents issues both for patients and for healthcare providers, and despite the many available technologies and drugs, blood glucose control is insufficient, and similarly, treatment of blood pressure and cholesterol is not fully satisfactory. Initiatives to deal with clinical inertia (the state where treatment is not appropriately enhanced despite treatment targets not being met) are in progress in many countries [Bodenheimer, 2014; Casagrande, 2013; Khunti, 2013].

Welldoc Inc. (Maryland, U.S.) has decided to develop software as a medical device using automated AI to achieve the following 4 targets.

- To manage blood glucose levels more appropriately using SMBG.
- To support self-management and education in relation to medication, meals, exercise and the like, for better management of diabetes mellitus.
- To provide real-time coaching to encourage instant and long-term behavioral change, to optimize blood glucose control.
- To monitor the patient's status as necessary based on guidelines founded on clinical evidence and provide data summaries and insights to medical institutions and healthcare professionals, to optimize treatment.

These measures are not new, but are the same as many human-intervention coaching programs that have already been reported.

Welldoc Inc. has developed BlueStar as a digital health product for supporting management of disease treatment in adult patients with diabetes mellitus, and has obtained 510(k) authorization from the FDA for it as a medical device. BAP0527 is an application based on BlueStar, with its specification tailored to Japan, with the user language translated to Japanese and with alterations to aspects such as its algorithms to take into account the Japanese medical environment and guidelines, and aspects of the Japanese cultural background such as diet.

The performance studies for BAP0527 include software verification and validation. Verification and validation of BlueStar, which BAP0527 is based on, has already been performed, and have demonstrated that it functions safely and efficaciously in the intended usage environment. Software verification has shown that the application operates as intended on different mobile platforms and web browsers. Validation has shown that the application functions as intended when operated in test scenarios anticipating actual use. Since the user language and some functions in the specification tailored to Japan have been altered from BlueStar for BAP0527, separate verification and validation have been performed, and have shown that it functions safely and efficaciously in the intended usage environment.

Measurement of blood glucose levels is important for BAP0527 to be fully functional, but in Japan, the adoption of SMBG in patients with type 2 diabetes mellitus is limited.

Accordingly, in Japan, the product for development has taken the form of a diabetes mellitus treatment support system (BAP0527 and the blood glucose meter, referred to below as “this product”) combining BAP0527 with a dedicated blood glucose meter (Accu-Chek Guide Me from Roche DC Japan K. K., Tokyo [certification number: 303AABZX00007000]).

Clinical studies using this product have not yet been performed. This study will be conducted to assess the efficacy and safety of using this product in combination with usual treatment in patients with type 2 diabetes mellitus, based on the change in HbA1c levels.

## 2.2 Background

The treatment policy for type 2 diabetes mellitus is to firstly provide education about diabetes mellitus, in preparation for diet therapy, exercise therapy and improvement of lifestyle habits. This education about diabetes mellitus and self-management behavior are important for achieving blood glucose control targets, and it is considered to be necessary to continue this even after drug therapy is started [The Japan Diabetes Society, 2020b]. Since the effect of diet and exercise varies between individual patients, even those whose diet and exercise are the same, it is necessary for patients themselves to obtain correct knowledge from directions by healthcare professionals and continue self-management in their daily lives, in order to control blood glucose through diet therapy or exercise therapy and prevent complications. On the other hand, since diet and exercise are rooted in the patient’s lifestyle, it is difficult for patients to change their existing lifestyle and continue self-management to manage diabetes mellitus, and the fourth Five-Year Diabetes Strategy states that continuity of diet therapy and exercise therapy is a constant problem. Patients experience few symptoms in the early stages of diabetes mellitus, and prior research suggests that the lack of experienced symptoms does not lead to an awareness of the need for therapy, and is one factor making it difficult to continue self-management [The Japan Diabetes Society, 2020a; Nishio, 2016; Ishii et al., 2012].

When encouraging self-management by patients, it is thought to be beneficial to know about daily blood glucose levels, and the “Japanese Clinical Practice Guideline for Diabetes 2019” states that the usefulness of SMBG in patients with type 1 diabetes mellitus and the efficacy of SMBG in type 2 diabetes mellitus receiving insulin therapy have been demonstrated. On the other hand, the introduction of SMBG in patients with type 2 diabetes mellitus not using insulin has not been found to have an effect improving HbA1c levels compared to usual care, and has been reported to increase costs and reduce QOL [The Japan Diabetes Society 2019]. However, meta-analysis comparing structured SMBG with the provision of education and directions about the timing of measurements versus unstructured SMBG found that structured SMBG has a significantly higher effect improving HbA1c levels [The Japan Diabetes Society 2019; Mannucci et al, 2018]. Additionally, the “Self-monitoring of blood glucose in non-insulin treated type 2 diabetes” guideline published by the International Diabetes Federation state that, although SMBG may promote improvement of blood glucose levels in non-insulin treated type 2 diabetes mellitus, it is limited when used in combination with training to learn

methods for adjustment of diet and lifestyle habits based on results [International Diabetes Federation, 2009]. These guidelines suggest that, in patients with type 2 diabetes mellitus not using insulin, it may show an effect improving HbA1c levels if patients receive instructions about the method for measuring SMBG and have an opportunity to learn about the method for adjusting lifestyle habits such as diet and exercise based on blood glucose levels. However, in Japan, SMBG and continuous blood glucose monitoring are performed in only a limited percentage of cases.

In response to these issues, we consider that BAP0527 can encourage change in patients' behavior through an objective understanding of their own lifestyle habits, including the influence of diet and exercise on blood glucose levels, and thus improve self-management of diabetes mellitus, by providing directions and education content focusing mainly on diet and exercise, without restrictions due to time or location, and based on the information that the patient inputs into BAP0527. Developing BAP0527 and the blood glucose meter as a single diabetes mellitus treatment support system for patients with type 2 diabetes mellitus with poor blood glucose control who are not receiving insulin therapy will allow patients to measure their blood glucose levels using the blood glucose meter and input the results into BAP0527 in their daily lives, together with other information. This is expected to give feedback to the patient based on changes in blood glucose level, promoting better quality diet therapy and exercise therapy. Patients showing healthcare professionals the information they have input into BAP0527, so that the healthcare professionals can find out detailed patient information about lifestyle between visits, is expected to contribute to improving the quality of directions about management of diabetes mellitus. Additionally, BAP0527 analyzes the information input by the patient based on Japanese clinical practice guidelines for diabetes mellitus and proposes healthcare intervention to healthcare professionals. By providing support for healthcare professionals preparing treatment plans for individual patients based on this information, BAP0527 is expected to contribute to providing healthcare that takes into account the different pathologies and lifestyle habits of individual patients.

The mechanism of the action of this product reducing blood glucose is the promotion of changes in behavior in patients and medical staff, and it is foreseen to have a low risk of occurrence of adverse reactions of the type associated with pharmaceuticals. We consider that effects such as reducing the risk of complications are extremely meaningful.

## **2.3 Risk/Benefit Assessment**

### **2.3.1 Risk Assessment**

#### **2.3.1.1 Expected Device-Related Adverse Events**

Collection of small amounts of blood is necessary for SMBG. This is associated with a risk of infection if pathogenic microbes have adhered to the blood collection site.

Safety information on BAP0527 is limited, and no expected serious adverse reactions have been identified. From risk analysis of BlueStar, the risk of occurrence of the following SAEs is expected.

- Serious hypoglycaemia

There is the expected risk of data that are different from the measured blood glucose data being communicated, for example due to input error, and if healthcare professionals change the treatment plan according to these data, or if the patient follows incorrect messages based on mistakenly input data, there is a risk of serious hypoglycaemia. If abnormal blood glucose data are input, feedback is always provided, with a message prompting the patient to follow the instructions from a healthcare professional.

- Serious hyperglycaemia

There is the expected risk of data that are different from the measured blood glucose data being communicated, for example due to input error, and if healthcare professionals change the treatment plan according to these data, or if the patient follows incorrect messages based on mistakenly input data, there is a risk of serious hyperglycaemia. If abnormal blood glucose data are input, feedback is always provided, with a message prompting the patient to follow the instructions from a healthcare professional.

Safety information about BAP0527 is limited, and no expected deficiencies have been identified.

For RSI relating to BAP0527 and the blood glucose meter, refer to the IB for BAP0527 and the package insert for Accu-Chek Guide Me.

### **2.3.1.2 Risks Relating to Study Participation**

Possible risks including the possibility of AEs due to BAP0527 and the blood glucose meter and the possibility of disadvantageous occurrences such as internal haemorrhage or redness due to blood collection.

Other possible disadvantages may occur due to some restrictions to concomitant medication being imposed from visit 1 until the end of tests for the efficacy endpoints at visit 12 (or at discontinuation) as a result of participation in this study.

### **2.3.1.3 Possibility of Interactions with Concomitant Drugs Considered Risk Analysis**

The mechanism of the action of this product reducing blood glucose is the promotion of changes in behavior in patients and medical staff, and it is foreseen to have a low risk of occurrence of adverse reactions of the type associated with pharmaceuticals. If this product improves control of blood glucose, hypoglycaemia may occur in patients concomitantly using hypoglycemics. There is no experience of clinical studies using this product (including information related to other indications of the investigational device).

### **2.3.1.4 Actions Taken to Manage or Reduce Risk**

The detailed usage method for the application for patients and the web application for healthcare professionals will be stated in the user's guide for each user. The investigator will train the patients in the method of using the equipment for SMBG and will take measures to ensure that the devices are used appropriately.

If AEs occur, the investigator will find out information about the situation and take action as necessary.

There is the risk that blood glucose may become poorly controlled due to some restriction to concomitant medication applying during the study period, and blood glucose may decrease due to the effect of this product, and therefore changing medication to hypoglycemics other than insulin preparations will be allowed if it is considered particularly necessary (for example, if there is a tendency towards markedly increased HbA1c levels or if there are reasons for concern about safety such as hypoglycaemia). Out of consideration for the safety of patients, the situation where it becomes necessary to newly introduce the use of insulin preparations is a criterion for discontinuing study intervention.

### **2.3.2 Benefit Assessment (Expected Clinical Benefits)**

We consider that BAP0527 can encourage change in patients' behavior through an objective understanding of their own lifestyle habits, including the influence of diet and exercise on blood glucose levels, and thus improve self-management of diabetes mellitus, by providing directions and education content focusing mainly on diet and exercise, without restrictions due to time or location, and based on the information that the patient inputs into BAP0527. Developing BAP0527 and the blood glucose meter as a single diabetes mellitus treatment support system for patients with type 2 diabetes mellitus with poor blood glucose control who are not receiving insulin therapy will allow patients to measure their blood glucose levels using the blood glucose meter and input the results into BAP0527 in their daily lives, together with other information. This is expected to give feedback to the patient based on changes in blood glucose level, promoting better quality diet therapy and exercise therapy. Patients showing healthcare professionals the information they have input into BAP0527, so that the healthcare professionals can find out detailed patient information about lifestyle between visits, is expected to contribute to improving the quality of directions about management of diabetes mellitus. Additionally, BAP0527 analyzes the information input by the patient based on Japanese clinical practice guidelines for diabetes mellitus and proposes healthcare intervention to healthcare professionals. By providing support for healthcare professionals preparing treatment plans for individual patients based on this information, BAP0527 is expected to contribute to providing healthcare that takes into account the different pathologies and lifestyle habits of individual patients.

The mechanism of the action of this product reducing blood glucose is the promotion of changes in behavior in patients and medical staff, and it is foreseen to have a low risk of occurrence of adverse reactions of the type associated with pharmaceuticals. We consider that, if this product is found to improve HbA1c levels, effects such as reducing the risk of complications would be extremely meaningful.

### **2.3.3 Overall Risk-Benefit Conclusion (Rationale for Benefit-Risk Ratio)**

By promoting changes in behavior in patients and medical staff, this product is expected to improve the lifestyle habits of patients and achieve good control of blood glucose. Diet therapy, exercise therapy and education about diabetes mellitus should be continued even

- CONFIDENTIAL -

after drug therapy is started, and this product is expected to have an additive effect if used in combination with hypoglycemics. The mechanism of the action of this product reducing blood glucose is the promotion of changes in behavior in patients and medical staff, and it is foreseen to have a low risk of occurrence of adverse reactions of the type associated with pharmaceuticals. As such, this product is expected to enable good control of blood glucose in patients with type 2 diabetes mellitus with insufficient control of blood glucose.

On the other hand, risks from using this product incorrectly are foreseen, but we concluded that major problems can be avoided by stating the detailed usage methods for each user in the user's guides and providing training for patients.

Thus, this product has a good benefit-risk balance and can likely become a new treatment option for patients with type 2 diabetes mellitus.

### 3 OBJECTIVES, ENDPOINTS AND ESTIMANDS

**Table 2 Study Objectives and Endpoints**

| Objectives                                                                                                   | Endpoints                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|--------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Primary</b>                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <ul style="list-style-type: none"> <li>To assess efficacy based on the change in HbA1c level.</li> </ul>     | <ul style="list-style-type: none"> <li>Change from baseline in HbA1c level at Week 24 (central lab measurement)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <b>Secondary</b>                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <ul style="list-style-type: none"> <li>To assess efficacy based on blood glucose-related indices.</li> </ul> | <ul style="list-style-type: none"> <li>Change from baseline in HbA1c level at each assessment time point (except Week 24) (central lab measurement)</li> <li>Percentage of participants with a baseline HbA1c level <math>\geq 8.0\%</math> who achieved an HbA1c level <math>&lt; 8.0\%</math> at Week 24 (central lab measurement)</li> <li>Change from baseline in fasting blood glucose level and fasting insulin level at Week 24 (central lab measurement)</li> <li>Percentage of participants with a decreased dose of antidiabetics or reduced number of antidiabetics by Week 24, relative to antidiabetic use at baseline</li> <li>Percentage of participants with an increased dose of antidiabetics or newly started hypoglycemics by Week 24, relative to antidiabetic use at baseline</li> </ul> |

- CONFIDENTIAL -

| Objectives                                                                                                                                               | Endpoints                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|----------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>To assess the persistence of the effect based on the change in HbA1c level in the follow-up period.</li> </ul>    | <ul style="list-style-type: none"> <li>Change from baseline in HbA1c level at each assessment time point in the follow-up period (central lab measurement)</li> <li>Change from Week 24 in HbA1c level at each assessment time point in the follow-up period (central lab measurement)</li> <li>Percentage of participants with a decreased dose of antidiabetics or reduced number of antidiabetics by Week 12 of the follow-up period, relative to antidiabetic use at Week 24</li> <li>Percentage of participants with an increased dose of antidiabetics or newly started hypoglycemics by Week 12 of the follow-up period, relative to antidiabetic use at Week 24</li> </ul>                                                                                                                                        |
| <ul style="list-style-type: none"> <li>To assess safety.</li> </ul>                                                                                      | <ul style="list-style-type: none"> <li>AEs, deficiencies, laboratory test values (hematology, blood biochemistry, urinalysis), vital signs</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Exploratory                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <ul style="list-style-type: none"> <li>To assess efficacy based on the change in HbA1c level in participants with no change in hypoglycemics.</li> </ul> | <ul style="list-style-type: none"> <li>Change from baseline in HbA1c level at Week 24 (central lab measurement)</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <ul style="list-style-type: none"> <li>To assess the effect on other efficacy endpoints.</li> </ul>                                                      | <ul style="list-style-type: none"> <li>Percentage of participants who achieved an HbA1c level &lt;7.0% at Week 24 (central lab measurement)</li> <li>Percentage of participants with a baseline HbA1c level <math>\geq 8.0\%</math> who achieved an HbA1c level &lt;8.0% at each assessment time point (except Week 24) (central lab measurement)</li> <li>Change from baseline in fasting blood glucose level and fasting insulin level at each assessment time point (except Week 24) (central lab measurement)</li> <li>Change from baseline in tests related to complications of diabetes mellitus (vital signs, lipid levels) at each assessment time point</li> <li>Percentages of each EQ-5D-5L level at each assessment time point</li> <li>Change from baseline in DTSQ at each assessment time point</li> </ul> |
| <ul style="list-style-type: none"> <li>To assess the effect on the number of unscheduled visits during the treatment period.</li> </ul>                  | <ul style="list-style-type: none"> <li>The number of unscheduled visits up to Week 24</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <ul style="list-style-type: none"> <li>To assess the relationship between the state of use of this product and effects.</li> </ul>                       | <ul style="list-style-type: none"> <li>The BAP0527 access rate and blood glucose level data input rate</li> <li>The relationship between the BAP0527 access rate and blood glucose level data input rate and the effect improving HbA1c level</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

DTSQ: diabetes treatment satisfaction questionnaire; EQ-5D-5L: EuroQol 5 dimension 5-level; HbA1c: hemoglobin A1c

### 3.1 Estimands

Not applicable.

## 4 STUDY DESIGN

### 4.1 Overall Study Design

This study is a Japanese multicenter, randomized, open-label study of this product with a usual treatment group as a comparator group. The blood glucose meter that will be used in combination with BAP0527 is Accu-Chek Guide Me from Roche DC Japan K. K. (certification number: 303AABZX00007000). For the inclusion/exclusion criteria of this study, refer to “5.1 Inclusion Criteria” and “5.2 Exclusion Criteria.” After a screening period of up to 4 weeks, participants will be randomized in a 1:1 ratio to the group using this product in combination with usual treatment (below, “the BAP0527 group”) and the usual treatment group. To address bias, the HbA1c level (central lab measurement: <8.5%, ≥8.5%) and BMI level (<25 kg/m<sup>2</sup>, ≥25 kg/m<sup>2</sup>) at screening have been selected as assignment factors. During the 24-week treatment period, participants in the BAP0527 group will use this product in addition to usual treatment. After the end of the treatment period, use of this product will not be allowed. After the end of the treatment period, usual treatment will be administered in a 12-week follow-up period in both the BAP0527 group and the usual treatment group. From visit 2 to the end of the follow-up period, changing medication to hypoglycemics other than insulin preparations will be allowed if it is considered particularly necessary (for example, if there is a tendency towards markedly increased HbA1c levels or if there are reasons for concern about safety such as hypoglycemia). The use of insulin preparations will be prohibited. After the end of the study, participants will transition to usual healthcare.

The objective of this study is to assess the efficacy and safety of the use of this product in combination with usual treatment in patients with type 2 diabetes mellitus aged ≥18 years not receiving treatment with insulin preparations.

- Screening period

The date of informed consent will be the registration date in this study. The screening period will be the period after registration from visit 1 until randomization at visit 2.

- All participants: All participants will receive screening (visit 1) within 4 weeks after the start of the treatment period. After this, participants will be randomized in a 1:1 ratio into the BAP0527 group and usual treatment group. The randomization date will be the date when the participant is randomized.

- Treatment period

The treatment period will be the period after randomization at visit 2 to the end of assessment at visit 9.

- BAP0527 group: During the treatment period, participants will use this product in addition to usual treatment at each site. Participants will continuously use BAP0527, while measuring their daily blood glucose levels using the blood glucose meter, and will input daily self-management records such as lifestyle habits (diet, exercise, sleep), use of medication and measurements (blood glucose level, blood pressure,

pulse rate, body weight) into BAP0527. The recommended timing for SMBG measurements is paired measurements, generally before meals (from 30 minutes before the start of a meal, until the start of the meal) and 2 hours after a meal, 15 times (generally, at breakfast, lunch and dinner, 5 times each) (a total of 30 times) per month. Participants will be allowed to optionally measure at other times, such as the time they wake up, the time they go to bed or before or after exercise. However, the maximum number of measurements will be 60 times per month. In addition to actions such as reviewing lifestyle habits according to the messages produced by BAP0527 based on the input data, participants will view educational content. In addition, the investigator will prepare treatment plans as necessary with reference to the web application for healthcare professionals, including the smart report produced based on the information input by participants.

- Usual treatment group: During the treatment period, participants will continue to receive the usual treatment they received before participating in the study.
- All participants: As self-management, participants will measure their vital signs and body weight between visits, in principle every day.
- Follow-up period

The follow-up period will be the period after the treatment period from the end of assessment at visit 9 to the end of assessment at visit 12. Follow-up will be performed in participants who have completed the treatment period.

- All participants: As self-management, participants will measure their vital signs and body weight between visits, in principle every day.

The expected study period for each participant, including the screening period, treatment period and follow-up period, is approximately 40 weeks.

## 4.2 Scientific Rationale for Study Design

- This study is a study to assess whether the use of this product in combination with usual treatment in patients with type 2 diabetes mellitus can achieve good control of blood glucose. Therefore, this product is a system that aims to support treatment of diabetes mellitus, and with reference to the guidelines on clinical evaluation of oral hypoglycemic agents (PFSB/ELD Notification No. 0709-1, “Guideline for Clinical Evaluation of Oral Hypoglycemic Agents,” on July 9, 2010) we selected HbA1c level as the primary endpoint, as it is the most highly recommended indicator of control of blood glucose.
- The same guideline states that if HbA1c level is the primary endpoint, in principle, a period of 24 weeks is preferable, and therefore we selected 24 weeks as the duration of the treatment period. We selected every 4 weeks as the timing of assessment point because the same guideline states that if HbA1c levels are used as an indicator of control of blood glucose, they should be measured every 4 weeks.
- Participants assigned to the BAP0527 group may have residual effects from behavioral change even after the end of the treatment period. To assess the persistence of the effect

after use of this product has ended, we selected 12 weeks as the duration of the follow-up period, in which HbA1c levels can be assessed.

- Since the “Japanese Clinical Practice Guideline for Diabetes 2019” states that, if enhancement of control of blood glucose is difficult for various reasons, the target level for control of blood glucose is an HbA1c level  $<8.0\%$ , and to ensure the safety of participants, we included patients with HbA1c levels  $\geq 8.0\%$  and  $\leq 10.0\%$ .
- Since it is not feasible to design a sham application for BAP0527, we did not establish a sham application group in this study, and the study will be an open-label study with the usual treatment group as a comparator group. So that efficacy assessment can be performed appropriately even under open-label conditions, we selected the objective indicator HbA1c level as the primary endpoint.

#### **4.2.1 Participant Input into Study Design**

In a survey conducted in patients with diabetes mellitus, the main reasons listed for experiencing issues with self-management such as diet and exercise in treatment for diabetes mellitus included the issue that it is difficult for patients themselves to judge whether they are performing self-management such as diet and exercise according to the instruction on diet and on exercise from medical staff. Therefore, in this study, we decided to establish visits every 2 weeks in the first month, and check the status of self-management such as diet and exercise at the visit in Week 2.

#### **4.3 Dose Rationale**

Not applicable.

#### **4.4 Start and End of Study Definitions**

##### **First act of recruitment**

The study start date is the date when registration of participants in this study is started, and is defined as the date when the first participant signs the ICF.

##### **End of study**

The study end date is the date when assessment of all participants participating in this study has ended, and is defined as the date when all participants have completed all periods of the study, including final assessment, shown in the schedule of assessments [Table 1].

### **5 STUDY POPULATION**

All screening assessments must be completed and reviewed to confirm the potential participant meets all eligibility criteria. Prospective approval of protocol deviations to eligibility criteria (also known as protocol waivers or exemptions) is not permitted.

#### **5.1 Inclusion Criteria**

Participant is eligible for participation in the study if all of the following apply:

**Age**

1. Participants who are at least 18 years old at the time of signing the ICF

**Type of Participant and Disease Characteristics**

2. Participants who have had a diagnosis of type 2 diabetes mellitus for at least 12 weeks (84 days) before visit 1
3. Participants being treated with only diet and exercise therapy, or participants being treated with hypoglycemics other than insulin preparations in addition to diet and exercise therapy, who have continued the same treatment for at least 12 weeks (84 days) as of visit 1
4. Participants who the investigator judges have potential for improvement from self-management of diabetes mellitus, including diet therapy and exercise therapy, and who are willing to improve their self-management of diabetes mellitus, while complying with the rules for participants relating to the use of BAP0527 and the blood glucose meter, as of visit 1
5. Participants who the investigator judges are able to perform outpatient management while participating in this study, as of visit 1
6. Participants judged by the investigator to have no problems inputting information into BAP0527 or using the blood glucose meter, from the perspective of cognitive function, visual acuity or device operating ability, as of visit 1
7. Participants having and using a smartphone device meeting the following operating system requirements as of visit 1
  - For iOS: Version 13 or later
  - For Android: Version 10 or later
8. Participants with an HbA1c level  $\geq 8.0\%$  and  $\leq 10.0\%$  (central lab measurement) as of visit 1
9. Participants who also meet inclusion criteria 3 to 7 at visit 2

**Sex and Contraceptive Requirements**

10. Female participant:
  - is not pregnant (see “10.2 Appendix 2 Contraception Requirements”) and at least 1 of the following conditions apply:
    - a. Not a WOCBP (see “10.2 Appendix 2 Contraception Requirements”)
    - b. WOCBP who has a negative urine or serum pregnancy test between the time of providing informed consent and visit 2 and agrees to follow the contraceptive guidance (see “10.2 Appendix 2 Contraception Requirements”) from the time of informed consent through the end of the follow-up period
  - Consenting not to breastfeed from the time of providing informed consent until the end of the follow-up period

**Informed Consent**

11. The participant has provided informed consent as described in “10.1.3 Informed Consent of Participants” which includes compliance with the requirements and restrictions listed in the ICF and protocol.

**Other Inclusion Criteria**

12. Participant agrees not to participate in another interventional study while participating in the present study.

**5.2 Exclusion Criteria**

Participant will be excluded from participation in the study if any of the following apply:

**Medical Conditions**

1. Participants diagnosed with a type of diabetes mellitus other than type 2 diabetes mellitus, such as type 1 diabetes mellitus or secondary diabetes mellitus
2. Participants with a history of, or currently receiving treatment for, diabetic ketoacidosis
3. Participants with retinopathy proliferative (however, if treatment such as photocoagulation has been performed and the investigator judges that symptoms are stable, the participant may be enrolled)
4. Participants diagnosed with clinically problematic cardiovascular or cerebrovascular disease such as myocardial infarction, poorly controlled angina pectoris/coronary artery disease, clinically problematic ventricular arrhythmia, cardiac failure (class III or IV according to the New York Heart Association classification) in the period of 12 weeks (84 days) before visit 1 (including the date of visit 1)
5. Participants with chronic disease requiring continuous use (such as oral use or injection) of adrenocortical steroids or immunosuppressants for their systemic action
6. Participants with concurrent malignant tumor (with a relapse-free period of less than 5 years)
7. Participants with concurrent serious infection
8. Participants with concurrent serious hepatic disorder
9. Participants with drug addiction, alcohol dependence or unstable psychiatric disease

**Prior/Concomitant Therapy**

10. Participants using insulin preparations
11. Participants who plan to be hospitalized or receive surgery during the period of participation in this study
12. Participants who have already been assigned in this study

**Prior/Concurrent Clinical Study Experience**

13. Participants who receive any study treatment (including a follow-up period) in the period of 12 weeks (84 days) before visit 1 (including the date of visit 1) or who participate in any study treatment, when 5 half-lives of this treatment have not elapsed as of 12 weeks (84 days) before visit 1
14. Participants who have used a mobile application operating on a smartphone device for managing, or assisting in the management of, diabetes mellitus in the 12 weeks (84 days) before visit 1 (including the date of visit 1), when the investigator judges that the possibility of this history of use affecting efficacy evaluation in this study cannot be ruled out

**Diagnostic Assessments**

15. Participants with a difference of more than 1.0% in the maximum and minimum HbA1c levels (measured at the hospital) measured in the 12 weeks (84 days) before visit 1 (including the date of visit 1)
16. Participants with SBP >180 mmHg or DBP >110 mmHg at rest in a sitting position at either visit 1, visit 2 or both, or participants with SBP >160 mmHg or DBP >100 mmHg at rest in a sitting position at both visit 1 and visit 2
17. Participants with concurrent diabetic nephropathy of stage 3 or higher (eGFR <30 mL/min/1.73m<sup>2</sup> or urine albumin ≥300 mg/gCre [each centrally measured values at visit 1])

**Other Exclusion Criteria**

18. Participants who have and use a smartphone device on which BAP0527 may not be displayed appropriately, or who plan to buy a new smartphone device on which BAP0527 may not be displayed appropriately between the time of providing informed consent and the end of the treatment period
19. Participants who are employees of Astellas Group, Welldoc Inc., Roche DC Japan K.K. or a study site, or the CRO involved in the study
20. Participant has any condition, which, in the investigator's opinion, makes the participant unsuitable for study participation.

**5.3 Lifestyle Considerations**

Not applicable.

**5.4 Screen Failures**

A screen failure is defined as a potential participant who signed the ICF, but did not meet 1 or more criteria required for participation in the study and was not randomized.

For screen failures, the demographic data, date of signing the ICF, inclusion and exclusion criteria, AEs up to the time of screen failure and reason for screen failure will be collected in the CRF.

- CONFIDENTIAL -

### 5.4.1 Rescreening

In the specific case where a participant is not assigned because visit 2 cannot be performed for the participant within the allowable time window, rescreening after the participant is judged to be ineligible for screening will be allowed. After a participant is registered as ineligible for screening, written consent for the study will be obtained again, a new participant identification number will be assigned to the participant and rescreening will be performed.

## 6 STUDY INTERVENTION AND CONCOMITANT THERAPY

Study interventions are all pre-specified medicinal products, medical devices, vaccines and other interventions (e.g. surgical and behavioral) intended to be administered to the study participants during the study conduct.

### 6.1 Study Intervention(s) Administered

**Table 3 Treatment Groups and Study Interventions**

|                                      | BAP0527 group                                                                                                                                                                                                                                       |                                                                    | Usual treatment group |
|--------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|-----------------------|
|                                      | BAP0527                                                                                                                                                                                                                                             | Blood glucose meter                                                |                       |
| <b>Intervention Name</b>             | BAP0527                                                                                                                                                                                                                                             | Accu-Chek Guide Me<br>(certification number:<br>303AABZX00007000)  | Not applicable        |
| <b>Intervention Description</b>      | Use of this product                                                                                                                                                                                                                                 | Use of this product                                                | Not applicable        |
| <b>Type</b>                          | Medical device for study<br>(application for patients +<br>web application for<br>healthcare professionals)                                                                                                                                         | Medical device                                                     | Not applicable        |
| <b>Use</b>                           | Investigational device                                                                                                                                                                                                                              | Device used in the clinical<br>study                               | Not applicable        |
| <b>Supplier</b>                      | Welldoc Inc.                                                                                                                                                                                                                                        | Roche DC Japan K. K.                                               | Not applicable        |
| <b>Intended Sourcing<sup>a</sup></b> | Application for patients:<br>installation of the<br>application from a web-<br>based cloud platform (the<br>App Store or Google Play<br>Store)<br>Web application for<br>healthcare professionals:<br>accessing the specified<br>URL from a browser | Provided centrally by the<br>sponsor <sup>b</sup>                  | Not applicable        |
| <b>Packaging and Labeling</b>        | Labels are displayed inside<br>the application according<br>to government<br>requirements.                                                                                                                                                          | The packaging and labeling<br>of the marketed product are<br>used. | Not applicable        |
| <b>Alias(es)</b>                     | Not applicable                                                                                                                                                                                                                                      | Accu-Chek Guide Me                                                 | Not applicable        |

a: Planned sourcing may be subject to change based on product availability.

b: Supplied by the sponsor to the study sites, including the accompanying test strips and puncture devices for use together with the device.

### 6.1.1 Overview of BAP0527 and the Blood Glucose Meter

BAP0527 is software as a medical device used on smartphones or personal computers in the home or at medical institutions, which consists of the application for patients and the web application for healthcare professionals. The application for patients is installed on the participant's smartphone from a source such as a web-based cloud platform. The web application for healthcare professionals is used by accessing the webpage constructed by the sponsor. The cloud server storing the data from these applications is not a medical device but is operated with the appropriate security measures. For the version number of BAP0527, refer to the IB for BAP0527.

Accu-Chek Guide Me (certification number: 303AABZX00007000) will be used as the blood glucose meter. Until their next visit to the medical institution, participants will measure their blood glucose levels in their daily life using Accu-Chek Guide Me and input the results into BAP0527.

For detailed information about the handling of study interventions and data storage, refer to the IB for BAP0527, the instruction manual for BAP0527, each of the user's guides, and the package insert for Accu-Chek Guide Me.

### 6.1.2 Control of Investigational Devices and Devices for Study Use

#### 6.1.2.1 BAP0527

Since BAP0527 is not a physical object, no physical storage location is necessary. Refer to the study device management procedure for details. The product ID of the BAP0527 product used by each participant will be collected on the CRF.

- Installing BAP0527

Participants will install BAP0527 on their own smartphones by accessing the URL provided by the investigator and downloading BAP0527.

- Creating a participant account

After installing BAP0527, each participant will create their own account by inputting the following information.

- Access code (provided by the investigator)
- Participant number (provided by the investigator)
- E-mail address
- Date of birth
- Sex
- Password
- PIN (personal identification number)

- CONFIDENTIAL -

- Management of participant accounts

The investigator will use the web portal for healthcare professionals to check that the relevant participant accounts have been created appropriately.

- Uninstalling BAP0527

When a participant ends the study or is discontinued from the study, participants will uninstall BAP0527 from their smartphones. The investigator will ensure that BAP0527 has been uninstalled from participants' smartphones.

- Deactivation of participant accounts

When a participant ends the study or is discontinued from the study, the investigator will contact the monitor to deactivate the participant's account. After this, the account administrator will deactivate the participant's account. The investigator will ensure using the web portal for healthcare professionals that the participant's account has been deactivated appropriately.

#### **6.1.2.2 Blood Glucose Meters**

- Delivery and control

Accu-Chek Guide Me is a certificated product, and identical products may already be in use at the study site. In this study, the sponsor will deliver Accu-Chek Guide Me to medical institutions as a device used in the clinical study. The investigator must take physical measures to prevent these devices from being accidentally used instead of devices purchased by the medical institution, for example by storing the delivered devices for study use separately from the devices used by the medical institution. The investigator must also appropriately control information such as the number of products dispensed, their serial numbers and individual device identification numbers when dispensing Accu-Chek Guide Me devices to participants.

In this study, the sponsor will deliver glucose kits for self-testing, puncture devices for blood collection and single-use automatic lancets to the medical institution as devices for concomitant use. Each of these are certificated products, and identical products may already be in use at the study site. The investigator must take physical measures to prevent these devices from being accidentally used instead of devices purchased by the medical institution, for example by storing the delivered devices for study use separately from the devices used by the medical institution. The investigator must also appropriately control information such as the number of products dispensed and their serial numbers when dispensing these devices for concomitant use to participants.

- Return and disposal

When a participant ends the study or is discontinued from the study, the investigator will retrieve the lent Accu-Chek Guide Me device from the participant. The investigator will check information including the model number of the returned Accu-Chek Guide Me device and perform appropriate controls, including recording the return on the management form.

- CONFIDENTIAL -

Since the returned Accu-Chek Guide Me devices are likely to have the participants' blood on them, they will be disposed of at the medical institution, according to the designated procedures of the medical institution, including measures for preventing infection. Records will be made of the items disposed of at the medical institution. For detailed procedures, refer to the study device management procedure.

When a participant ends the study or is discontinued from the study, the investigator will retrieve the lent devices for concomitant use from the participant. The investigator will check information including the model number of the returned devices and perform appropriate controls, including recording the return on the management form. Since there is a high risk that the used puncture devices and disposal boxes for infectious waste will have the participants' blood on them, they will be disposed of at the medical institution, according to the designated procedures of the medical institution. Records will be made of the items disposed of at the medical institution. For detailed procedures, refer to the study device management procedure.

#### **6.1.2.3 Other Medical Devices and Other Equipment**

In this study, medical devices and other equipment will be used for laboratory tests and measuring data such as vital signs, height and body weight. These medical devices and other equipment will be maintained and calibrated according to the control methods of the study site and central laboratory.

### **6.1.3 Method for Ensuring Traceability During and After the Study**

#### **6.1.3.1 BAP0527**

- During the treatment period
  - The investigator will ensure on the web portal for healthcare professionals that participant accounts with the participant numbers of the relevant participants have been created.
- After the end of the treatment period
  - The investigator will ensure on the web portal for healthcare professionals that the participant accounts with the participant numbers of the relevant participants are in a deactivated state.
  - The investigator will ensure that BAP0527 has been deleted from the smartphones of the relevant participants.

#### **6.1.3.2 Blood Glucose Meters**

- During the treatment period
  - The investigator will find out how the blood glucose meters are being used and, if necessary, will check that their serial numbers are identical to those of the devices lent at the start of the study.

- After the end of the treatment period
  - The investigator will ensure that the serial numbers of the blood glucose meters returned by the relevant participants are identical to those of the blood glucose meters lent at the start of the study.

#### **6.1.4 Training**

##### **6.1.4.1 BAP0527**

The sponsor will provide the following content as training for using BAP0527 appropriately. Training content may be added during the conduct of this study. The investigator will be able to use BAP0527 after completing the training specified by the sponsor. If a participant or investigator has queries about BAP0527, for example how to operate it, they will contact the BAP0527 call center described below with their inquiries to resolve these questions.

- Application for patients

Participants assigned to the BAP0527 group at visit 2 will install BAP0527 on their own smartphones. Participants will receive an explanation from the investigator about the basic method of using BAP0527. When using BAP0527, participants will refer to the following documents. Participants will be directed to contact the BAP0527 call center or investigator if they have any queries or questions, for example about how to operate BAP0527, when using BAP0527 from day to day.

- Instruction manual (for participants)
- Quick user's guide (for participants)

- Web application for healthcare professionals

The investigator must complete the training specified by the sponsor before starting the study. During the use of BAP0527, the following documents will be referenced. If the investigator has any queries or concerns that cannot be resolved during use, he or she must contact the BAP0527 call center, the sponsor or the monitor.

- Instruction manual (for healthcare professionals)
- Quick user's guide (for healthcare professionals)

##### **6.1.4.2 Blood Glucose Meters**

After assignment at visit 2, the investigator will dispense the following to participants assigned to the BAP0527 group. The only device for concomitant use in this study that is subject to deficiency reporting and proper control is the device used in the clinical study, "Accu-Chek Guide Me (certification number: 303AABZX00007000)."

- Accu-Chek Guide Me (certification number: 303AABZX00007000)
- Glucose kits for self-testing (in this study, Accu-Chek Guide Strip [approval number: 22900EZX0000100] will be used)

- Puncture device for blood collection (in this study, Accu-Chek Semidispo [notification number: 33B2X00002000005] will be used)
- Single-use automatic lancets (in this study, Accu-Chek Semidispo lancets [certification number: 224AFBZX00050000] will be used)

Participants will receive an explanation about how to use the devices including Accu-Chek Guide Me from the investigator. Participants will receive an instruction manual for Accu-Chek Guide Me and, after receiving explanations with all of the educational content, they will practice SMBG under the directions from the investigator. Participants will be directed to contact the investigator if they have any queries about the use of blood glucose meters.

### 6.1.5 The BAP0527 Call Center

In this study, a BAP0527 call center will be established as a service for responding to queries about the explanation of how to use BAP0527, technical problems, the general method of operating a smartphone to use BAP0527 and any problems with this. The BAP0527 call center will be available for the use of study site staff including the investigator and participants assigned to the BAP0527 group.

**Table 4 Details and Roles of Suppliers of the Investigational Device and Devices for Study Use**

| Role                                | Sponsor                                                                                                                                                                         | Investigational device supplier/<br>manufacturer/localizer                                                                                                                      | Supplier of devices for<br>study use                                                                                                                       |
|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Details of role</b>              | Collecting and handling deficiency and safety information on BAP0527, delivering Accu-Chek Guide Me and collecting and responding to deficiency and safety information about it | Development and design of BAP0527, server administration, data administration, localization, account administration, support for deficiency assessment and handling improvement | Supplying Accu-Chek Guide Me, collecting deficiency and safety information as post-marketing information, sharing it with the sponsor and responding to it |
| <b>Company name</b>                 | API                                                                                                                                                                             | Welldoc, Inc.                                                                                                                                                                   | Roche DC Japan K. K.                                                                                                                                       |
| <b>Address and telephone number</b> | 2-5-1 Nihonbashi-honcho, Chuo-ku, Tokyo<br><br>Telephone number: +81-(0)3-3244-2618                                                                                             | 10221 Wincopin Circle, Suite 150, Columbia, MD 21044                                                                                                                            | 15F Shinagawa Season Terrace 1-2-70 Konan, Minato-ku, Tokyo                                                                                                |

API: Astellas Pharma, Inc.

## 6.2 Preparation/Handling/Storage/Accountability

### 6.2.1 Packaging and Labeling

All sponsor-provided study intervention used in this study will be prepared, packaged and labeled under the responsibility of qualified personnel at API or sponsor's designee in accordance with API or sponsor's designee SOPs, current QMS ministerial ordinances, ISO13485, GCP guidelines and applicable local laws/regulations.

- CONFIDENTIAL -

BAP0527 will bear a label conforming to regulatory guidelines, QMS ministerial ordinances, ISO13485 and laws and regulations, and the labeling will state that it is for study use. The blood glucose meters will be labeled with the label for the marketed product in compliance with legal regulations.

Refer to the IB for detailed information regarding packaging and labeling of the study intervention.

### **6.2.2 Handling, Storage and Accountability**

The head of the study site or the study intervention storage manager should take accountability of the study intervention:

- The study intervention storage manager should store and take accountability of the study intervention in conforming to the study device management procedure written by the sponsor.
- The study intervention storage manager should prepare and retain records of the study intervention's receipt, inventory at the study site, use by each participant, and return of unused study intervention to the sponsor or alternative disposal. These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable) and the unique code numbers assigned to the study intervention and participants.
- The study intervention storage manager should prepare and retain records that document adequately that the participants were provided the quantities specified in the protocol and reconcile all the study intervention supplied from the sponsor.

Refer to the study device management procedure for detailed information regarding handling, storage and accountability of the study intervention.

## **6.3 Assignment to Study Intervention**

Randomization will be performed using the IRT system. When the study site staff perform case registration in the IRT system, participants will be randomized in a 1:1 ratio to the BAP0527 group and usual treatment group. To address bias, stratified assignment will be performed using the HbA1c level (central lab measurement:  $<8.5\%$ ,  $\geq 8.5\%$ ) and BMI level ( $<25 \text{ kg/m}^2$ ,  $\geq 25 \text{ kg/m}^2$ ) at screening as assignment factors. The specific procedures for randomization via the IRT system will be included in the case registration procedure.

This study will be conducted as a multicenter study, and no particular restrictions will be set on the number of participants registered at each site.

## **6.4 Study Intervention Compliance**

The investigator must explain to the participants about all items that participants must comply with. The specific notes about what participants should comply with are listed below.

- All participants
  - Follow all instructions from the investigator or other staff.
  - Make all study visits according to the schedule.
  - Do not eat breakfast before visits on the specified study visit dates.

- CONFIDENTIAL -

- Tell the investigator or other staff if you have any queries or anxieties.
- Let the investigator or other staff know immediately if you suffer any injury to your health, discomfort or AEs.
- Consult the investigator before using any new medication or receiving any new treatment.
- Let the investigator or other staff know immediately if you receive emergency treatment.
- Carry the issued study participant card at all times and tell other physicians that you are participating in the study.
- Do not participate in other studies at the same time as this study.
- While participating in the study, do not use any new diabetes mellitus management apps or a diabetes mellitus management diary.
- Only participants assigned to the BAP0527 group
  - Use BAP0527 and the blood glucose meter correctly.
  - Use the blood glucose meter continuously to measure blood glucose levels.
  - Use BAP0527 continuously and record self-management including lifestyle habits (meals, exercise, body weight, sleep) and indicators (medication use, blood pressure, blood glucose levels).
  - Review your lifestyle habits according to the real-time feedback messages produced by BAP0527 based on the input data.
  - Contact the study staff immediately if a deficiency occurs in BAP0527 or the blood glucose meter.
  - Do not share BAP0527 or the blood glucose meter with anyone else.
  - Do not share the BAP0527 screen with anyone other than the study staff or call center.
- WOCBP participants only
  - Use an appropriate method of contraception during the study period.
  - If you become pregnant, immediately let the investigator know.
- Breastfeeding female participants only
  - Do not breastfeed during the study period.

## **6.5 Continued Access to Study Intervention After the End of the Study**

Continued use will not be allowed.

## **6.6 Prior and Concomitant Therapy**

The drug names, indications, and durations of use of prior medication and concomitant medication used in the period from 12 weeks (84 days) before visit 1 until the end of the follow-up period will be investigated and recorded on CRFs. The dosages of hypoglycemics will also be investigated and recorded on CRFs. If hypoglycemics are changed, the reasons for judging that the change is necessary will be recorded on CRFs. Whether any change to diet or exercise restrictions was necessary due to concurrent diseases will also be recorded on CRFs.

### 6.6.1 Prohibited Concomitant Medications

- Newly starting the use of insulin preparations will be prohibited from visit 1 until the end of tests for efficacy endpoint evaluation at visit 12 (or the time of early discontinuation).
- Continuous use of adrenocortical steroids or immunosuppressants (such as oral use or injections) as systemic use for chronic diseases such as rheumatism or asthma will be prohibited from visit 1 until the end of tests for efficacy endpoint evaluation at visit 12 (or the time of early discontinuation). Topical use, such as application, or temporary use will be allowed.
- Continuous use (intravenous drip use or injection) of treatments such as glucose or glucagon that are likely to directly influence blood glucose will be prohibited from visit 1 until the end of tests for efficacy endpoint evaluation at visit 12 (or the time of early discontinuation). However, temporary use will be allowed.

### 6.6.2 Prohibited Concomitant Therapies

Newly starting the use of diabetes mellitus management apps or diabetes mellitus diaries will be prohibited from visit 1 until the end of tests for efficacy endpoint evaluation at visit 12 (or the time of early discontinuation).

### 6.6.3 Restricted Concomitant Medications

Not applicable.

### 6.6.4 Restricted Concomitant Therapies

Not applicable.

## 7 STUDY PROCEDURES AND ASSESSMENTS

- Study procedures and their timing are summarized in the schedule of assessments [Table 1]. Adherence to the study design requirements, including those specified in the schedule of assessments [Table 1], is essential and required for study conduct. Prospective protocol waivers or exemptions are not allowed.
- Any change, divergence or departure from the study design or procedures identified in the protocol is considered a protocol deviation. All deviations from the protocol are to be recorded.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (e.g., imaging, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the schedule of assessments [Table 1].
- In the event of a significant study-continuity issue (e.g., caused by a pandemic), alternate strategies for participant visits, assessments, product distribution and monitoring may be

implemented by the sponsor or the investigator, as per local health authority/ethics requirements. These alternate strategies are described in “10.7 Appendix 7 Clinical Study Continuity.”

- General maintenance and inspection of devices used at the study site such as height gauges, scales for weight measurement, and sphygmomanometers will be performed at the study site.

## **7.1 Efficacy Assessments**

Planned timepoints for all efficacy assessments are provided in the schedule of assessments [Table 1]. Efficacy assessment will be performed with visit 2 as the baseline.

### **7.1.1 Laboratory Assessments**

The laboratory tests used in efficacy assessment (HbA1c level and fasting blood glucose level, fasting insulin level, and lipid levels [total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol]) will be performed according to the schedule of assessments [Table 1]. Since all of these will be measured at the central laboratory, samples will be sent to the central laboratory.

### **7.1.2 Vital Signs**

Systolic and diastolic blood pressure (mmHg) at rest in a sitting position will be measured according to the schedule of assessments [Table 1] and recorded on the CRF.

### **7.1.3 Physical Examination**

Height (visit 1 only) and body weight will be measured according to the schedule of assessments [Table 1] and recorded on the CRF. BMI at each measurement time point will be calculated from the height measured at visit 1 and the body weight at that measurement point.

### **7.1.4 Participants with Changes of Antidiabetics**

As stated in “6.6 Prior and Concomitant Therapy,” the drug names, indications, dosages, and durations of use of all hypoglycemics that are prior medication and concomitant medication used in the period from 12 weeks (84 days) before visit 1 until the end of the follow-up period will be investigated and recorded on CRFs. Participants whose antidiabetics have changed (including changes in dosage) will be identified.

### **7.1.5 EuroQol 5 Dimension 5-level (EQ-5D-5L)**

EQ-5D-5L will be performed according to the schedule of assessments [Table 1]. EQ-5D-5L is an internationally standardized scale for describing and assessing health status that can be applied to any disease “10.9 Appendix 9 EuroQol 5 Dimension 5-level (EQ-5D-5L).” EQ-5D-5L is an assessment scale for health-related QOL with multiple items, can be expressed as a single indicator, and is especially designed to supplement other scale for health status [EuroQol Group, 1990; Herdman et al, 2011]. Participants will self-assess and record their responses on an electronic device.

### 7.1.6 Diabetes Treatment Satisfaction Questionnaire (DTSQ)

DTSQ will be performed according to the schedule of assessments [Table 1]. DTSQ has been developed specifically for diabetes mellitus as a questionnaire for the level of satisfaction with treatment, and is currently used in countries around the world as a method for quantifying the level of satisfaction with treatment “10.10 Appendix 10 Diabetes Treatment Satisfaction Questionnaire (DTSQ).” A Japanese translation has also been prepared and its usefulness has been confirmed [Ishii et al., 2000]. Participants will self-assess and record their responses on an electronic device.

### 7.1.7 Percentage of Accesses to BAP0527 and Percentage of Data Inputs into BAP0527

Welldoc, Inc., the supplier of BAP0527, will manage records of the number of accesses to BAP0527 and the number of inputs of blood glucose level data by participants in the BAP0527 group.

The definitions of the percentage of accesses to BAP0527 and the percentage of data inputs into BAP0527 are as follows.

- Percentage of app accesses: The percentage of days for which the app was used out of the period of 28 days  
The days for which the app was used represents days for which any input or record was made (any of the following: input of blood glucose level, input of blood pressure, input of meals, input of body weight, completion of educational content). Every 28 days, the percentage of days for which any input or record was made will be calculated.
- Percentage of inputs of blood glucose level: The percentage of days for which blood glucose level was recorded out of the period of 28 days  
Every 28 days, the percentage of days for which blood glucose level was recorded will be calculated.

## 7.2 Safety Assessments

Planned timepoints for all safety assessments are provided in the schedule of assessments [Table 1]. In safety assessment in the screening period, data will be compared with the data obtained at and before visit 1, and safety assessment in the treatment period and the follow-up period will be performed with visit 2 as the baseline. If clinically meaningful changes are observed, they will be recorded on the CRF as AEs.

### 7.2.1 Laboratory Assessments

Laboratory tests will be performed according to the schedule of assessments [Table 1]. Since all of those will be measured at the central laboratory, samples will be sent to the central laboratory. The measured items are shown in “Laboratory Tests” [Table 6].

### 7.2.2 Vital Signs

Systolic and diastolic blood pressure (mmHg) at rest in a sitting position, pulse rate (beats/minute) and body temperature will be measured according to the schedule of assessments [Table 1] and recorded on the CRF.

### 7.2.3 Physical Examination

The status of participants will be checked by tests such as interview, inspection and palpation according to the schedule of assessments [Table 1]. Body weight will be measured at each physical examination. Height will be measured only at visit 1. If abnormal findings are observed, details will be recorded in medical records or other source documents.

### 7.2.4 Order of Assessments

DTSQ will be performed after interview at each visit. In addition, in the BAP0527 group, DTSQ will be performed after setting target values for diabetes mellitus treatment, checks on and directions about the participant's use of this product, looking back at the participant's lifestyle between visits by the investigator and the participant using BAP0527 data, and reviewing set target values.

## 7.3 Adverse Events, Deficiencies and Other Safety Aspects

The definitions of AEs, SAEs or deficiencies and deficiencies that may cause SAEs can be found in "10.3.1 Definition of Adverse Events, 10.3.2 Definition of Serious Adverse Events and 10.3.3 Definition of Deficiencies" respectively.

AEs or deficiencies will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's LAR), users or other persons.

The investigator and any qualified designees are responsible for detecting, documenting and recording events meeting the definitions of AEs, SAEs or deficiencies, and deficiencies that may cause SAEs, and remain responsible for following up serious adverse thought to be related to study intervention, and AEs resulting in discontinuation of the study intervention or the study (refer to "10.3 Appendix 3 Adverse Events and Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting").

The methods for recording, evaluating and assessing causality of AEs, SAEs or deficiencies, and deficiencies that may cause SAEs, and the procedure for completing and transmitting SAE reports are provided in "10.3 Appendix 3 Adverse Events and Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting."

### 7.3.1 Time Period and Frequency for Collecting Adverse Events, Serious Adverse Events, Deficiencies and/or Deficiencies That May Cause Serious Adverse Events

All SAEs will be collected at the time points specified on the schedule of assessments [Table 1] from the signing of the ICF until EOS/EDT/EDF, and will be reported on the CRF and JUTOKUNA YUUGAIJISHOU OYOBIFUGUAI HOUKOKUSHO.

- CONFIDENTIAL -

All AEs will be collected at the time points specified on the schedule of assessments [Table 1] from the signing of the ICF until EOS/EDT/EDF, and will be reported on the CRF.

All deficiencies and deficiencies that may cause SAEs will be collected at the study site from the time when this product is dispensed until it is disposed of or returned, and will be reported on the CRF.

If the severity of an SAEs/AE according to the grade assessment scale defining the severity of AEs [Table 5] worsens, the end date will be recorded and the event will be entered on the CRF again, together with the new severity and new onset date.

If the severity according to the grade assessment scale defining the severity of AEs [Table 5] improves, the end date will be recorded and the SAE/AE will be entered on the CRF again, together with the severity and new onset date. Events that have persisted since before study intervention, persisted after study intervention and improved after study intervention are an exception. Events like this should not be entered again.

If the severity of an SAE according to the grade assessment scale defining the severity of AEs [Table 5] improves, the details must be entered on the JUTOKUNA YUUGAIJISHOU OYOBI FUGUAI HOUKOKUSHO so that healthcare assessors can assess the course of serial events.

All SAEs and deficiencies that may cause SAEs will be recorded and reported to the sponsor or designee without undue delay but not later than within 24 hours of obtaining knowledge of the event, as indicated in “10.3 Appendix 3 Adverse Events and Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting.” The investigator will submit any updated data of SAEs and deficiencies that may cause SAEs to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek any AE or SAE after conclusion of the study participation. However, if the investigator becomes aware of any SAE with a suspected causal relationship to the study intervention, including a death, at any time after a participant has been discharged from the study, the investigator must promptly report the SAE to the sponsor.

The RSI used to judge the predictability of the SAEs in this study is the IB for BAP0527 and the package insert and Accu-Chek Guide Me instruction manual for Accu-Chek Guide Me.

### **7.3.2 Method of Detecting Adverse Events, Serious Adverse Events, Deficiencies and/or Deficiencies That May Cause Serious Adverse Events**

Care will be taken not to introduce bias when detecting AEs and/or SAEs (deficiencies and/or deficiencies that may cause SAEs). Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

### **7.3.3 Follow-up of Adverse Events, Serious Adverse Events, Deficiencies and/or Deficiencies That May Cause Serious Adverse Events**

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in “8.3 Lost to Follow-up”). Further information on follow-up procedures is provided in “10.3 Appendix 3 Adverse Events and Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting.”

If after the protocol-defined AE collection period (see “7.3.1 Time Period and Frequency for Collecting Adverse Events, Serious Adverse Events, Deficiencies and/or Deficiencies That May Cause Serious Adverse Events”), an AE progresses to an SAE, or the investigator learns of any (S)AE or new information about a previously reported SAE including death, where the investigator considers there is reasonable possibility it is related to the study intervention or study participation, the investigator must promptly notify the sponsor.

After a deficiency is first reported, the investigator has a duty to investigate, explain and make judgments, on his/her own initiative or in response to requests by the sponsor, to completely elucidate information such as the details of the deficiency and the situation in which it occurred, as far as possible. The investigator will not dispose of the medical device in which the deficiency occurred but will return it to the sponsor and cooperate in a detailed investigation, to elucidate the cause. If a deficiency occurs in BAP0527, which is installed on the smartphones of participants, the investigator will follow the instructions from the sponsor about the handling of the defective BAP0527 since electronic return is not possible.

### **7.3.4 Regulatory Reporting Requirements for Serious Adverse Events and Deficiencies That May Cause Serious Adverse Events**

- Prompt notification by the investigator to the sponsor of an SAE and deficiency that may cause SAEs is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE, deficiency that may cause SAEs or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the BAP0527 IB, Accu-Chek Guide Me package insert and Accu-Chek Guide Me instruction manual and will notify the IRB/IEC, if appropriate according to local requirements.

### **7.3.5 Disease-related Events and/or Disease-related Outcomes Not Qualifying as Adverse Events or Serious Adverse Events**

In the protocol of this study, the worsening of the primary disease (type 2 diabetes mellitus) is not handled as a (serious) AE.

Information on this event will be collected and assessed as efficacy endpoints such as the change from baseline in HbA1c level.

### **7.3.6 Regulatory Requirements Relating to Deficiencies in Medical Devices**

- The investigator will promptly report all device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of device deficiencies to the IRB/IEC.

## **7.4 Pharmacokinetics**

Not applicable.

## **7.5 Electronic Clinical Outcome Assessment**

EQ-5D-5L will be performed to assess the influence of this product on QOL and DTSQ will be performed to assess the influence of this product on the level of satisfaction with diabetes mellitus treatment. HLS-14 will also be performed to investigate the health literacy of participants as participant background information. The responses to these will be obtained electronically. For details, refer to “1.3 Schedule of Assessments, 7.1 Efficacy Assessment, and 7.7.3 14-item Health Literacy Scale (HLS-14).”

## **7.6 Total Amount of Blood**

The total amount of blood collected from participants throughout this study will be approximately 141 mL. Additional blood samples will only be collected if clinically necessary or for follow-up of abnormal laboratory test values.

- Hematology: 22 mL (2 mL × 11 visits)
- Serum chemistry: 77 mL (7 mL × 11 visits)
- HbA1c: 22 mL (2 mL × 11 visits)
- Blood glucose levels: 20 mL (2 mL × 10 visits)

The amount of blood collected for SMBG from participants in the BAP0527 group will be 0.6 µL per measurement.

## **7.7 Other Assessment**

### **7.7.1 Participant Backgrounds**

Information on age and sex will be collected on the CRF at the time of obtaining informed consent.

### **7.7.2 Medical History and Concurrent Diseases**

All clinically problematic medical conditions that have not cured at the time of obtaining informed consent will be identified as concurrent diseases, and details of concurrent diseases will be collected on the CRF. Medical history will be checked based on the inclusion criteria and exclusion criteria.

### **7.7.3 14-item Health Literacy Scale (HLS-14)**

HLS-14 will be performed according to the schedule of assessments [Table 1]. HLS-14 has been developed as a questionnaire about the health literacy of patients “10.11 Appendix 11 14-Item Health Literacy Scale (HLS-14),” [Suka et al, 2013]. Participants will assess themselves and record the answers on their electronic devices.

### **7.7.4 Status of Directions About the Use of Sphygmomanometers and Scales for Weight Measurement**

The investigator will direct all participants to measure vital signs and body weight using sphygmomanometers and scales during the treatment period and follow-up period, in principle every day. Whether or not the investigator gave directions will be collected on the CRF. Sphygmomanometers and scales will be lent to all participants so that they can be used.

## **8 PARTICIPANT DISCONTINUATION**

For discontinuation of a study site or the entire study, refer to “10.1.8 Study and Site Closure.”

### **8.1 Discontinuation of Individual Participant(s) from Study Intervention**

Discontinuation of individual participant(s) from study intervention is defined as a participant who enrolled in the study and for whom investigational study intervention is permanently discontinued for any reason.

The participant is free to withdraw from the study intervention and study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to discontinue the participant from study intervention or to terminate a participant's involvement in the study at any time if the participant's clinical condition warrants it.

The reason for discontinuation from study intervention must be documented in the participant's medical records.

A participant must discontinue study intervention for any of the following reasons:

1. Participant requests to stop study intervention.
2. Any clinical AE, laboratory abnormality or intercurrent illness, in the opinion of the investigator, indicates continued study intervention is not in the best interest of the participant.
3. If the participant requests that use of this product be discontinued.

4. If it becomes necessary to newly start the use of insulin preparations.
5. If the blood glucose level is input into BAP0527 fewer than 4 times per month between visits (BAP0527 group).
6. If a participant in the BAP0527 group becomes unable to use BAP0527 appropriately.
7. If a female participant is discovered to be pregnant.
8. If a participant is hospitalized and the investigator judges that it is inappropriate for the participant to continue the study.
9. If the participant continuously fails to comply with the protocol in the judgment of the investigator or sponsor.
10. If the investigator judges that it is necessary to discontinue the study in the participant.

## **8.2 Discontinuation of Individual Participant(s) from Study**

The participant is free to withdraw from the study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The investigator is also free to terminate a participant's involvement in the study at any time if the participant's clinical condition warrants it.

The reason for discontinuation from study must be documented in the participant's medical records.

All participants who discontinue study intervention will remain in the study and must continue to be followed for protocol-specific procedures as outlined in "7.3 Adverse Events, Deficiencies and Other Safety Aspects." The only exception to this is when the participant specifically withdraws consent for any further contact with them or persons previously authorized by the participant to provide this information.

## **8.3 Lost to Follow-up**

Every reasonable effort is to be made to contact any participant lost to follow-up during the course of the study in order to complete study-related assessments, record outstanding data and retrieve study intervention. These contact attempts should be documented in the participant's medical record.

# **9 STATISTICAL CONSIDERATIONS**

## **9.1 Statistical Hypotheses**

The superiority with respect to the primary endpoint will be verified using an MMRM. The following null hypothesis and alternative hypothesis will be verified.

- H0: Change from baseline in the HbA1c level at Week 24 in the BAP0527 group = change from baseline in the HbA1c level at Week 24 in the usual treatment group
- H1: Change from baseline in the HbA1c level at Week 24 in the BAP0527 group  $\neq$  change from baseline in the HbA1c level at Week 24 in the usual treatment group

## 9.2 Analysis Sets

Analysis will be performed using the following analysis sets based on ICH guidelines E3 and E9.

The following populations are defined:

| Population                                      | Description                                                                                                                                                                                                                                |
|-------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Enrolled                                        | All participants who sign the ICF.                                                                                                                                                                                                         |
| Randomized                                      | All participants who are randomized.<br>Participants will be analyzed according to the treatment group to which they are randomized.                                                                                                       |
| Full Analysis Set (FAS)                         | All participants who are randomized and have at least 1 post baseline HbA1c measurement.<br>Participants will be analyzed according to the treatment group to which they are randomized.                                                   |
| Full Analysis Set for Follow-up Analysis (FAS2) | Participants in the FAS for whom follow-up was started, and who have at least 1 (one) measured value for HbA1c level from Week 24 onwards.<br>Participants will be analyzed according to the treatment group to which they are randomized. |
| Safety Analysis Set (SAF)                       | All participants who are randomly assigned to study intervention.<br>Participants will be analyzed according to the treatment group to which they are randomized.                                                                          |

FAS: full analysis set; SAF: safety analysis set

## 9.3 Statistical Analyses

For efficacy analysis, the FAS will be used unless otherwise stated. SAP will be written to provide details of the analyses, along with specifications for tables, listings and figures to be produced. Changes from the planned analyses in the SAP finalized before randomization that impact the statistical analyses will be justified in the CSR.

### 9.3.1 General Considerations

In general, data will be summarized with descriptive statistics for continuous endpoints, and frequency and percentage for categorical endpoints, unless otherwise specified. Percentages by categories will be based on the number of participants with no missing data (i.e., will add up to 100%).

Unless explicitly stated, baseline is defined as the value measured at visit 2.

### 9.3.2 Primary Endpoint(s) Analysis

#### 9.3.2.1 Primary Analysis

Since the treatment effect will be assessed under the assumption that the study treatment assigned to all participants is continuing, MAR will be assumed for any missing data. In the FAS, the change from baseline in HbA1c level at Week 24 of the treatment period in the BAP0527 group and usual treatment group will be compared using an MMRM. A two-sided 0.05 significance level will be used. The MMRM will include the change from baseline in HbA1c level at each time point as the response variable and treatment group (BAP0527 group or usual treatment group), BMI level at screening ( $<25 \text{ kg/m}^2$ ,  $\geq 25 \text{ kg/m}^2$ ), baseline levels, time point, interaction of treatment group and time point, and interaction of baseline

and time point as explanatory variables. An unstructured covariance structure shared across treatment groups will be used to model the within-patient errors. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom and adjust standard errors. This analysis will use a restricted maximum likelihood-based repeated-measures approach.

### 9.3.2.2 Sensitivity Analysis

- In the FAS, the change from baseline in HbA1c level at Week 24 of the treatment period will be analyzed using a simplified MMRM, with the treatment group, time point, baseline level, interaction of treatment group and time point, and interaction of baseline level and time point as explanatory variables.
- The primary endpoint will be analyzed using the multiple imputation method based on the reason for discontinuation. Details will be provided in the SAP.

### 9.3.3 Secondary Endpoint(s) Analysis

- The change from baseline in HbA1c level (central lab measurement) at each assessment time point (except Week 24) will be analyzed using the MMRM described in “9.3.2.1 Primary Analysis.”
- The percentage of participants with a baseline HbA1c level  $\geq 8.0\%$  who achieved an HbA1c level  $< 8.0\%$  at Week 24 (central lab measurement) will be analyzed with a logistic regression model. If the HbA1c level at Week 24 is missing, the imputed HbA1c level under the assumption of MAR will be used. Details of the model will be provided in the SAP.
- The change from baseline in fasting blood glucose level and fasting insulin level at Week 24 (central lab measurement) will be analyzed using the MMRM described in “9.3.2.1 Primary Analysis.”
- The percentage of participants with a decreased dose of antidiabetics or reduced number of antidiabetics by Week 24, relative to antidiabetic use at baseline, will be analyzed with a logistic regression model. Details of the model will be provided in the SAP.
- The percentage of participants with an increased dose of antidiabetics or newly started hypoglycemics by Week 24, relative to antidiabetic use at baseline, will be analyzed with a logistic regression model. Details of the model will be provided in the SAP.
- The change from baseline in HbA1c level at each assessment time point in the follow-up period (central lab measurement) will be analyzed using the MMRM described in “9.3.2.1 Primary Analysis.” The FAS2 will be used as the analysis set.
- The change from Week 24 in HbA1c level at each assessment time point in the follow-up period (central lab measurement) will be analyzed using the MMRM described in “9.3.2.1 Primary Analysis.” The FAS2 will be used as the analysis set.
- The percentage of participants with a decreased dose of antidiabetics or reduced number of antidiabetics by Week 12 of the follow-up period, relative to antidiabetic use at Week 24, will be analyzed with a logistic regression model. Details of the model will be provided in the SAP. The FAS2 will be used as the analysis set.
- The percentage of participants with an increased dose of antidiabetics or newly started hypoglycemics by Week 12 of the follow-up period, relative to antidiabetic use at Week

24, will be analyzed with a logistic regression model. Details of the model will be provided in the SAP. The FAS2 will be used as the analysis set.

#### 9.3.4 Exploratory Endpoint(s) Analysis

- In participants with no changes in hypoglycemics, the change from baseline in HbA1c level at Week 24 will be analyzed using the MMRM described in “9.3.2.1 Primary Analysis.”
- The percentage of participants who achieved an HbA1c level <7.0% at Week 24 (central lab measurement) will be analyzed with a logistic regression model. If the HbA1c level at Week 24 is missing, the imputed HbA1c level under the assumption of MAR will be used. Details of the model will be provided in the SAP.
- The percentage of participants with a baseline HbA1c level  $\geq 8.0\%$  who achieved an HbA1c level <8.0% at each assessment time point (except Week 24) (central lab measurement) will be analyzed with a logistic regression model. Details of the model will be provided in the SAP. If the HbA1c level at the relevant assessment time point is missing, the imputed HbA1c level under the assumption of MAR will be used.
- The change from baseline in fasting blood glucose level and fasting insulin level at each assessment time point (except Week 24) (central lab measurement) will be analyzed using the MMRM described in “9.3.2.1 Primary Analysis.”
- The change from baseline in tests related to complications of diabetes mellitus (vital signs, lipid levels) at each assessment time point will be calculated for each treatment group.
- For each level and for each item of EQ 5D-5L at each assessment time point, the frequencies and percentages will be calculated for each treatment group.
- The change from baseline in DTSQ at each assessment time point will be calculated for each treatment group. The frequencies and percentages for each item will be calculated for each treatment group.
- The number of unscheduled visits up to Week 24 will be tabulated for each treatment group.
- The BAP0527 access rate and the data input rate such as blood glucose level will be calculated.

#### 9.3.5 Safety Analyses

Safety analysis will be performed in the SAF. Unless otherwise specified, analysis will be performed for each treatment group.

##### 9.3.5.1 Adverse Events and Deficiencies

AEs will be encoded using MedDRA. AEs observed after randomization, within the treatment period and follow-up period will be defined as TEAEs. All TEAEs that the investigator records as having a causal relationship will be defined as TEAEs related to the study intervention.

The number and percentage of participants with each of AEs, SAEs, AEs resulting in discontinuation and AEs related to this product, in the treatment period, in the follow-up

period and in the entire period will be calculated. The number and percentage of participants with AEs by severity will also be calculated.

For the deficiencies of this product in the BAP0527 group, the number of deficiencies and the number and percentage of participants will be calculated with reference to the IMDRF (International Medical Device Regulators Forum) deficiency terminology.

#### **9.3.5.2 Laboratory Assessments**

For quantitative laboratory tests, descriptive statistics for the measurement results and change from baseline at each time point will be calculated.

For qualitative laboratory tests, the number and percentage of participants for each category at each time point will be calculated.

#### **9.3.5.3 Vital Signs**

Descriptive statistics for the measurement results of vital signs and change from baseline at each time point will be calculated.

#### **9.3.6 Subgroup Analyses**

Subgroup analysis will be performed for the group of participants who received assessment and intervention related to the study in the DCT and for the group of participants who received assessment and intervention at usual study sites. Details of the analysis and information on other subgroup analysis will be provided in the SAP. For details of the DCT, refer to “10.8 Appendix 8 Decentralized Clinical Trial (DCT).”

#### **9.3.7 Assessment of Variation Between Study Sites**

The change from baseline in HbA1c level at each study site will be calculated. If there is an unacceptably large difference between sites, then add an analysis that includes sites as a model variable. Details, including details about integrating sites with small numbers of registered patients, will be provided in the SAP.

The consistency of the observed effects between sites will be checked using a multivariate regression model. The change from baseline in HbA1c level at Week 24 will be the result variable, and treatment, site, BMI, HbA1c level, and interaction of treatment and site will be explanatory variables. Statistical significance of interaction items (significance level 0.15) will indicate that the observed effects are not uniform between sites.

### **9.4 Interim Analysis**

Not applicable.

### **9.5 Sample Size Determination**

For the primary endpoint, which is the change from baseline in HbA1c level, the difference between the BAP0527 group and the usual treatment group is presumed to be 0.44% and the standard deviation common to both is presumed to be 1.0%. In this case, with a two-sided significance level of 0.05 and a power of 90%, using a 2-sample t test, the sample size necessary to detect a statistically significant difference in the BAP0527 group relative to the

- CONFIDENTIAL -

usual treatment group is 110 participants per group, or a total of 220 participants. Assuming a discontinuation rate of approximately 10% before measurement of the efficacy endpoint in the treatment period, and accounting for discontinuations, a sample size for randomization of approximately 240 participants is required. The intergroup difference of 0.44% has been selected with reference to sources including the opinion of the medical expert, considering that the design allows changes of concomitant hypoglycemics during the study period.

## **9.6 Additional Conventions**

If HbA1c levels are missing, these will be treated as missing data. For missing data, MAR will be assumed.

## **10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS**

### **10.1 Appendix 1 Ethical, Regulatory and Study Oversight Considerations**

#### **10.1.1 Regulatory and Ethical Considerations**

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS international ethical guidelines
  - Applicable ICH GCP guidelines and ISO14155
  - Applicable laws and regulations
- The protocol and protocol revisions will be finalized after an approval process by the sponsor.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- The funding for this study has been provided by API. To conduct the study, the study site will conclude a study contract with API.

#### **10.1.2 Financial Disclosure**

Investigators and subinvestigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

#### **10.1.3 Informed Consent of Participants**

##### **10.1.3.1 Informed Consent Process**

- The investigator or the investigator's representative will explain the nature of the study to the potential participant and answer all questions regarding the study.
- The information provided shall be provided in writing and shall:

- CONFIDENTIAL -

- Enable the participant to understand:
  - The nature, objectives, benefits, implications, risks and inconveniences of the clinical study;
  - The conditions under which the clinical study is to be conducted, including the expected duration of the participant's participation in the clinical study;
  - The possible treatment alternatives, including the follow-up measures if the participation of the participant in the clinical study is discontinued;
- Be kept comprehensive, concise, clear, relevant, and understandable to a layperson;
- Be provided in a prior interview with an appropriately qualified member of the study team. Special attention shall be paid to the information needs of specific patient populations and of individual participants, as well as to the methods used to give the information. Care should be taken to verify that the participant has understood the information;
- Include information about the applicable damage compensation system;
- Include the study ISN number and information about the future availability of the clinical study results in terms understandable to a layperson;
- Potential participants must be informed that their participation is voluntary and shall have their protective rights and guarantees explained. In particular their right to refuse to participate and the right to withdraw from the clinical study at any time without any resulting detriment and without having to provide any justification shall be explained.
- Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, EU CTR 536/2014 (including Article 29), local regulations, ICH GCP guidelines, ISO14155, the Declaration of Helsinki, HIPAA requirements, where applicable, and the IRB/IEC or study center.
- If the participant is a minor who is capable of forming an opinion and assessing the information given, their assent, in order to participate in a clinical study, shall also be obtained.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

#### **10.1.3.2 Supply of New and Important Information Influencing the Participant's Consent and Revision of the Written Information**

- The investigator or the investigator's representative will immediately inform the participant verbally whenever new information becomes available that may be relevant to the participant's consent or may influence the participant's willingness to continue participating in the study. The communication must be documented in the participant's medical records and whether the participant is willing to remain in the study or not must be confirmed and documented.

- CONFIDENTIAL -

- The investigator must update the participant's ICF and submit it for approval to the IRB/IEC. The investigator or the investigator's representative must obtain written informed consent from the participant on all updated ICFs throughout their participation in the study. The investigator or the investigator's designee must reobtain consent from participants with the updated ICF even if relevant information was provided verbally. The investigator or the investigator's representative who obtained the written informed consent and the participant should sign and date the ICF. A copy of the signed ICF will be given to the participant and the original will be placed in the participant's medical record. An entry must be made in the participant's records documenting the reobtain process.

#### 10.1.4 Data Protection

The sponsor will use the personal data collected from participants in order to run the study and to use and publish the results of the study. The personal data of participants will be used throughout the development program of the investigational study intervention; e.g., to develop a product, obtain permission to market the product, monitor its safety and obtain coverage by health insurance and reimbursement schemes.

API relies on the permission (or "consent") in order to use the data of participants and their permission is obtained by signing the ICF.

- API's obligation to comply with legal obligations to which API is subject, related in particular to pharmacovigilance, i.e., safety reporting of AEs and deficiencies and for compliance with other local laws and regulations. In these cases, processing of the participants' personal information is necessary for reasons of public interest in the area of public health, such as ensuring high standards of quality and safety of the investigational study intervention;
- API's legitimate interest to evaluate the efficacy of the investigational study intervention. In that case, processing of the participants' personal information is necessary for scientific research purposes.

The investigator and/or the site personnel will record information from the medical file of study participants in CRF and in an external (electronic) data file (e.g., central laboratory data). These study records will identify the participants with a code instead of their name or other personal data. Only the investigator and the site personnel can match the code with the name of the study participant which will be retained in the medical file at the site only. Non-medical personnel acting on behalf of API and being bound by a duty of confidentiality, as well as health authorities and/or IRB/IECs, may also be given access to this data at the site only to verify that the study is carried out in compliance with legal and quality requirements.

The sponsor collects personal data from the participants during the study that may be used for:

- Submission to government regulatory authorities and IRB/IEC
- Use in reports or public scientific presentations, and
- Use in research, now or in the future.

- CONFIDENTIAL -

However, the identity of participants will not be revealed if study participants' personal data are shared for these purposes.

The personal data of participants may be shared with:

- API and its present or future affiliates,
- Research, collaboration and licensing partners and/or service providers (such as laboratories conducting tests on behalf of API) and authorized representatives of API,
- Study monitors appointed by API or API's service providers, and
- Auditors/inspectors appointed by API or API's service providers or by health and regulatory authorities for GCP inspections.

The sponsor will inform the participants about their privacy rights and how to exercise them via the ICF which participants will sign in order to participate in the study. The sponsor will provide the investigator and study staff with a privacy notice explaining how their personal data will be used and how to exercise their privacy rights.

The sponsor will comply and process personal data in accordance with all applicable privacy laws and regulations.

The contract between sponsor and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

#### **10.1.5 Dissemination of Clinical Study Data**

The medical advisor and/or the representative for the principal investigator(s) will have the responsibility to review the final study results to confirm to the best of their knowledge that it accurately describes the conduct and results of the study. The signatory will be the medical advisor and/or the representative for the principal investigator(s).

##### **10.1.5.1 Disclosure of Study Information and Results**

API complies with relevant laws, regulatory requirements and industry guidance for registration of clinical studies, posting of clinical study information, and disclosure of clinical study results.

API commits to registering all interventional clinical studies sponsored by API that seek to evaluate the safety and/or efficacy profile of an API owned or in-licensed product. Clinical studies sponsored by API that are covered under API policy are registered on a publicly accessible clinical study registry (e.g., [www.clinicaltrials.gov](http://www.clinicaltrials.gov)). In addition, other API sponsored studies are registered on national registries, if required by local/regional laws or regulations.

- CONFIDENTIAL -

API commits to disclosing summary results in API clinical study websites for all phase 1 to 4 interventional clinical studies for products sponsored by API, conducted in the target patient population, with API products that have health authority approval. In addition, summary results for other API-sponsored studies are disclosed on national registries, if required by local/regional laws or regulations.

Summary of end of study results will be available only after all data have been obtained from all participating countries/sites. When all related data have been obtained, the data will be locked, and statistical analysis of the results at the end of the study will be performed. After this, the data will be stored and managed appropriately according to API's procedures.

#### **10.1.5.2 Access to Study Data**

Subject to compliance with the applicable laws and regulations relevant to protection of personal data, API provides a platform ([www.clinicalstudydatarequest.com](http://www.clinicalstudydatarequest.com)) where researchers may request access to participant level data, study level data and protocols from API-sponsored clinical studies conducted in patients that are completed after January 1, 2010.

Access to this data is granted for products and indications approved in any country after the request has been reviewed and approved by an independent panel of experts ("Scientific Review Board") based on scientific merit and the qualifications of the researcher. Access is given by API after review and approval by the Scientific Review Board and execution of a data sharing agreement.

Before participant-level data are shared, it is anonymized to respect the rights of the clinical study participants to privacy and to protection of their personal health information.

#### **10.1.6 Data Quality Assurance**

- All participant data relating to the study will be recorded on the CRF unless transmitted to the sponsor or designee electronically in an external data file (e.g., central laboratory data). The investigator is responsible for verifying that data entries on the CRF are accurate and correct by physically or electronically signing the CRF.
- The data science staff of the sponsor or a person contracted by the sponsor will perform data management based on the data management SOP. Procedures and definitions specific to this study will be documented by the data management department. Medical technical terms and drugs will be coded using MedDRA and the Iyakuhinmei Data File respectively.
- Guidance on completion of CRFs will be provided in a separate eCRF Completion Guideline.
- As defined in "7.5 Electronic Clinical Outcome Assessment," the participant will fill out the questionnaire contained in the digital device and host processing of the collected electronic source data will be performed by the vendor.
- The investigator or a designated person will review the questionnaire data throughout the study period and verify that they have been input without fail, and that they comply with the protocol.

- CONFIDENTIAL -

- The questionnaire data will be electronically sent to the sponsor or a designated person at pre-specified intervals during the study period. The vendor will provide a complete and clean copy of the study site data to the investigator and a complete and clean copy of the study data to the sponsor or a designated person. Those copies of the data will be the property of the investigator, and if changes to the participant report data are subsequently requested, these changes will be made using a DCF submitted to the sponsor. If a change is requested, it must be supported by documented evidence at the study site. The period of data input to the questionnaire will be the allowable time window for each visit date. Data not input within the allowable time window will not be accepted.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- QTLs will be predefined in the applicable plan(s) to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote or on-site monitoring) are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator according to ICH or applicable local regulatory requirements, whichever is longer, after study completion. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

#### **10.1.7 Source Documents**

- Source data must be available at the study site to document the existence of the participants and to substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the participant.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator is responsible for ensuring the source data are attributable, legible, contemporaneous, original, accurate and complete whether the data are handwritten on paper or entered electronically. If source data are created (first entered), modified, maintained, archived, retrieved or transmitted electronically via computerized systems (and/or other kind of electronic devices) as part of regulated study activities, such

- CONFIDENTIAL -

systems must be compliant with all applicable laws and regulations governing use of electronic records and/or electronic signatures. Such systems may include, but are not limited to, electronic medical/health records, protocol-related assessments, AE tracking, electronic clinical outcome assessment and/or investigational device accountability.

- Paper records from electronic systems used in place of electronic format must be certified copies. A certified copy must be an exact copy and must have all the same attributes and information as the original. Certified copies must include signature and date of the individual completing the certification. Certified copies must be a complete and chronological set of study records (including notes, attachments, and audit trail information, if applicable). All printed records must be kept in the participant file and be available for archiving.
- The sponsor or designee will perform ongoing source data review to confirm that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

The following are the major documents to be retained at the study site.

- Source documents (clinical data, documents and records for preparing the CRF) hospital records, medical records, test records, memoranda, survey forms, usage records, administration records, data recorded by automatic measuring instruments, reproductions or transcripts verified as precise copies, microfiche, negative films, microfilms/magnetic media, X-ray films, participant files and study-related records kept at either a pharmacy, a laboratory, or medical technical office, as well as participant registration records, laboratory test slips including central measurement, worksheets specified by the sponsor, records of clinical coordinators, and records related to the study selected from those verified in other departments or hospitals.
- Study contracts, written ICFs, written information and other documents or their copies prepared by the study personnel. A letter of request for study (including a request for continuation/amendment), letter of request for review, notice of study contract, study contract, notification of discontinuation or completion of clinical study, written information for informed consent (including revisions), signed and dated written informed consent (including revisions), curriculum vitae of investigators, list of subinvestigators, list of signatures and print of seals (copy) and CRF (copy), etc.
- The protocol, documents obtained from the IRB related to the adequacy of conducting the study by the head of the study sites (Article 32-1, MHW Ordinance No. 28), documents obtained from the IRB related to the adequacy of conducting a study whose period exceeds 1 year or the adequacy of continuously conducting the study from which information on adverse reactions is obtained, and other documents obtained. A finalized protocol (including revisions), finalized IB (including revisions), operational procedures for the investigator, materials and information supplied by the sponsor (e.g., AE report), matters reported by the investigator (revisions of the protocol, AE reports, etc.), operational procedures for the IRB, the list of names of the IRB members, materials for

- CONFIDENTIAL -

IRB review (including continuous deliberation), IRB review records (including continuous deliberation) and the review result report of the IRB (including continuous deliberation), etc.

- Records of control for study intervention and other duties related to the study. Study intervention and device inventory and management records and vouchers for the receipt and return of the study intervention.

Data input into BAP0527 will be managed appropriately by Welldoc Inc.

### **10.1.8 Study and Site Closure**

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

For study termination:

- Discontinuation of further investigational study intervention development

For site termination:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures or GCP guidelines
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants enrolled earlier than expected

If the study is prematurely terminated or suspended, the sponsor or designee shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

### **10.1.9 Publication Policy**

- The results of this study may be published or presented at scientific meetings. If the investigator plans to do this, he/she makes a contract with the sponsor and agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

- CONFIDENTIAL -

- The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Publication of the study results is discussed in the study agreement.

#### **10.1.10 Insurance of Participants and Others**

If a participant suffers any study-related injury, the sponsor will compensate the participant appropriately according to the severity and duration of the damage. However, if the injury was caused intentionally or was due to gross negligence by the study site, the sponsor will consult with the study site about handling the injury, based on the agreed study contract. Compensation for the study-related injury is provided by the following procedures:

- If a participant incurs an injury as a result of participation in the study, the study site should provide medical treatment and other necessary measures. The sponsor should be notified of the injury.
- When the participant claims compensation from the study site for the above study-related injury, or such compensation may be claimed, the study site should immediately communicate the fact to the sponsor. Both parties should work together towards a compensation settlement.
- The sponsor shall pay compensation or indemnification and bear expenses necessary for the settlement as provided in the study contract.
- The sponsor shall make an arrangement for insurance and take measures necessary to ensure the compensation or indemnification mentioned above.

#### **10.1.11 Quality Assurance (QA)**

The sponsor is implementing and maintaining QA and QC systems with written SOPs to ensure that studies are conducted and data are generated, documented, recorded, and reported in compliance with the protocol, the ordinance on the standards for conducting clinical studies of medical devices (the GCP ordinance for medical devices) and applicable regulatory requirement(s). Where applicable, the QA and QC systems and written SOPs of the CRO will be applied.

The sponsor or sponsor's designee may arrange to audit the study at any or all study sites and facilities. The audit may include on-site review of regulatory documents, CRFs and source documents. Direct access to these documents will be required by the auditors.

#### **10.1.12 Other Study Organization and Planned Study Period/Duration**

For details, refer to the attachment.

## 10.2 Appendix 2 Contraception Requirements

WOCBP who are eligible for participation in the study, including those who choose complete abstinence, must have pregnancy tests as specified in the schedule of assessments [Table 1]. Pregnancy test results must confirm that the participant is not pregnant.

### WOMEN OF CHILDBEARING POTENTIAL DEFINITIONS AND METHODS OF CONTRACEPTION DEFINITIONS

A female is considered fertile (i.e., WOCBP) following menarche and until becoming postmenopausal unless permanently sterile.

#### Females in the following categories are not considered WOCBP

- Premenarchal
- Premenopausal with 1 of the following (i.e., permanently sterile):
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy
- Postmenopausal

A postmenopausal state is defined as at least 12 months after last menstrual bleeding without an alternative medical cause.

In case the last menstrual bleeding cannot be clearly determined, confirmation with more than 1 FSH measurement of at least > 40 IU/L (or higher per local institutional guidelines) is required.

Females on HRT and whose menopausal status is in doubt will be required to use 1 of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status by repeated FSH measurements before study enrollment.

Documentation of any of these categories can come from the study site personnel's review of the female participant's medical records, medical examination or medical history interview.

### CONTRACEPTION GUIDANCE FOR FEMALE PARTICIPANTS OF CHILDBEARING POTENTIAL

Participants who are WOCBP are eligible for participation in the study if they agree to use one of the highly effective methods of contraception listed below from the time of signing the ICF until the end of the treatment period and follow-up period.

- Highly effective methods of contraception (failure rate of < 1% per year when used consistently and correctly): Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation

- CONFIDENTIAL -

- Oral
- Other hormonal methods of contraception containing progestogen
  - Intrauterine hormone-releasing system
- Other methods of contraception
  - Copper or hormonal IUD
  - Bilateral tubal occlusion
- Vasectomized partner
- A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
- Use of a condom by the male partner

**Birth control methods considered unacceptable:**

- Periodic abstinence (calendar, ovulation, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicides only
- Lactational amenorrhea

## **10.3 Appendix 3 Adverse Events and Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up and Reporting**

### **10.3.1 Definition of Adverse Events**

#### **AE Definition:**

An AE is any untoward medical occurrence in a patient, clinical study participant, user or other person, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. This includes events related to the device used in the clinical study, if applicable, and events related to the (study) procedures.

A device-related AE is an AE that is related to the use of a device used in the clinical study. This includes AEs caused by an omission in the instruction manual for the use, dispensing or operation of a device used in the clinical study, or a deficiency in the device used in the clinical study. It also includes AEs occurring due to the improper use (including intentional improper use) of a device used in the clinical study.

#### **Events Meeting the AE Definition**

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., physical exam, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.

Persons other than study staff (other persons such as physicians, healthcare professionals, and family members) will also take the above into account when making judgments.

#### **Events NOT Meeting the AE Definition**

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

- CONFIDENTIAL -

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

**Events not handled as AEs specific to this study**

- This study requires daily blood glucose measurements made using the blood glucose meter (Accu-Chek Guide Me), which is the device used in the clinical study. Blood glucose involves the invasive act of using the puncture device on the fingertip, but pain at the puncture site when measuring SMBG will not be an AE subject to reporting. However, if events other than the minimal pain expected, such as events in which pain is judged to be more severe than usual, infections of the puncture site, or vasovagal response due to the puncture, are observed, they will be handled as AEs in the same way as usual AEs or the like.

**10.3.1.1 Abnormal Laboratory Findings**

Any abnormal laboratory test result (e.g., hematology, biochemistry or urinalysis) or other safety assessment (e.g., vital signs or physical examination), including those that worsen from baseline, that is considered to be clinically significant in the medical and scientific judgment of the investigator and not related to underlying disease, is to be reported as an (S)AE.

Any clinically significant abnormal laboratory finding or other abnormal safety assessment, which is associated with the underlying disease, does not require reporting as an (S)AE, unless judged by the investigator to be more severe than expected for the participant's condition.

Repeating an abnormal laboratory test or other safety assessment, in the absence of any of the above criteria, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

**10.3.2 Definition of Serious Adverse Events**

**An SAE is defined as any untoward medical occurrence that, at any dose:**

- Results in death
- Is life-threatening

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.

- CONFIDENTIAL -

- Requires inpatient hospitalization or prolongation of existing hospitalization
  - In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.
  - Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
- Results in persistent or significant disability/incapacity
  - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
  - This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Other situations:
  - Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

If an event is not an AE per definition in "10.3.1 Definition of Adverse Events," then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

### 10.3.3 Definition of Deficiencies

#### Definition of deficiencies

A deficiency in a device is the situation where a device used in the clinical study is broadly in a poor condition in relation to quality, safety or performance, such as device damage or malfunctions, regardless of whether this occurs at the stage of design, dispensing, storage or use.

- CONFIDENTIAL -

Specific deficiencies of devices and the like include breakdown, usage errors or inappropriate labeling. All deficiencies of devices will be documented throughout the entire study period and appropriately controlled by the sponsor. In this study, information on deficiencies in the investigational device BAP0527 and the device used in the clinical study Accu-Chek Guide Me will be collected.

**Events meeting the definition of deficiencies:**

- Differences in behavior, shape or durability expected from the specification or absent or insufficient identity or the like between devices for study use
- Contamination, breakage or insufficiency at any stage, including dispensing or storage
- Negative influence on participant, users or similar people (including electrical leaks, noise or the like)
- Malfunctions, outages or breakdowns (excluding those due to social environmental factors such as natural disasters or power outages)

**Deficiencies that may cause SAEs:**

Deficiencies in the device used in the clinical study with a risk of leading to SAEs are defined as deficiencies that may cause SAEs. It is necessary for the investigator to judge appropriately whether the deficiency has a risk of leading to an SAE, considering their effect on life, and on nature and performance of the device used in the clinical study. If the sponsor judges that the deficiency has a risk of leading to an SAE from its frequency or the trend in this deficiency, it will be necessary to take action consistent with regional regulations.

**10.3.4 Assessment of Causality**

- The investigator is obligated to assess the relationship between study intervention, study procedures and each occurrence of each AE/SAE.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or product information, for marketed products, in the assessment.
- For each AE/SAE, the investigator must document in the medical notes that they have reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.

- CONFIDENTIAL -

- The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment between study intervention is 1 of the criteria used when determining regulatory reporting requirements.

Following a review of the relevant data, the causal relationship between the study intervention and each (S)AE will be assessed by answering “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the study intervention?” Whether the causal relationship to the study intervention is based on BAP0527, the blood glucose meter, or both, will be assessed.

When making an assessment of causality, the following factors are to be considered when deciding if there is evidence and/or arguments to suggest there is a “reasonable possibility” that an (S)AE may have been caused by the study intervention (rather than a relationship cannot be ruled out) or if there is evidence to reasonably deny a causal relationship:

- Has the participant been administered study intervention?
- Plausibility (i.e., could the event have been caused by the suspect study intervention? Consider literature evidence, preclinical and study data, etc.)
- Dechallenge/rechallenge:
  - Dechallenge: Did the (S)AE resolve or improve after only stopping the suspect study intervention without any treatment?
  - Rechallenge: Did the (S)AE reoccur if the suspected study intervention was reintroduced after having been stopped?
- Laboratory or other test results: a specific laboratory investigation supports the assessment of the relationship between the (S)AE and the study intervention (e.g., based on values pre-, during and post-treatment)
- Available alternative explanations independent of study intervention; such as other concomitant interventions, medical history, concurrent or underlying disease, risk factors including medical and family history, season, location, etc., and strength of the alternative explanation
- Temporal relationship between the study intervention and (S)AE onset and/or resolution. Did the (S)AE occur in a reasonable temporal relationship to the administration of the study intervention?
- Finally, judging which are more likely based on all the above contents, factors of reasonable possibility or confounding factors, comprehensive judgment of plausibility will be provided.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. While it is very important that the investigator always assesses causality for every event before the initial transmission of the SAE data to the sponsor, the initial report should be submitted without delay (i.e., within 24 hours of awareness). With limited or insufficient information about the event to make an informed medical judgment and in absence of any indication or evidence to establish a causal

relationship, a causality assessment of “no” is to be considered. In such instance, the investigator is expected to obtain additional information regarding the event as soon as possible and to re-evaluate the causality upon receipt of additional information. The medically qualified investigator may revise their assessment of causality in light of new information regarding the SAE and shall send an SAE follow-up report and update the CRF with the new information and updated causality assessment.

### 10.3.5 Assessment of Severity

The investigator will use the following definitions to rate the severity of each AE:

**Table 5 Grading Scale Defining the Severity of an Adverse Event**

| Grade                | Assessment Standard                                                                                                                                   |
|----------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 - Mild             | Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated                                                   |
| 2 - Moderate         | Minimal local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL                                                        |
| 3 - Severe           | Medically significant but not immediately life-threatening, hospitalization or prolonged hospitalization indicated; disabling; limiting self-care ADL |
| 4 - Life-threatening | Life-threatening consequences, urgent intervention indicated                                                                                          |
| 5 - Death            | Death related to AE                                                                                                                                   |

ADL: activities of daily living

### 10.3.6 Recording and Follow-up of AEs, SAEs, Deficiencies and/or Deficiencies That May Cause SAEs

#### Recording of AEs, SAEs, deficiencies and/or deficiencies that may cause SAEs

- When an AE/SAE, deficiency and/or deficiency that may cause an SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- After this, the investigator will record information on all related AEs, SAEs, deficiencies and/or deficiencies that may cause SAEs (AE name, AE onset date, reason for judging the event to be serious, outcome of the AE, deficiency name, deficiency onset date, application or usage period of the study device, causal relationship between the AE and the study device) on the CRF.
- It is not acceptable for the investigator to send photocopies of the participant’s medical records to the sponsor in lieu of completion of the CRF.
- There may be instances when copies of medical records for certain cases are requested by the sponsor. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

**Follow-up of AEs and SAEs**

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

**10.3.7 Reporting Procedures for SAEs or Deficiencies That May Cause SAEs**

In the case of a SAE or deficiency that may cause SAEs, the principal investigator or subinvestigator must report to the head of the study site and must contact the sponsor by fax or email immediately (within 24 hours of awareness).

The investigator should complete and submit JUTOKUNA YUUGAIJISHOU OYOBIFUGUAI HOUKOKUSHO containing all information that is required by the appropriate regulatory authorities to the sponsor by fax or email immediately (within 24 hours of awareness) and to the head of the hospital.

For contact details, see “CONTACT DETAILS OF SPONSOR’S KEY PERSONNEL.” Fax or email the JUTOKUNA YUUGAIJISHOU OYOBIFUGUAI HOUKOKUSHO to:

Astellas Pharma Inc. – Japan  
Pharmacovigilance  
Fax number: +81-(0)3-3243-5747  
Electronic mail: rk-safety-jp@astellas.com

For detailed contact information, refer to “CONTACT DETAILS OF SPONSOR’S KEY PERSONNEL.” “JUTOKUNA YUUGAIJISHOU OYOBIFUGUAI HOUKOKUSHO” will be sent to the above fax number or electronic mail address.

**10.3.7.1 Detection of Adverse Events, Serious Adverse Events or Deficiencies via the BAP0527 Call Center**

If a participant calls the BAP0527 call center and information suggesting an AE or deficiency, such as the information shown below, is received from the participant, the call center staff member will promptly contact the investigator of the study site based on the separately specified procedure. After being contacted by the call center, the investigator must

- CONFIDENTIAL -

spontaneously contact the participant and confirm the situation in detail. If the information is an AE or deficiency, it must be reported according to the designated procedure.

**Deficiencies:**

Problems with the functions, performance or behavior of BAP0527 that cannot be resolved with the information in the instruction manual, unless the problem is considered to have obviously occurred due to the participant (refer to \*Exceptions).

\* Exceptions: The smartphone failing to work due to loss of battery power. Spontaneous termination of a mobile telecommunications contract or the like. Breakage of, water damage to or similar damage to the smartphone or blood glucose meter. Forgetting the password of the smartphone itself, or the like.

**AEs:**

- Hospitalization (or planned hospitalization)
- Report of the death of the participant, for example by family members, or comments by the participant suggesting suicidal ideation
- Comments suggesting the occurrence of an AE  
Examples: Recently my ears hurt. I have had a fever since yesterday. I cannot move my hand properly.

The BAP0527 call center does not have the ability or responsibility to make medical judgments but has the function and responsibility of fulfilling the assistive role of detecting AEs, deficiencies and SAEs. The BAP0527 call center will not provide explanations or offer consultations about the method of using the device used in the clinical study, Accu-Chek Guide Me (certification number: 303AABZX00007000), because this will be used under the supervision of the investigator.

**10.3.8 Supply of New Information Affecting the Conduct of the Study**

When new information becomes available that is necessary to allow for proper conduct of the study, the sponsor will inform all investigators involved in the study, as well as the appropriate regulatory authorities. Investigators should inform the IRB/IEC of such information when needed.

The investigator will also inform the participants, who will be required to sign an updated ICF in order to continue in the study.

- When information is obtained regarding SUSARs (or other) that are specified in Article 273 of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics, in compliance with Article 80-2 Paragraph 6 of the Pharmaceutical Affairs Law, the sponsor should inform all investigators involved in the study, head of the study site and appropriate regulatory authorities of such information. The head of the study site

who receives such information will decide whether the study should be continued after hearing the opinions of the IRB. The investigator will supply the new information to the participants, in compliance with “10.1.3.2 Supply of New and Important Information Influencing the Participant’s Consent and Revision of the Written Information.”

- In addition, when the head of the study site receives the revisions of the IB, protocol, written information, information on the matters covering the quality of the study intervention, efficacy and safety, information necessary for conducting the study properly or documents to be examined by the IRB, these documents should be sent to the IRB.

### **10.3.9 Urgent Safety Measures**

An USM is an intervention that is not defined by the protocol and can be put in place with immediate effect without needing to gain prior approval by the sponsor, relevant HA, IRB/IEC, where applicable, in order to protect participants from any immediate hazard to their health and/or safety. Either the investigator or the sponsor can initiate a USM. The cause of a USM can be safety-, product- or procedure-related.

#### **10.3.9.1 Deviations from the Protocol and Other Actions Taken to Avoid Life-threatening Risks to Participants**

The investigator must not deviate from or amend the protocol, excluding an emergency case for avoiding risks to the participants. When the investigator does not follow the protocol in order to avoid urgent risks for participants, the investigator should take the following actions.

- Describe the contents of the deviation or amendment and the reasons for it in a written notice, and immediately send the document stating the deviation or amendment and the reasons to the sponsor and the head of the study site. Keep a copy of the notice.
- Consult with the sponsor at the earliest possibility for cases in which it is necessary to amend the protocol. Obtain approval for a draft of the amended protocol from the IRB and the head of the study site as well as written approval from the sponsor.
- Take appropriate measures to prevent recurrence of similar deviations or amendments.

### **10.3.10 Reporting Urgent Safety Measures**

In the event of a potential USM, the investigator must contact the medical monitor and/or the contact address for the study (CMIC, Inc.) (within 24 hours of awareness). Full details of the potential USM are to be recorded in the participant’s medical records. The sponsor may request additional information related to the event to support their evaluation.

If the event is confirmed to be a USM, the sponsor will take appropriate action to ensure the safety and welfare of the participants. These actions may include, but are not limited to, a change in study procedures or study intervention, halting further enrollment in the study, or stopping the study in its entirety. The sponsor or sponsor's designee will notify the relevant competent authorities and concerned ethics committee within the timelines required per current local regulations, and will inform the investigators, as required. When required, investigators must notify their IRB/IEC within timelines set by regional regulations.

- CONFIDENTIAL -

## **10.4 Appendix 4 Liver Safety Monitoring and Assessment**

Not applicable.

- CONFIDENTIAL -

**10.5 Appendix 5 List of Excluded Concomitant Medications****Insulin preparations**

| <b>Category name</b>              | <b>Generic name</b>                                                                 | <b>Product name</b>                                  | <b>Dosage form</b> |
|-----------------------------------|-------------------------------------------------------------------------------------|------------------------------------------------------|--------------------|
| Ultrafast insulin analog          | Insulin lispro (genetical recombination)                                            | Insulin Lispro BS Injection 100 units/mL HU “Sanofi” | Injection          |
|                                   |                                                                                     | Insulin Lispro BS Injection Cartridge HU “Sanofi”    | Injection          |
|                                   |                                                                                     | Insulin Lispro BS Injection SoloStar HU “Sanofi”     | Injection          |
|                                   |                                                                                     | Humalog Injection 100 units/mL                       | Injection          |
|                                   |                                                                                     | Humalog Injection Cartridge                          | Injection          |
|                                   |                                                                                     | Humalog Injection Milio Pen                          | Injection          |
|                                   |                                                                                     | Humalog Injection Milio Pen HD                       | Injection          |
|                                   |                                                                                     | Lyumjev Injection 100 units/mL                       | Injection          |
|                                   |                                                                                     | Lyumjev Injection Cartridge                          | Injection          |
|                                   |                                                                                     | Lyumjev Injection Milio Pen                          | Injection          |
|                                   |                                                                                     | Lyumjev Injection Milio Pen HD                       | Injection          |
|                                   | Insulin aspart (genetical recombination)                                            | Insulin Aspart BS Injection 100 units/mL NR “Sanofi” | Injection          |
|                                   |                                                                                     | Insulin Aspart BS Injection Cartridge NR “Sanofi”    | Injection          |
|                                   |                                                                                     | Insulin Aspart BS Injection SoloStar NR “Sanofi”     | Injection          |
|                                   |                                                                                     | NovoRapid Injection 100 units/mL                     | Injection          |
|                                   |                                                                                     | NovoRapid Injection InnoLet                          | Injection          |
|                                   |                                                                                     | NovoRapid Injection FlexTouch                        | Injection          |
|                                   |                                                                                     | NovoRapid Injection FlexPen                          | Injection          |
|                                   |                                                                                     | NovoRapid Injection Penfill                          | Injection          |
|                                   |                                                                                     | Fiasp Injection 100 units/mL                         | Injection          |
|                                   |                                                                                     | Fiasp Injection FlexTouch                            | Injection          |
|                                   |                                                                                     | Fiasp Injection Penfill                              | Injection          |
|                                   | Insulin glulisine (genetical recombination)                                         | Apidra Injection 100 units/mL                        | Injection          |
|                                   |                                                                                     | Apidra Injection Cartridge                           | Injection          |
|                                   |                                                                                     | Apidra Injection SoloStar                            | Injection          |
| Fast acting human insulin         | Insulin human (genetical recombination)                                             | Novolin R Injection 100 units/mL                     | Injection          |
|                                   |                                                                                     | Novolin R Injection FlexPen                          | Injection          |
|                                   |                                                                                     | Humulin R Injection 100 units/mL                     | Injection          |
|                                   |                                                                                     | Humulin R Injection Cartridge                        | Injection          |
|                                   |                                                                                     | Humulin R Injection Milio Pen                        | Injection          |
| Mixed/ biphasic insulin analog    | Insulin lispro (genetical recombination)                                            | Humalog Mix 25 Injection Cartridge                   | Injection          |
|                                   |                                                                                     | Humalog Mix 25 Injection Milio Pen                   | Injection          |
|                                   |                                                                                     | Humalog Mix 50 Injection Cartridge                   | Injection          |
|                                   |                                                                                     | Humalog Mix 50 Injection Milio Pen                   | Injection          |
|                                   | Insulin aspart (genetical recombination)                                            | NovoRapid 30 Mix Injection FlexPen                   | Injection          |
|                                   |                                                                                     | NovoRapid 30 Mix Injection Penfill                   | Injection          |
|                                   |                                                                                     | NovoRapid 50 Mix Injection FlexPen                   | Injection          |
| Mixed/ biphasic human insulin     | Insulin human (genetical recombination)                                             | InnoLet 30R Injection                                | Injection          |
|                                   |                                                                                     | Novolin 30R Injection FlexPen                        | Injection          |
|                                   |                                                                                     | Humulin 3/7 Injection 100 units/mL                   | Injection          |
|                                   |                                                                                     | Humulin 3/7 Injection Cartridge                      | Injection          |
|                                   |                                                                                     | Humulin 3/7 Injection Milio Pen                      | Injection          |
| Combined soluble insulin analog   | Insulin degludec (genetical recombination)/insulin aspart (genetical recombination) | Ryzodeg Combination Injection FlexTouch              | Injection          |
| Combination insulin/GLP-1         | Insulin glargine (genetical recombination)/lixisenatide                             | Soliqua Injection SoloStar                           | Injection          |
|                                   | Insulin degludec (genetical recombination)/liraglutide (genetical recombination)    | Xultophy Combination Injection FlexTouch             | Injection          |
| Intermediate-acting human insulin | Insulin human (genetical recombination)                                             | Novolin N Injection FlexPen                          | Injection          |
|                                   |                                                                                     | Humulin N Injection 100 units/mL                     | Injection          |
|                                   |                                                                                     | Humulin N Injection Cartridge                        | Injection          |
|                                   |                                                                                     | Humulin N Injection Milio Pen                        | Injection          |

- CONFIDENTIAL -

| Category name                      | Generic name                               | Product name                                    | Dosage form |
|------------------------------------|--------------------------------------------|-------------------------------------------------|-------------|
| Long-acting soluble insulin analog | Insulin glargine (genetical recombination) | Insulin Glargine BS Injection Cartridge “Lilly” | Injection   |
|                                    |                                            | Insulin Glargine BS Injection Kit “FFP”         | Injection   |
|                                    |                                            | Insulin Glargine BS Injection Milio Pen “Lilly” | Injection   |
|                                    |                                            | Lantus XR SoloStar S.C. Injection               | Injection   |
|                                    |                                            | Lantus Vial S.C. Injection 100 units/mL         | Injection   |
|                                    |                                            | Lantus Cart S.C. Injection                      | Injection   |
|                                    |                                            | Lantus SoloStar S.C. Injection                  | Injection   |
|                                    | Insulin degludec (genetical recombination) | Tresiba Injection FlexTouch                     | Injection   |
|                                    |                                            | Tresiba Injection Penfill                       | Injection   |
|                                    | Insulin detemir (genetical recombination)  | Levemir Injection InnoLet                       | Injection   |
|                                    |                                            | Levemir Injection FlexPen                       | Injection   |
|                                    |                                            | Levemir Injection Penfill                       | Injection   |

## 10.6 Appendix 6 Clinical Laboratory Assessments

Laboratory tests will be performed according to the schedule of assessments [Table 1] and sent to a central laboratory for analysis.

**Table 6 Clinical Laboratory Tests**

| Time of test                                                                                                             | Panel/Assessments  | Parameters to be Analyzed                                                                                                                                                                                                                                                                                                                   | Sample collection container                  |
|--------------------------------------------------------------------------------------------------------------------------|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Visit 1<br>Visit 2<br>Visit 4<br>Visit 5<br>Visit 6<br>Visit 7<br>Visit 8<br>Visit 9<br>Visit 10<br>Visit 11<br>Visit 12 | Hematology         | Hematocrit<br>Hemoglobin<br>Mean corpuscular volume<br>Mean corpuscular hemoglobin<br>Mean corpuscular hemoglobin concentration<br>Platelet count<br>Red blood cell count<br>White blood cell count<br>White blood cell count differential (neutrophils, eosinophils, basophils, monocytes, lymphocytes)                                    | EDTA-2K blood sample collection tube         |
| Visit 1<br>Visit 2<br>Visit 4<br>Visit 5<br>Visit 6<br>Visit 7<br>Visit 8<br>Visit 9<br>Visit 10<br>Visit 11<br>Visit 12 | Blood biochemistry | Albumin<br>ALT<br>ALP<br>AST<br>Blood urea nitrogen<br>Calcium<br>Chloride<br>Creatinine<br>eGFR<br>Creatine phosphokinase<br>Lactate dehydrogenase<br>Magnesium<br>Potassium<br>Sodium<br>TBL<br>Total protein<br>Phosphorus<br>Total cholesterol<br>HDL cholesterol<br>LDL cholesterol<br>Triglycerides<br>Insulin level (except visit 1) | Plain blood sample collection tube           |
| Visit 1<br>Visit 2<br>Visit 4<br>Visit 5<br>Visit 6<br>Visit 7<br>Visit 8<br>Visit 9<br>Visit 10<br>Visit 11<br>Visit 12 | HbA1c level        | HbA1c level                                                                                                                                                                                                                                                                                                                                 | Sodium fluoride blood sample collection tube |

- CONFIDENTIAL -

| Time of test                                                                                                             | Panel/Assessments   | Parameters to be Analyzed                                                                                                                        | Sample collection container                  |
|--------------------------------------------------------------------------------------------------------------------------|---------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|
| Visit 2<br>Visit 4<br>Visit 5<br>Visit 6<br>Visit 7<br>Visit 8<br>Visit 9<br>Visit 10<br>Visit 11<br>Visit 12            | Blood glucose level | Blood glucose level                                                                                                                              | Sodium fluoride blood sample collection tube |
| Visit 1<br>Visit 2<br>Visit 4<br>Visit 5<br>Visit 6<br>Visit 7<br>Visit 8<br>Visit 9<br>Visit 10<br>Visit 11<br>Visit 12 | Urinalysis          | Bilirubin<br>Glucose<br>Ketones<br>pH<br>Protein<br>Urobilinogen<br>Specific gravity<br>Occult blood<br>Leukocyte esterase<br>Nitrite<br>Albumin | Urine sample collection tube                 |

ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; TBL: total bilirubin

## **10.7 Appendix 7 Clinical Study Continuity**

### **INTRODUCTION**

The purpose of this appendix is to provide acceptable alternate methods to assess safety and efficacy parameters, as appropriate, in the event the clinical study is interrupted at the country, state, site or participant level during any crisis (e.g., natural disaster, pandemic).

### **BENEFIT-RISK RATIONALE**

Maintaining the safety of clinical study participants and delivering continuity of care in the clinical study setting is paramount during any crisis. The site is expected to follow the protocol and associated schedule of assessments [Table 1] unless the site principal investigator discusses the need with the API medical monitor to implement the alternate measures.

The approach outlined within this appendix defines which assessments are required to maintain a favorable benefit/risk to the participant, to maintain overall study integrity and to provide acceptable alternate methods to complete the study-required assessments and procedures if study activities are unable to be performed.

### **INFORMED CONSENT**

Participants who need to follow any or all of the alternate measures outlined in this Appendix will be required to provide informed consent, which explicitly informs them of the nature of and rationale for these changes, and gain their agreement to continue participation in the study prior to the implementation of any of these changes. In the event the urgency of implementing the alternate measures does not allow for the participant to provide written consent prior to implementation, the principal investigator or designee will obtain oral agreement from the participant followed by written documentation as soon as is feasible. A separate addendum to the study ICF will be provided to document the participant's consent to the changes.

### **Participant PROCEDURES ASSESSMENT**

Sites with participants who are currently enrolled into this clinical study may consider implementing the alternate methods outlined below if 1 or more of the following conditions are met:

- Regional or local travel has been restricted, inclusive of mandatory shelter in place measures, which makes participant travel to/from the study site nearly impossible.
- Site facilities have been closed for clinical study conduct.
- Site has been restricted to treating patients with conditions outside of the scope of the study.

- CONFIDENTIAL -

- Site personnel have temporarily relocated the conduct of the study to a location that place a burden on the participant with respect to time and travel.
- Participant(s) have temporarily relocated from the current study site to an alternate study site to avoid placing a burden on the participant with respect to travel.
- Participant(s) have temporarily relocated from their home location and the new distances from the site would cause undue burden with respect to time and travel.
- Participant has risk factors for which traveling to the site poses an additional risk to the participant's health and safety.

Adherence to the original protocol as reflected in the schedule of assessments [Table 1] is expected, where plausible, in the case of a crisis. The alternate measures listed below are only permissible in the event of a crisis, and after discussing the need with the API medical monitor to implement the alternate measures. This is to allow for continuity of receiving study intervention and maintaining critical safety and efficacy assessments for participants in the study at a time of crisis.

If 1 or more of the alternate measures noted below is implemented for a participant, the site should document in the participant's source document the justification for implementing the alternate measure and the actual alternate measures that were implemented, along with the corresponding timepoint(s).

- Weight, vital signs, physical exam, pregnancy test may be completed at a local clinic, where possible.
- Prior/concomitant medication, subsequent therapy after treatment and adverse event assessment may be conducted as remote/virtual televisits.
- Clinical laboratory tests, including CBC, biochemistry, coagulation and urinalysis may be collected at a local facility if results can be made available to the investigative site

## **STUDY INTERVENTION SUPPLY**

If any of the conditions outlined above in the Participants Procedures Assessment are met, 1 or all of the following mitigating strategies will be employed, as needed, to ensure continuity of study intervention supply to the participants:

- Increase stock of study intervention on site to reduce number of shipments required, if site space will allow.

## **Data Collection Requirements**

Additional data may be collected in order to indicate how participation in the study may have been affected by a crisis and to accommodate data collection resulting from alternate measures implemented to manage the conduct of the study and participant safety.

- CONFIDENTIAL -

- Critical assessments for safety and efficacy based on study endpoints to be identified as missing or altered (performed virtually, at alternative locations, out of window or other modifications) due to the crisis.

## 10.8 Appendix 8 Decentralized Clinical Trial (DCT)

In this study, only at study sites that agree in advance with the sponsor about conducting the DCT (hereafter, referred to as “DCT sites”), the concept of a DCT will be partially incorporated. DCT sites will not be required to perform examination of all participants registered at their facilities using the DCT format, and the DCT will include only participants who wish to participate in the DCT.

The relevant visit will be a visit chosen freely from among visit 4, visit 5, visit 7, visit 8, visit 10 and visit 11, and online examination and a nursing visit will be performed. At the online examination, the following procedures will be performed: checks on and directions about the participant’s use of this product, looking back at the participant’s lifestyle between visits by the investigator and the participant using BAP0527 data, reviewing set target values (HbA1c level, amount of carbohydrates, body weight, blood pressure), and assessment of concomitant medications/concomitant therapies and AEs/deficiencies. The visiting nurse will measure body weight and vital signs, perform EQ-5D-5L and DTSQ, retrieve samples for specified tests and perform a urine pregnancy test.

For the schedule, refer to the schedule of assessments [Table 1].

**10.9 Appendix 9 EuroQol 5 Dimension 5-level (EQ-5D-5L)**

Under each heading, please tick (✓) the ONE box (☐) that best describes your health TODAY.

**MOBILITY**

- I have no problems in walking about ☐
- I have slight problems in walking about ☐
- I have moderate problems in walking about ☐
- I have severe problems in walking about ☐
- I am unable to walk about ☐

**SELF-CARE**

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

**USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)**

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

**PAIN / DISCOMFORT**

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

**ANXIETY / DEPRESSION**

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

## 10.10 Appendix 10 Diabetes Treatment Satisfaction Questionnaire (DTSQ)

The following questions are concerned with the treatment for your diabetes (including insulin, tablets and/or diet) and your experience over the past few weeks.

Please answer each question by circling a number on each of the scales.

1. How satisfied are you with your current treatment?  

|                |               |                   |
|----------------|---------------|-------------------|
| very satisfied | 6 5 4 3 2 1 0 | very dissatisfied |
|----------------|---------------|-------------------|
2. How often have you felt that your blood sugars have been unacceptably high recently?  

|                  |               |                  |
|------------------|---------------|------------------|
| most of the time | 6 5 4 3 2 1 0 | none of the time |
|------------------|---------------|------------------|
3. How often have you felt that your blood sugars have been unacceptably low recently?  

|                  |               |                  |
|------------------|---------------|------------------|
| most of the time | 6 5 4 3 2 1 0 | none of the time |
|------------------|---------------|------------------|
4. How convenient have you been finding your treatment to be recently?  

|                 |               |                   |
|-----------------|---------------|-------------------|
| very convenient | 6 5 4 3 2 1 0 | very inconvenient |
|-----------------|---------------|-------------------|
5. How flexible have you been finding your treatment to be recently?  

|               |               |                 |
|---------------|---------------|-----------------|
| very flexible | 6 5 4 3 2 1 0 | very inflexible |
|---------------|---------------|-----------------|
6. How satisfied are you with your understanding of your diabetes?  

|                |               |                   |
|----------------|---------------|-------------------|
| very satisfied | 6 5 4 3 2 1 0 | very dissatisfied |
|----------------|---------------|-------------------|
7. Would you recommend this form of treatment to someone else with your kind of diabetes?  

|                                                 |               |                                                    |
|-------------------------------------------------|---------------|----------------------------------------------------|
| Yes, I would definitely recommend the treatment | 6 5 4 3 2 1 0 | No, I would definitely not recommend the treatment |
|-------------------------------------------------|---------------|----------------------------------------------------|
8. How satisfied would you be to continue with your present form of treatment?  

|                |               |                   |
|----------------|---------------|-------------------|
| very satisfied | 6 5 4 3 2 1 0 | very dissatisfied |
|----------------|---------------|-------------------|

Please make sure that you have circled one number on each of the scales.

## 10.11 Appendix 11 14-Item Health Literacy Scale (HLS-14)

1. When you read instructions or leaflets from hospitals or pharmacies, how do you agree or disagree about the following?

病院や薬局からもらう説明書やパンフレットなどを読む際に、下記の項目について、あなたはどのように考えていますか？

|                                                                                             | Strongly disagree<br>全くそう思わない | Disagree<br>あまりそう思わない | Not sure<br>どちらでもない | Agree<br>まあそう思う | Strongly agree<br>強くそう思う |
|---------------------------------------------------------------------------------------------|-------------------------------|-----------------------|---------------------|-----------------|--------------------------|
| Q1 I find characters that I cannot read<br>読めない漢字がある                                        | 5                             | 4                     | 3                   | 2               | 1                        |
| Q2 The print is too small for me (even though I wear glasses)<br>字が細かくて読みにくい（メガネなどをかけた状態でも） | 5                             | 4                     | 3                   | 2               | 1                        |
| Q3 The content is too difficult for me<br>内容が難しくて分かりにくい                                     | 5                             | 4                     | 3                   | 2               | 1                        |
| Q4 It takes a long time to read them<br>読むのに時間がかかる                                          | 5                             | 4                     | 3                   | 2               | 1                        |
| Q5 I need someone to help me read them<br>誰かに代わりに読んでもらうことがある                                | 5                             | 4                     | 3                   | 2               | 1                        |

2. If you are diagnosed as having a disease and you have little information about the disease and its treatment, how do you agree or disagree about the following?

ある病気と診断されてから、その病気やその治療・健康法に関することについて、下記の項目について、あなたはどのように考えていますか？

|                                                                                                        | Strongly disagree<br>全くそう思わない | Disagree<br>あまりそう思わない | Not sure<br>どちらでもない | Agree<br>まあそう思う | Strongly agree<br>強くそう思う |
|--------------------------------------------------------------------------------------------------------|-------------------------------|-----------------------|---------------------|-----------------|--------------------------|
| Q6 I collect information from various sources<br>いろいろなところから知識や情報を集めた                                   | 1                             | 2                     | 3                   | 4               | 5                        |
| Q7 I extract the information I want<br>たくさんある知識や情報から、自分の求めるものを選び出した                                    | 1                             | 2                     | 3                   | 4               | 5                        |
| Q8 I understand the obtained information<br>自分が見聞きした知識や情報を、理解できた                                       | 1                             | 2                     | 3                   | 4               | 5                        |
| Q9 I tell my opinion about my illness to my doctor, family, or friends<br>病気についての自分の意見や考えを、医師や身近な人に伝えた | 1                             | 2                     | 3                   | 4               | 5                        |
| Q10 I apply the obtained information to my daily life<br>見聞きした知識や情報をもとに、実際に生活を変えてみた                    | 1                             | 2                     | 3                   | 4               | 5                        |

3. If you are diagnosed as having a disease and you can obtain information about the disease and its treatment, how do you agree or disagree about the following?

ある病気と診断されてから、その病気やその治療・健康法に関することで、自分で見聞きした知識や情報について、下記の項目について、あなたはどのように考えていますか？

|                                                                                    | Strongly disagree<br>全くそう思わない | Disagree<br>あまりそう思わない | Not sure<br>どちらでもない | Agree<br>まあそう思う | Strongly agree<br>強くそう思う |
|------------------------------------------------------------------------------------|-------------------------------|-----------------------|---------------------|-----------------|--------------------------|
| Q11 I consider whether the information is applicable to me<br>自分にもあてはまるかどうか考えた     | 1                             | 2                     | 3                   | 4               | 5                        |
| Q12 I consider whether the information is credible<br>信頼性に疑問をもった                   | 1                             | 2                     | 3                   | 4               | 5                        |
| Q13 I check whether the information is valid and reliable<br>正しいかどうか聞いたり、調べたりした    | 1                             | 2                     | 3                   | 4               | 5                        |
| Q14 I collect information to make my healthcare decisions<br>病院や治療法などを自分で決めるために調べた | 1                             | 2                     | 3                   | 4               | 5                        |

## 11 REFERENCES

- Bodenheimer T, Sinsky C. From triple to quadruple aim: care of the patient requires care of the provider. *Ann Fam Med*. 2014;12(6):573-6.
- Casagrande SS, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988-2010. *Diabetes Care*. 2013;36(8):2271-9.
- EuroQol Group. EuroQol-a new facility for the measurement of health-related quality of life. *Health Policy*. 1990;16(3):199-208.
- Herdman M, Gudex C, Lloyd A, Janssen Mf, Kind P, Parkin D, et al. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*. 2011;20(10):1727-36.
- 池田俊也, 白岩健, 五十嵐中, 能登真一, 福田敬, 齋藤信也, 他. 日本語版 EQ-5D-5L におけるスコアリング法の開発. *保健医療科学*. 2015;64(1):47-55.
- International Diabetes Federation. Self-monitoring of blood glucose in non-insulin treated type 2 diabetes. 2009 [Internet]. [Cited from the Internet 22 Mar 2023]. Available from: <https://diabetesnet.org/en/library/190-self-monitoring-of-blood-glucose-in-non-insulin-treated-type-2-diabetes.html>.
- 石井千有季, 山田和子, 森岡郁晴. 教育入院後に再入院した 2 型糖尿病患者の特徴と再入院に至る要因. *日本看護研究学会雑誌*. 2012;35:25-35.
- 石井均, Bradley C, Riazi A, Barendse S, 山本壽一. 糖尿病治療満足度質問表 (DTSQ) の日本語翻訳と評価に関する研究. *医学のあゆみ*. 2000;192:809-14.
- Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical inertia in people with type 2 diabetes: a retrospective cohort study of more than 80,000 people. *Diabetes Care*. 2013;36(11):3411-7.
- Mannucci E, Antenore A, Giorgino F, Scavini M. Effects of Structured Versus Unstructured Self-Monitoring of Blood Glucose on Glucose Control in Patients With Non-insulin-treated Type 2 Diabetes: A Meta-Analysis of Randomized Controlled Trials. *J Diabetes Sci Technol*. 2018;12:183-9.
- 日本糖尿病学会. 第 4 次「対糖尿病戦略 5 ヶ年計画」. 2020a.
- 日本糖尿病学会. 糖尿病治療ガイド 2020-2021. 2020b.
- 日本糖尿病学会. 糖尿病診療ガイドライン 2019. 2019.
- 西尾育子. 2 型糖尿病患者の食事療法継続の阻害因子と看護援助に関する国内文献の知見の統合. *日本糖尿病教育・看護学会誌*. 2016;20:49-56.
- Suka M, Odajima T, Kasai M, Igarashi A, Ishikawa H, Kusama M, et al. The 14-item health literacy scale for Japanese adults (HLS-14). *Environ Health Prev Med*. 2013;18:407-15.

## 12 INVESTIGATOR'S SIGNATURE

### Multicenter, Randomized, Open-label Study of Diabetes Treatment Support System (BAP0527 and Blood Glucose Meter) in Patients with Type 2 Diabetes Mellitus

ISN/Protocol 0527-CL-0002, Amendment 1

24-Oct-2023

I have read all pages of this protocol for which Astellas is the sponsor. I agree to conduct the study as outlined in the protocol and to comply with all the terms and conditions set out therein. I confirm that I will conduct the study in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) guidelines and applicable local regulations. I will also ensure that subinvestigator(s) and other relevant members of my personnel have access to copies of this protocol and the ICH GCP guidelines to enable them to work in accordance with the provisions of these documents.

**Principal Investigator:**

Signature: \_\_\_\_\_

Date (DD MMM YYYY) \_\_\_\_\_

Printed Name: \_\_\_\_\_

&lt;Insert name and qualification of the investigator&gt;

Address of  
study site: \_\_\_\_\_

### **13 SPONSOR'S SIGNATURE**

Required sponsor signatures as required by ICH GCP 4.5.1 are located in the first attachment

|                     |                               |
|---------------------|-------------------------------|
| <b>Attachment 1</b> | Electronic Sponsor Signatures |
|---------------------|-------------------------------|