



STATISTICAL ANALYSIS PLAN

Evaluation of virtual versus traditional study conduct in a 6-month, multicenter, randomized, open-label, 2-parallel group pilot study in adult patients with Type 1 diabetes mellitus

HOE901-MSC15146-eSTUDY

NCT03260868

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DATE OF ISSUE: 08-Jul-2019

Total number of pages: 107

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	american diabetes association
ADaM:	analysis data model
AEs:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
BMI:	body mass index
CI:	confidence interval
CLcr:	creatinine clearance
ClinRO:	investigator (CLInician) reported outcome
DDS:	diabetes distress scale
DTSQ:	diabetes treatment satisfaction questionnaire
DTSQc:	diabetes treatment satisfaction questionnaire change
e-CRF:	electronic case report form
FPG:	fasting plasma glucose
GFR:	glomerular filtration rate
HbA1c:	glycosylated hemoglobin A1c
HFS-B:	hypoglycemia fear survey-behavior
HFS-W:	hypoglycemia fear survey-worry
HLGT:	high-level group term
HLT:	high-level term
IMP:	investigational medicinal product
ITT:	intent to treat
KM:	Kaplan-Meier
LLT:	lower-level term
LS:	least square
MDRD:	modification of diet in renal disease
MedDRA:	Medical Dictionary for Regulatory Activities
MMRM:	mixed-effect model with repeated measures
MRN:	Medical Research Network
NIMP:	non-investigational medical product
OSEP:	overall study experience-participation
OSES:	overall study experience-sites
PRO:	Patient Reported Outcome
PT:	preferred term , preferred term
RBC:	red blood cell
RUQ:	resource use questionnaire
SAE(s):	serious adverse event(s)
SAS:	statistical analysis system
SEs:	standard error
SMPG:	self-monitoring plasma glucose
SOC:	system organ class

T1DM: Type I Diabetes Mellitus
TEAE: treatment-emergent adverse event
US: United States
WHO-DD: world health organization-drug dictionary
WIWI: was it worth it
WPAI: work productivity and impairment

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is an open label, 1:1 randomized, 2 groups approach, multicenter pilot study. The study is a post-marketing Phase 4 trial which will recruit outpatients with Type 1 diabetes mellitus (T1DM) currently treated with insulin glargine 100 U/mL (eg, Lantus or Basaglar) plus rapid-acting insulin analogs. The patients must have access to mobile technology (eg, smartphone) and be digital-literate. They will eSign the consent on the study website or on the “Subject application”. The patients will be switched at randomization to insulin glargine 300 U/mL (eg, Toujeo) plus rapid-acting insulin analogs.

The study will be conducted in the US and in Canada with approximately 6 participating investigational centers. It is planned to randomize 150 patients (250 patients will be recruited).

Eligible patients will be randomized 1:1 (virtual: traditional) into 2 study groups to follow one of two approaches for completion of all study procedures:

- A remote, virtual approach (n = 75 patients); patients of this group will not visit the study sites during the entire study course, except for a physical examination before IMP initiation. All study assessments, including vital signs, weight, lab variables, etc, will be completed via the Bluetooth devices that instantly transfer the digital data, available for investigators’ view. Video chat between the patients and investigators/designees may occur for safety reason in addition to the planned study visits.
- A traditional approach (n = 75 patients).

Stratification factors for randomization include study site and HbA1c <7.6% or ≥7.6%. The rationale for stratification by study site is the small number of sites and the fact that some assessments for patient care are done at site level. It is therefore deemed important to ensure balance at site level in number of patients randomized across the virtual and traditional approach groups. Patients of both groups will receive the same IMP: daily subcutaneous (SC) injection of Toujeo as the basal insulin. Protocol-mandated background therapy consists of the existing rapid acting insulin analogs (Humalog, Novolog, or Apidra) that have been used before the start of the study and will be continued throughout the study. This background treatment will not be supplied by the sponsor.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to evaluate the effect of virtual approach via novel technologies versus traditional study conduct on glycemic control in terms of HbA1c.

1.2.2 Secondary objectives

The study secondary objective is to evaluate the appropriate utilization of virtual approach via novel technologies during the study and to assess the effect of the virtual versus traditional study conduct on multiple outcomes in terms of study methodology and diabetes control:

- Study methodology with the two approaches:
 - Patient satisfaction with the trial experience via a PRO
 - Impact of clinical trial participation via a PRO
 - Patient burden with the clinical trial experience via a PRO
 - Resource use via a PRO
 - Medication and key study activity compliance
 - Patient retention
- Diabetes control with the two approaches:
 - Diabetes related PROs
 - Glycemic control (HbA1c, FPG, SMPG)
- Patient care with the two approaches:
 - Doctor/site-patient relationship
 - Site satisfaction with provisioned care
 - Patient experience in the clinical trial via a qualitative exit interview
- Safety assessment managed by the two approaches including:
 - Hypoglycemic events
 - Adverse Events (AEs)

1.3 DETERMINATION OF SAMPLE SIZE

A sample size of 150 patients (75 in virtual approach and 75 in traditional approach) will be randomized using a 1:1 ratio (virtual: traditional); this sample size was not powered for confirmatory testing, only descriptive statistics will be provided.

As this is a pilot study, no formal sample size calculation was performed.

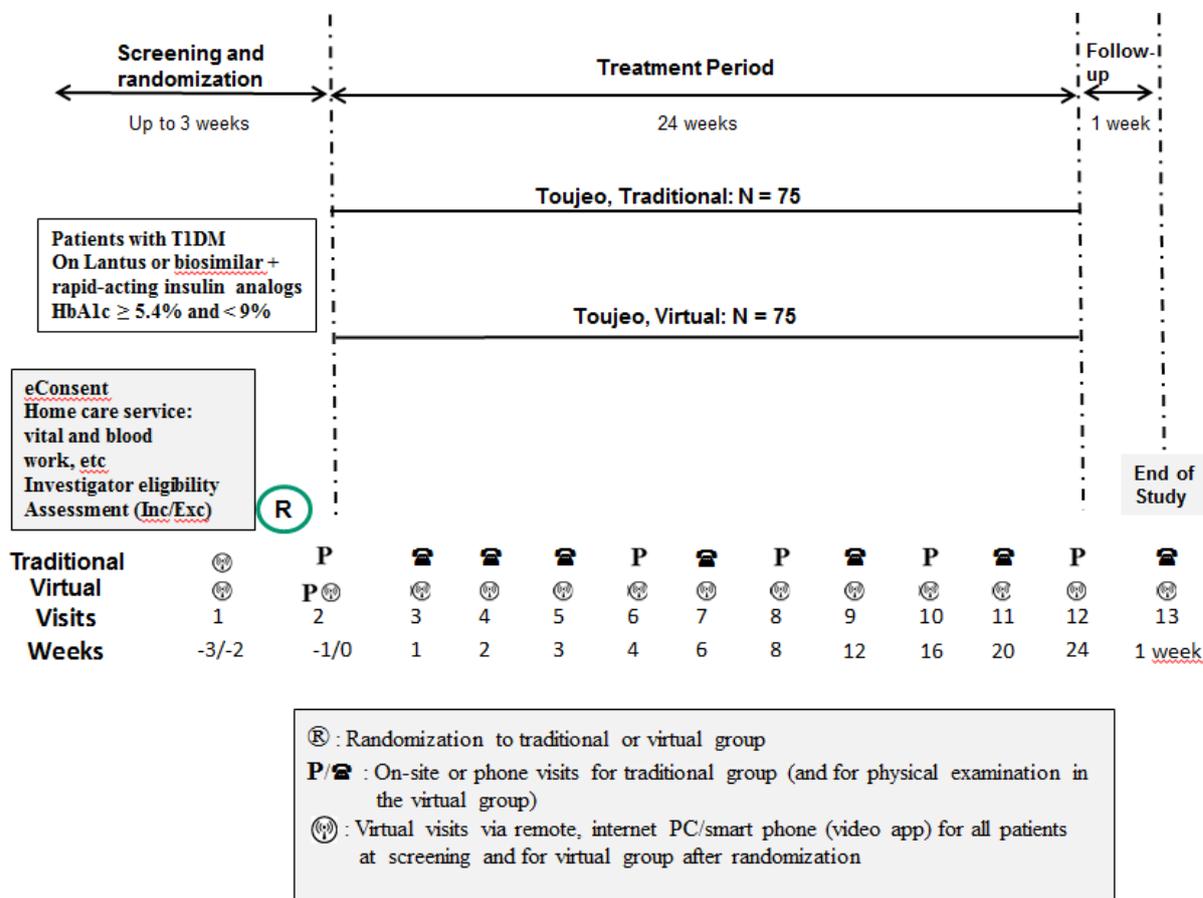
Nevertheless, a precision calculation of the primary endpoint based on the 2-sided 95% confidence interval (CI) shows that the change in HbA1c from baseline in virtual approach, the change in HbA1c from baseline in traditional approach and the difference in HbA1c change between the two approaches will be estimated with a precision of approximately 0.37%, using a standard deviation (SD) of 1.1 and taking into account an up to 10% rate of non-evaluable patients for HbA1c.

These calculations were made using nQuery Advisor 7.0.

1.4 STUDY PLAN

The following figure describes the design of the study:

Figure 1 - Study design



The study consists of 3 periods:

- An up-to-3 week screening period.
- A 24-week treatment period.
- A 1-week post-treatment period (follow-up).

The **screening period** includes 2 steps to complete the digital consent process via the study-specific webpage and the eligibility assessment by the study site. Screening procedures will be performed by Homecare services (via the Medical Research Network [MRN]) provided medical professional in collaboration with the investigators. The investigators will then complete the eligibility assessments at the end of screening, the randomization, and the shipment of study material (Step 2).

During the 24-week **treatment period**, the patients in both groups will receive the same study treatment with Toujeo as the basal insulin plus their existing rapid-acting mealtime insulin

analogs (Humalog, Novolog, or Apidra) to manage their diabetes. Toujeo dose will be titrated to target the fasting SMPG between 80 and 130 mg/dL; meal time insulin analogs will be adjusted following investigators' instructions to maintain postprandial SMPG within a range of 130 to 180 mg/dL.

All patients will monitor their plasma glucose via the study provided glucose meter. The SMPG values will be used to guide the insulin dose adjustment and document the hyper- or hypoglycemic events.

Any post-treatment safety information will be collected during the 1-week post-treatment period.

In total the study duration per patient will be approximately 28 weeks (3 weeks of screening + 24 weeks on treatment + 1 week post-treatment follow-up).

See the study flowchart with details of all assessments in [Appendix B](#).

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

Not applicable

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

Not applicable

2 STATISTICAL AND ANALYTICAL PROCEDURES

The study was early terminated by the Sponsor on November 2018 **due to prolonged low patient recruitment**. At this date 15 patients were randomized instead of 150 as expected. Therefore the primary and secondary objectives will not be analyzed as initially planned as detailed below in this Statistical analysis Plan. Consequently only basics descriptive statistics will be provided using tables or listings according to the availability of assessments for each endpoints and parameters.

Any technical details related to computation, dates and imputation for missing dates are described in [Section 2.5](#).

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value is defined as the last available value prior to the first injection of open-label IMP and up to randomization for patients randomized not treated.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the on-treatment summary statistics in the safety and efficacy sections ([Section 2.4.5](#) and [Section 2.4.4](#)).

Demographic characteristics

- Age (years).
- Age qualitative categories: <65, [65-75[and ≥ 75 years.
- Gender (Male, Female).
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not reported, Unknown).
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown /Not Reported).

Vital signs

- Baseline body weight (kg),
- Baseline body weight categories (kg) : <50, ≥ 50 and <100, ≥ 100 kg.
- Baseline Body Mass Index (kg/m²).
- Baseline body mass index (BMI) categories (kg/m²): <25, [25-30[, [30-40[and ≥ 40 kg/m².

Renal function

- Baseline Creatinine ($\mu\text{mol/L}$).
- Baseline Creatinine Clearance (CLcr): CLcr (mL/min) estimated using Cockcroft-Gault formula ([Section 2.5.1](#)).

- Creatinine clearance category (mL/min): ≥ 90 , [60-90[, [30-60[, <30
- Baseline estimated glomerular filtration rate ([GFR], using modification of diet in renal disease [MDRD] formula, mL/min/1.73m²), ([Section 2.5.1](#)).
- Baseline estimated glomerular filtration rate (GFR, using MDRD formula, mL/min/1.73m²) categories : <15 End stage, [15-30[Severe decrease, [30-60[Medium decrease, [60 -90[Mild decrease, ≥ 90 Normal.

Medical or surgical history

All medical/surgical history information (including allergies, diabetic complications, history of seizure/coma and/or hospitalization due to severe hypoglycemia), will be coded to a “lower level term (LLT)”, “preferred term (PT)”, “high level term (HLT)”, “high level group term (HLGT)” and associated primary “system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Disease characteristics at baseline

Specific disease history includes:

- Duration of diabetes (years).
- Category of duration of diabetes (<10, ≥ 10 years).
- Age (years) at onset of diabetes.
- Previous basal insulin treatment:
 - Daily dose (U and U/kg) = median of previous basal insulin daily doses during the last 3 days prior to the first IMP,
 - Product, for last 3 months before Visit 1 only, (insulin glargine, insulin detemir, NPH, other); daily dose and daily injection number will be provided by product too (in U and U/kg).
- Previous mealtime insulin treatment:
 - Daily dose (U and U/kg) = median of previous mealtime insulin daily doses during the last 3 days prior to the first IMP,
 - Product; daily dose will be provided by product too (in U and U/kg).
- Previous total insulin treatment:
 - Daily dose (U and U/kg): sum of previous basal plus mealtime, during the last 3 days prior to the first IMP (or prior to randomization for not treated patients).
- Diabetic complications at baseline:
 - Diabetic retinopathy (Yes, No, Unknown), including type (proliferative/non-proliferative),
 - Diabetic neuropathy (Yes, No, Unknown),
 - Diabetic nephropathy (Yes, No, Unknown),

Other baseline characteristics

- Randomization strata of screening HbA1c categories (<7.6; ≥7.6%).
- Randomization strata of site.

Baseline efficacy data

The following baseline efficacy data will be provided:

- HbA1c (% and mmol/mol).
- FPG (mmol/L and mg/dL).
- Mean of SMPG (mmol/L and mg/dL) from 7-point profiles measured on a 24-hour period.
- Average pre-breakfast SMPG (mmol/L and mg/dL) = Mean of pre-breakfast (fasting) SMPG values in the last 7 days prior the 1st IMP (see [Section 2.5.2](#) for handling missing data).

Other baseline efficacy endpoints are presented along with the summary statistics.

Insulin dose at baseline

- Basal insulin daily dose at baseline (U and U/kg) = planned and actual dose reported in the e-CRF.
- Mealtime insulin daily dose at baseline (U and U/kg) = median of mealtime insulin daily doses of the 3 first days from the first IMP. The first mealtime insulin daily dose is identified by the start date reported on the Visit 1 form for the IMP exposure in the e-CRF.
- Total insulin daily dose at baseline (U and U/kg) = planned and actual dose of basal insulin plus median of mealtime insulin daily dose.

Smoking/alcohol habits

- Tobacco habits (never, current, former, including the average number of cigarettes per day).
- Alcohol habits (never, occasional, at least monthly, at least weekly, at least daily) including the number of daily standard drink (1 or 2, >2).

Any technical details related to computation, dates and imputation for missing dates are described in [Section 2.5](#).

Other baseline characteristics (such as quality of life/health economic endpoints) are presented along with the summary statistics.

2.1.2 Prior or concomitant medications

All medications taken within the past 3 months before screening and until the end of the study are to be reported in the eCRF form pages.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the patient used within 3 months before screening and from screening to first investigational medicinal product (IMP) intake. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP, from first injection of IMP to the last injection of IMP+2 days (0 day for antidiabetic therapy). A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the post-treatment period (as defined in the observation period in [Section 2.1.4](#)).
- Post-treatment medications are those the patient continued or started on or after 3 days (1 day for antidiabetic therapy) after the last dose of open-label IMP.

Any technical details related to computation, dates, imputation for missing dates are described in [Section 2.5](#).

Anti-diabetic medications will be identified by a pre-defined list of ATC codes provided in the ADaM metadata.

2.1.3 Efficacy endpoints

The baseline value for efficacy endpoints is the last available value prior to the first injection of open-label IMP and up to randomization for patients randomized not treated.

HbA1c and FPG are measured at a central laboratory, for scheduled and unscheduled time points.

In case of premature permanent IMP discontinuation, the process described in [Section 2.5.4](#) will be applied to retrieve efficacy assessments performed at the end of treatment visit.

Observation period for efficacy endpoints

- The 24-week randomized period (ITT estimand) for efficacy variables is defined as the time from randomization up to Week 24 (Visit 12) for randomized patients, regardless of study treatment discontinuation.
- The 24-week on-treatment period for efficacy variables is defined as the time from the first dose of IMP up to Week 24 (Visit 12) or, in case of premature treatment discontinuation before Week 24, up to:
 - 7 days after the last dose of IMP for HbA1c,
 - 1 day after the last dose of IMP for FPG,
 - 0 day after the last dose of IMP for SMPG value and insulin dose.

2.1.3.1 Primary efficacy endpoint(s)

The primary efficacy variable is the change in HbA1c from baseline to Week 24 which is defined as: HbA1c value at Week 24 – HbA1c value at baseline (%) in the ITT population, using all HbA1c values regardless of adherence to treatment (ITT estimand). Results for primary efficacy endpoint will also be presented in mmol/mol.

2.1.3.2 Secondary efficacy endpoint(s)

All secondary endpoints are calculated on the 24-week randomized period using the ITT population (ITT estimand).

- HbA1c: change from baseline to Week 16 (Visit 10)
- FPG: change from baseline to Week 16 (Visit 10) and Week 24 (Visit 12)
- Mean 7-point SMPG: change from baseline to Week 16 (Visit 10) and Week 24 (Visit 12)
- 7-point SMPG at each timepoint (preprandial and 2-hour postprandial plasma glucose at breakfast, lunch and dinner, and bedtime): change from baseline to Week 16 (Visit 10) and Week 24 (Visit 12)

2.1.3.3 Secondary endpoints related to compliance

The following additional endpoints will be considered:

- Compliance with medication during the treatment period (from Day 1 to Week 24), expressed in terms of IMP exposure time and the percentage of actual dose over the prescribed dose
- Compliance with key study activities during the treatment period (from Day 1 to Week 24), including:
 - Number of times the patient used the Bluetooth devices in accordance with the study instructions
 - Number of times the patient completed the blood draw visits (Visit 10 and Visit 12) in accordance with the study instructions
 - Patient withdrawal during the treatment period (from Day 1 to Week 24)

2.1.3.4 Exploratory efficacy endpoints

- Mean of fasting pre-breakfast SMPG (mean over the last 7 days before each on-site visit).

2.1.4 Safety endpoints

The safety analysis will be based on:

- All hypoglycemia events (according to American Diabetes Association [ADA] Workgroup on Hypoglycemia).

- Local tolerability at injection site.
- Hypersensitivity reactions.
- Adverse events with special interest (AESI):
 - Pregnancy;
 - Symptomatic overdose with IMP/NIMP;
 - Unusual lack of efficacy of IMR (Canada only)
- Other adverse events (AE) or serious adverse events (SAEs),
- Vital signs including body weight.

In case of premature permanent IMP discontinuation, the process described in [Section 2.5.4](#) will be applied to retrieve safety assessments performed at the end of treatment visit.

Observation period for safety endpoints

The observation period of safety data will be divided into 3 segments:

- The **pre-treatment period** is defined as the time between the date of the informed consent and the first injection of open-label IMP.
- The **treatment-emergent AE (TEAE) period** is defined as the time from the first injection of open-label IMP up to 2 days after the last injection of IMP.
- The **post-treatment period** is defined as the time starting 3 days after last injection of open-label IMP (after the TEAE period).

The **on-study observation period** is defined as the time from start of treatment until the end of the study (defined as last protocol planned visit or the resolution/stabilization of all serious adverse events and adverse events with pre-specified monitoring).

The baseline value for safety endpoints will be the last available value prior to the first injection of open-label IMP.

2.1.4.1 Hypoglycemia events

All hypoglycemia will be categorized according to the ADA definitions (1) as described below:

- **Severe hypoglycemia:** Severe hypoglycemia will be derived as an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
- **Documented symptomatic hypoglycemia:** Documented symptomatic hypoglycemia will be derived as an event with symptoms of hypoglycemia and with a measured plasma glucose concentration less than or equal to 3.9 mmol/L (70 mg/dL).

- **Asymptomatic hypoglycemia:** Asymptomatic hypoglycemia will be derived as an event without symptoms of hypoglycemia but with a measured plasma glucose concentration less than or equal to 3.9 mmol/L (70 mg/dL).
- **Probable symptomatic hypoglycemia:** Probable symptomatic hypoglycemia will be derived as an event with symptoms of hypoglycemia and missing plasma glucose concentration.
- **Relative hypoglycemia:** Relative hypoglycemia (recently termed “pseudo-hypoglycemia”) will be derived as an event with symptoms of hypoglycemia but with a measured plasma glucose concentration greater than 3.9 mmol/L (70 mg/dL).

Hypoglycemia episodes will be analyzed regardless of the time of onset and in the following time periods defined by time of the day:

- Nocturnal hypoglycemia (defined by time of the day): any hypoglycemia that occurs between 00:00 and 05:59 a.m. hours, regardless whether patient was awake or woke up because of the event.
- Daytime hypoglycemia (defined by time of the day): any hypoglycemia that occurs between 6:00 a.m. to 23:59.
- Nocturnal hypoglycemia (defined by sleep status): any hypoglycemia waking the patient up from sleep after having gone to bed in the evening and before getting up in the morning (ie, before the morning determination of fasting pre-breakfast SMPG and before administration of insulin (IMP or NIMP)).

Some analyses will be also performed by distribution by hour of the day (0:00-23:59).

Hypoglycemia episodes will be analyzed only during the following period:

- 24-weeks TEAE period,

2.1.4.2 Adverse events variables

Adverse event observation period

- Pretreatment adverse events are adverse events that developed or worsened or became serious from the signed informed consent date up to first administration of IMP.
- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the treatment-emergent adverse event period.
- Posttreatment adverse events are adverse events that developed or worsened or became serious during the posttreatment period.

All adverse events (including serious adverse events and adverse events with special interest) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

The occurrence of adverse events (including serious adverse events and adverse events with special interest) is recorded from the time of signed informed consent until the end of the study.

Injection site reaction adverse events and hypersensitivity reactions adverse events will be identified using MedDRA searches listed in the ADaM metadata.

Adverse events of special interest include:

- Pregnancy occurring in a female patient entered in the clinical trial.
- Symptomatic overdose (serious or non-serious) with IMP/NIMP (event suspected by the investigator or spontaneously notified by the patient/parent [not based on systematic drug accountability]).
- Unusual lack of efficacy of IMR (Canada only).

2.1.4.3 Deaths

The deaths observation period are per the observation periods defined above.

- Death on-study: deaths occurring during the on-study observation period (defined as the time from the signed informed consent date up to the end of the study, ie, last protocol planned visit or the resolution/stabilization of all SAEs).
- Death pretreatment: deaths occurring before the on-study observation period.
- Death on-treatment: deaths occurring during the on-treatment period.
- Death post study: death occurring after the end of study.

2.1.4.4 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values after conversion will be describe into standard international units and international units will be used in all listings and tables.

Blood samples for clinical laboratories will be taken at screening visit (Visit 1 – Week -2) for identifying patients with exclusion criteria or safety consideration and will be test at screening visit. The laboratory parameters will be classified as follows:

- Hematology,
 - Erythrocytes, hemoglobin, hematocrit, leukocytes and platelets;
- Clinical chemistry,
 - Sodium, potassium, uric acid, creatinine, estimated creatinine clearance, eGFR (derived), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total and conjugated bilirubin;

- Urine samples will be collected as follows:
 - Urinalysis - quantitative analyses: pH, glucose, ketones, leucocytes, blood/hemoglobin, protein.

Technical formulas are described in [Section 2.5.1](#).

2.1.4.5 Vital signs variables

Vital signs include: heart rate (bpm), sitting systolic and diastolic blood pressure (mmHg) as well as body weight (kg).

2.1.4.6 Electrocardiogram variables

Not applicable.

2.1.5 Pharmacokinetic variables

Not applicable

2.1.6 Pharmacodynamic/genomics endpoints

Not applicable

2.1.7 Patient reported outcome endpoints

All the following endpoints are considered as secondary endpoints.

All PROs will be administered electronically using mobile technology.

2.1.7.1 Study methodology endpoints: Patient satisfaction with trial experience (WIWI)

Patient satisfaction with trial experience will be measured using the Was It Worth It (WIWI) Questionnaire, completed at Week 24 (Visit 12). The WIWI has 5 items, each with a 3-level categorical response scale. Each item is scored separately.

See questionnaire in [Appendix C](#).

2.1.7.2 Study methodology endpoints: Impact of trial participation (WPAI)

The effect of the trial on a patients' ability to work and perform regular activities will be measured using an adaptation of the Work Productivity and Impairment (WPAI) Questionnaire, administered at baseline and Week 24 (Visit 12).

The WPAI-SP has 6 items, and scoring follows that of the WPAI-SHP. As such, each item is presented separately, expressed as impairment percentages, with higher numbers indicating

greater impairment and less productivity, ie, worse outcomes. In addition, the following combined items will be reported:

- the percent work time missed due to study participation [$Q2/(Q2 + Q4)$].
- the percent impairment while working due to study participation [$Q5/10$].
- the percent overall work impairment due to study participation [$Q2/(Q2 + Q4) + (1 - (Q2/(Q2 + Q4))) \times (Q5/10)$].
- the percent activity impairment due to study participation [$Q6/10$].

See questionnaire in [Appendix D](#).

2.1.7.3 Study methodology endpoints: Patient burden with trial participation (OSEP)

Patient burden with trial participation will be measured using a new PRO: the Overall Study Experience-Participation (OSEP) Questionnaire. Each item will be scored separately. The OSEP has 2 parts:

- OSEP Part 1 contains 4 items to examine perceptions of diabetes control; it will be administered at baseline and Week 24 (Visit 12).
- OSEP Part 2 contains 9 items to examine perceptions of study participation; it will be administered only at Week 24 (Visit 12).

See questionnaire in [Appendix E](#).

2.1.7.4 Study methodology endpoints: Resource use (RUQ)

Healthcare resource use will be measured using a new PRO: the resource use questionnaire (RUQ). The RUQ will be administered every 4 weeks from baseline to Week 24. The RUQ asks the patients to report the resources used (time and expenses) during the previous 4 weeks in terms of visits to healthcare professionals.

See questionnaire in [Appendix F](#).

2.1.7.5 Diabetes control endpoints: Diabetes-related patient reported outcomes (DTSQs, DTSQc, HFS-II, DDS)

Diabetes Treatment Satisfaction Questionnaire (DTSQ)

Treatment satisfaction will be measured with the Diabetes Treatment Satisfaction Questionnaire (DTSQ). The DTSQ is available in two versions:

- The DTSQ status (DTSQs) version evaluates absolute treatment satisfaction in the “past few weeks” and will be administered at baseline and Week 24 (Visit 12).

- The DTSQ change (DTSQc) version measures the relative change in treatment satisfaction from previous therapy and will be administered (after the DTSQs) at Week 24 (Visit 12) only.

The DTSQs and DTSQc conceptually contain the same 8 items, each scored on a 7-point scale but with different response options. Six items are summed to produce a measure of treatment satisfaction, with total scores ranging from 0 (very dissatisfied) to 36 (very satisfied) for the DTSQs and -18 (much less satisfied) to +18 (much more satisfied) on the DTSQc. The remaining 2 items, which measure perceived frequency of hyperglycemia and perceived frequency of hypoglycemia, are treated independently. These items are scored on a scale ranging from 0 (none of the time) to 6 (most of the time) on the DTSQs and -3 (much less of the time now) to +3 (much more of the time now) on the DTSQc.

See questionnaire in [Appendix G](#) and [Appendix H](#).

Hypoglycemia Fear Survey-II (HFS-II)

Fear of hypoglycemia will be measured with the Hypoglycemia Fear Survey-II (HFS-II) at baseline and Week 24 (Visit 12). The HFS-II comprises 33 items:

- The hypoglycemia fear survey-behavior subscale [HFS-B]: 15 items explore behaviors that patients may engage in to avoid low blood sugar and its negative consequences.
- The hypoglycemia fear survey-worry subscale [HFS-W]: 18 items relate to concerns that patients may have about their hypoglycemia.
- HFS-total score : all 33 items.

Responses are made on a 5-point Likert scale where 0 = “Never” and 4 = “Always” with a past 3 months recall period.

Higher total score reflects greater fear of hypoglycemia. A higher Behavior score reflects greater tendency to avoid hypoglycemia and/or its negative consequences. A higher Worry score reflects higher worry concerning episodes of hypoglycemia and its consequences.

See questionnaire in [Appendix I](#).

Diabetes Distress Scale (DDS)

Diabetes-related distress will be measured using the Diabetes Distress Scale (DDS) at baseline and Week 24 (Visit 12).

The DDS contains 17 items related to potential problem areas that people with diabetes may experience. Patients are asked to consider the degree to which each of the items may have distressed or bothered them during the past month, and respond between 1 (not a problem) and 6 (a very serious problem).

The DDS yields a total diabetes distress score and 4 subscale scores, each addressing a different kind of distress (emotional burden, physician distress, regimen distress, interpersonal distress).

Each score (total and subscales) are presented as an average, by summing the patient's responses to the appropriate items and divide by the number of items in that scale.

In addition, total and subscale scores will be categorized: a mean score 2.0 – 2.9 should be considered 'moderate distress' and a mean score >3.0 should be considered 'high distress'.

See questionnaire in [Appendix J](#).

2.1.8 Investigator (clinician) reported outcome (ClinRO) endpoints

Overall Study Experience-sites (OSES) questionnaire

Site investigators (one per site) will be asked to complete the Overall Study Experience-sites (OSES) questionnaire. The OSES has 2 parts:

- OSES Part 1 contains 1 item to examine resource requirements: "Approximately how much time did you spend with this participant (in person or via phone) during this scheduled visit/communication?". OSES Part 1 will be administered following each study visit.
- OSES Part 2 contains 2 items to examine relationship ("I had a good relationship with this patient during the study") and satisfaction with care ("I am satisfied with the level of care I have provided for this participant in this study"). OSES Part 2 will be administered at Week 24 (Visit 12) only.

Each item is scored separately.

See questionnaire in [Appendix K](#).

2.1.9 Health economic endpoints

Not applicable

2.1.10 Patient interviews

English-speaking patients of the virtual group who consent will be invited to participate in interviews following their Week 24 (Visit 12) study visit (ie, after completion of the trial). These qualitative exit interviews will be conducted one-on-one with up to 30 patients to:

- Examine patients' experiences of trial participation, in their own words.
- Explore the positive and negative aspects of trial participation.
- Provide some context to responses given in the PRO questionnaires.

Analysis plan and analysis report will be performed and details by an external vendor in specific separate documents.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as any patients who met the inclusion criteria and signed the informed consent.

Randomized patients consist of all patients with a signed informed consent form who have had a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table:

- Screened patients.
- Screen failure patients and reasons for screen failure.
- Non randomized but treated patients.
- Randomized patients.
- Randomized but not treated patients.
- Randomized and treated patients.
- The intent-to-treat (ITT) population [Section 2.3.1.1](#)) analyzed as randomized.
- The randomization strata (sites and screening HbA1c categories [$<7.6\%$, $\geq 7.6\%$] assigned by IRT); the discrepancy between the strata assigned by IRT and the information reported on e-CRF will be listed for all randomized patients.
- Patients who completed the 24-week treatment period (patients who have attended Visit 12 [Week 24] and who did not permanently discontinue treatment).
- Patients who permanently discontinued the IMP during the 24-week treatment period, and the reasons for permanent treatment discontinuation.
- Patients who completed the 24-week study period (patients who have performed Visit 12 [Week 24], whichever the treatment duration).
- Patients who discontinued the study during the 24-week period, and the reason for study discontinuation.
- Patient's decision for treatment discontinuation decision for treatment discontinuation during the 24-week period.
- Status at last study contact.

For all categories of patients (except for the screened and nonrandomized categories) percentages will be calculated using the number of randomized patients as denominator for different study conduct approach groups. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by study conduct approach group.

Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by study conduct approach group. A listing of patients who prematurely discontinued study treatment with further reason (“other reason”) provided in free text will be provided.

Patients with the following deviations will be identified and described in separate listings:

- Treated but not randomized.
- Randomized but not treated.
- Randomized but allocated to one approach (virtual or traditional) by randomization, and actually switched of study conduct approach.

A list of patients who prematurely discontinued the treatment, along with reasons for discontinuation, will be provided.

Kaplan-Meier (KM) plots/estimates of the cumulative incidence of IMP discontinuation due to any reason, or due to AE, will be provided for the 24-week on-treatment period separately. Time to treatment discontinuation will be defined as the number of days from the first dose of IMP until the day of treatment discontinuation. All completers will be considered as censored observations. The censoring time will be the number of days from the first dose of IMP until the last dosing date.

All critical or major deviations potentially impacting efficacy analyses, randomization, and drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by study conduct approach group.

Additionally, the analysis populations for safety, efficacy will be summarized in a table by number of patients on the randomized population.

- Efficacy population: intent-to-treat (ITT) population.
- Safety population.

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, c) a patient is randomized twice, or d) in a dynamic randomization scheme the treatment assignment is, in fact, not random, due to a computer program error.

OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Nonrandomized, treated patients will be described separately.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

- Kit dispensation without IRT transaction.
- Erroneous kit dispensation.
- Kit not available.
- Randomization by error.
- Patient randomized twice.
- Forced randomization.
- Stratification error.
- Patient switched to another site.

2.3 ANALYSIS POPULATIONS

Patients treated without or before being randomized will not be considered randomized and will not be included in any efficacy population.

The randomized population includes any patient who has been allocated to a study conduct approach group regardless of whether the study conduct approach group is followed.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

2.3.1 Efficacy populations

The primary efficacy analysis population will be the intent-to-treat (ITT) population, as defined in the protocol.

2.3.1.1 Intent-to-treat population

The intent-to-treat population is all randomized patients, irrespective of the trial approach group actually being used, analyzed according to the approach group allocated by randomization.

The ITT population will be used to analyze all non-safety endpoints.

2.3.2 Safety population

The safety population is defined as all randomized patients who did actually receive at least one dose of IMP, regardless of the amount of IMP administered.

In the event of patients having followed a trial approach that differed from the one assigned according to the randomization schedule, the safety analyses will be conducted according to the trial approach group assigned by randomization.

Patients will not be considered exposed if there is documented evidence that patients have not taken the study drug:

- If a patient is dispensed IMP and is lost to follow-up without any documented evidence, the patient will be considered exposed and included in the safety population.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.

In addition:

- Nonrandomized but treated patients (or treated before being randomization (if any)) will not be part of the safety population; however, their safety data will be presented separately.
- For patients following more than one study approach (virtual and traditional), the patient will be analyzed in the study conduct approach group as randomized.

2.3.3 PRO and ClinRO populations

The analysis of PROs and ClinROs will be conducted on the ITT population.

2.4 STATISTICAL METHODS

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum and maximum for each study conduct approach group. For insulin dose and PROs and ClinROs, summary statistics will include quartiles Q1, Q3 and medians.

Categorical and ordinal data will be summarized using the number and percentage of patients in each study conduct approach group.

In general, descriptive statistics of quantitative efficacy and safety parameters (result and change from baseline) by scheduled post-baseline visits will be provided on observed cases, ie, the inclusion of only patients having non-missing assessments at a specific visit. All statistical analyses (descriptive statistics, plots, and statistical models) will be performed on visits defined using the time windows provided in [Section 2.5.4](#).

2.4.1 Demographics and baseline characteristics

Parameters described in [Section 2.1.1](#) will be summarized by study conduct approach group and overall using descriptive statistics.

Parameters will be summarized on the randomized population analyzed in the study conduct approach group to which patients were randomized.

Medical/surgical history will be classified into primary system organ class (SOCs) and HLTs using MedDRA and will be summarized by study conduct approach groups. Events will be sorted by SOC internationally agreed order and decreasing frequency of HLT based on incidence in the overall population.

P-values on demographic and baseline characteristic data will not be calculated.

2.4.2 Prior or concomitant medications

The prior, concomitant and post-treatment medications will be presented on the randomized population, separately for anti-diabetic medications and non-anti-diabetic medications. Anti-diabetic medications will be identified by a pre-defined list of ATC codes.

Medications will be summarized by treatment group and overall (only for prior medications) according to the WHO-DD dictionary. Non-anti-diabetic medications will be summarized considering the first digit of the ATC class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication. Anti-diabetic medications will be presented by pharmacological class (ATC3), chemical class (ATC4), and standardized medication name.

The tables for prior medications will be sorted by decreasing frequency within the ATC categories presented based on the overall incidence across treatment groups. In case of equal frequency, alphabetical order will be used.

The tables for concomitant and post-treatment medications will be sorted by decreasing frequency within the ATC categories presented based on the incidence in the Virtual group. In case of equal frequency, alphabetical order will be used.

Frequency statistics including number of patients and percentage will be provided. No statistical test for the between-group difference will be performed.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by study conduct approach actual group within the safety population ([Section 2.3.2](#)).

2.4.3.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure.

The duration of exposure to the IMP during the study will be the total number of days of administration of IMP, ignoring temporary drug discontinuation (see [Section 2.5.3](#) for calculation in case of missing or incomplete data) and is defined as:

(Date of the last IMP administration – date of the first IMP administration) + 1

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

- up to 4 weeks.
- >4 to 8 weeks.
- >8 to 12 weeks.
- >12 to 16 weeks.
- >16 to 20 weeks.
- >20 to 22 weeks.
- >22 to 23 weeks.
- >23 to 24 weeks.
- >24 weeks.

Additionally, the cumulative duration of treatment exposure will be provided, defined as the sum of the duration of treatment exposure for all patients, and will be expressed in patient years.

2.4.3.2 Daily insulin doses

The process described in [Section 2.5.4](#) will be applied to assign visits to the insulin doses transferred from the e-diary into the clinical database, and to retrieve doses in case of premature treatment discontinuation.

At each visit, the average daily basal, mealtime, and total (basal plus mealtime) insulin doses (U and U/kg body weight) will be calculated as the mean of daily insulin doses collected in the week before the visit. No minimum number of available doses will be required. Technical details related to the computation and handling of missing data are described in [Section 2.5.3](#).

The daily insulin doses (basal, mealtime, total) will be described at each visit, as well as the changes from baseline, relative change from baseline and change from previous visit.

The calculation of daily insulin doses at baseline is defined in [Section 2.1.1](#).

2.4.3.3 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Percentage of compliance for a patient will be defined as the exposure duration of study minus number of days with a dose equal to 0 divided by the duration of the IMP exposure.

Treatment compliance will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). The percentage of patients whose compliance is <80% will be summarized.

2.4.3.4 Compliance with key study activities

For the following endpoints, descriptive statistics will be calculated including the number of available data, mean, SD, median, minimum, and maximum by study conduct approach group.

- The number of times the patient used the Bluetooth devices in accordance with the study instructions from baseline to Week 24. Qualitative deviations will be used to collect this information.
- Number of times the patient completed the blood draw visits (Visit 10 and Visit 12) in accordance with the study instructions will be based on the protocol deviations.

Number of patient withdrawal during the treatment period (from Day 1 to Week 24) will be described in patient disposition [Section 2.2](#).

2.4.4 Analyses of efficacy endpoints

For statistics where international and conventional units do not impact the results (eg, means and least square (LS) means for percent changes from baseline, p-values for both percent and absolute changes from baseline, rates of patients below a threshold), derivations will be done and statistical models will be run using conventional units. For other statistics (eg, descriptive statistics at baseline and over time, absolute changes from baseline), derivations will be done with both international and conventional units.

Figures will be provided with 2 different axes by parameter when applicable. For example, for HbA1c, figures will be presented by % and mmol/mol.

2.4.4.1 Analysis of primary efficacy endpoint(s)

2.4.4.1.1 Primary efficacy analysis

The primary efficacy variable, change in HbA1c from baseline to Week 24 in % as defined in [Section 2.1.3.1](#) will be analyzed in the ITT population using available data during the 24-week randomized period (defined in [Section 2.1.3](#), used to assess the ITT estimand). A mixed-effect model with repeated measures (MMRM) approach will be used, under the missing at random

framework carried out via SAS PROC MIXED using an adequate contrast at Week 16 and Week 24).

The model will include fixed categorical effects of study conduct approach group (Virtual, Traditional), visit (Week 16, Week 24), study conduct approach-by-visit interaction, visit-by-study conduct approach-by-baseline HbA1c interaction, randomization stratum of site as well as, the continuous fixed covariates of baseline HbA1c value and baseline HbA1c value-by-visit interaction.

This model will be run with an unstructured correlation matrix to model the within-patient errors.

Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Denominator degrees of freedom will be estimated using Satterthwaite's approximation.

This model will provide baseline adjusted least squares (LS) means estimates at Week 24 for both study conduct approach groups, as well as, the differences of these estimates, with their corresponding standard error (SEs) and 95% CIs.

This analysis will be performed using the randomization strata as per IVRS.

No formal comparison and no p-value will be provided.

Model assumption checks

As no formal comparison the analysis of the residuals of MMRM based on studentized residuals will be not performed.

2.4.4.1.2 Subgroup analyses

Where appropriate for the size of a subgroup, exploratory analyses will be performed on the primary endpoint to summarize the treatment effects across subgroups.

For each subgroup, the primary efficacy variable will be analyzed in the ITT population using post-baseline HbA1c data available on the 24-week randomized period, (to assess the ITT estimand). A similar MMRM approach as described for primary analysis will be applied adding the corresponding subgroup factor, subgroup factor-by-study conduct approach arm interaction, subgroup factor-by-visit interaction and subgroup factor-by-visit-by study conduct approach arm interaction.

The subgroups will be defined by the following baseline and screening factors:

- Age group (<65, [65-75[and ≥ 75 years).
- Gender (male, female).
- Baseline BMI (<25, [25-30[, [30-40[and ≥ 40 kg/m²).
- Randomization stratum of screening HbA1c (<7.6%, $\geq 7.6\%$).
- Randomization stratum of site, ("only if the size of the subgroup will be relevant,"
- Duration of diabetes (<10, ≥ 10 years).
- Baseline estimated GFR categories (mL/min/1.73m²): (<60; ≥ 60).

If the subgroup factor is a randomization stratification factor, then the strata as per IVRS will be used.

The randomization strata of screening HbA1c and site will not be included in the model.

Least Square Means Difference Virtual versus Traditional approach at Week 24 will be provided, as well as the corresponding SEs and 95% CI, within each subgroup. The significance level of the study conduct approach-by-subgroup factor interaction term at Week 24 will be not provided for each factor as no formal comparison. Forest plots will be provided.

Subgroups analyses using randomization strata derived as per electronic case report form (e-CRF), should be performed only if necessary (in case of high number of discrepancies between stratum as per IRT and stratum as per e-CRF) and should be considered as sensitivity analysis.

Further subgroup analyses may be performed if deemed necessary for interpretation of results.

2.4.4.2 Analyses of secondary efficacy endpoints

Secondary efficacy endpoints are described in [Section 2.1.4](#).

All secondary efficacy endpoints will be analyzed or summarized on the 24-week randomized period (to assess the ITT estimand) using the ITT population.

The following secondary efficacy endpoints will be analyzed using the same model (same analysis) as the one used for primary endpoint (MMRM model) as described in [Section 2.4.4.1.1](#).

- HbA1c (%): change from baseline to Week 16;

The following secondary efficacy endpoints will be analyzed using the same approach as the one used for primary endpoint (MMRM model) as described in [Section 2.4.4.1.1](#). The model will include fixed categorical effects of study conduct approach group, visit, study conduct approach-by-visit interaction, randomization stratum of site, randomization stratum of HbA1c (<7.6 % and ≥ 7.6%), the continuous fixed covariates of the corresponding baseline value, and baseline value-by-visit interaction.

- FPG: change from baseline to Week 16 and Week 24;
- Change in mean 24-hour plasma glucose based on 7-point SMPG from baseline to Week 16 and Week 24;

For the model on change in FPG and on the mean 24-hour plasma glucose based on 7-point SMPG, the visit term has 2 levels (Week 16 and Week 24).

No formal comparison and no p-value will be provided.

The following secondary endpoints will be analyzed using descriptive measures:

- Change in 7-point SMPG profiles per time-point from baseline to Week 16 and Week 24;

For all continuous endpoints, observed values and change from baseline will be also described for all visits with mean, median, SD, minimum and maximum. A figure representing the mean (+/- SE) change from baseline at each visit will be produced by study conduct approach group.

2.4.4.3 Multiplicity issues

No formal comparison and no p-value will be provided; 95% CIs presented for these endpoints will be calculated for descriptive purpose only.

2.4.4.4 Additional efficacy analyses

Not applicable.

2.4.5 Analyses of safety data

The summary of safety results will be presented by study conduct approach group.

General common rules

All safety analyses will be performed on the safety population as defined in [Section 2.3.2](#), unless otherwise specified, using the following common rules:

- Safety data in patients who do not belong to the safety population (eg, exposed but not randomized) will be listed separately
- The baseline value is defined as the last available value prior to the first injection of IMP.
- When the time of assessment is not available, the value is considered as baseline if assessment date is the date of 1st IMP intake.
- For clinical vital signs only, the potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor (PCSA criteria will be provided in the ADaM metadata).
- For clinical vital signs only, PCSA criteria will determine which patients had at least 1 PCSA during the TEAE period, taking into account all evaluations performed during the TEAE period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.
- For clinical vital signs only, the treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period by study conduct approach group on the safety population.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results.
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.

2.4.5.1 Analyses of hypoglycemia

All analyses of hypoglycemia events will be performed on the safety population, separately on events occurring during the 24-Weeks TEAE period (as defined in [Section 2.1.4](#)). The analyses planned to be done during the 24-Weeks TEAE period only (as defined in [Section 2.1.4.1](#)).

Patients with at least one hypoglycemia event

- Number and incidence of patients with at least one hypoglycemia event will be presented for any hypoglycemia and for each hypoglycemia ADA category, overall and by time of the day (as described in [Section 2.1.4.1](#)).
- For any hypoglycemia and for each hypoglycemia ADA category (except probable, pseudo), incidence of patients with at least one hypoglycemia will be compared, overall and by time of the day. Odds Ratio and its corresponding 95% CI of Virtual group over Traditional group for each hypoglycemic event will be estimated by a logistic regression model adjusted on randomization strata of screening HbA1c (<7.6%, ≥7.6%) and randomization strata of sites.
- Percentage (%) of patients with at least one severe hypoglycemia event will be summarized by symptom during 24 weeks TEAE period,

Number and rate of hypoglycemia event

- Number and rate of hypoglycemia event per patient-year will be summarized for any hypoglycemia and for each hypoglycemia ADA category (as described in [Section 2.1.4.1](#)), overall and by time of the day (as described in [Section 2.1.4.1](#)). Non classified hypoglycemia will be displayed.
- For any hypoglycemia and for each hypoglycemia ADA category (except probable, pseudo), the number of hypoglycemia events per patient-year will be compared, overall and by time of the day. For each hypoglycemic event, the rate ratio, and its corresponding 95% CI, of Virtual group over Traditional group will be estimated using an over-dispersed Poisson regression model adjusted on randomization strata of screening HbA1c (<7.6%, ≥7.6%) and randomization strata of sites.

For Hypoglycemic ADA categories, only the threshold hypoglycemia episodes with plasma glucose ≤70 mg/dL (3.9 mmol/L) will be analyzed.

Subgroups analyses

- The incidence of patients with at least one any hypoglycemia during the 24-week TEAE period, will also be presented by the following subgroups (defined below) and analyzed using a similar logistic regression model approach as presented previously, but adding the corresponding subgroup factor and study conduct approach arm-by-subgroup interaction factor. Odds ratio estimates and 95% CI will be provided in each subgroup category. The interaction study conduct approach arm-by-subgroup p-value will be provided for descriptive propose. When the subgroup considered is equal to one of the randomization strata or is part of one of the adjustment factor, this randomization stratum/adjustment factor is removed from the model. If the logistic regression model does not converge (eg, due to sparse data) some of the randomization strata may be removed. Forest plots will be

provided. Further subgroup analyses may be performed if deemed necessary for interpretation of results.

- Age group (<65, [65-75[and ≥ 75 years),
- Gender (male, female),
- Baseline BMI (<25, [25-30[, [30-40[and ≥ 40 kg/m²),
- Randomization stratum of screening HbA1c (<7.6%, $\geq 7.6\%$),
- Randomization stratum of site. (only if the size of subgroup is relevant)
- Duration of diabetes (<10, ≥ 10 years),
- Baseline estimated GFR categories (mL/min/1.73m²): (<60[; ≥ 60),

2.4.5.2 Analyses of adverse events

Generalities

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pre-treatment and post-treatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pretreatment, treatment-emergent, or post-treatment. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pretreatment or post-treatment. Details on classification of adverse events with missing or partial onset dates are provided in [Section 2.5.3](#).

Adverse event incidence tables will present by SOC, HLG, HLT, and PT, sorted in alphabetical order for each study conduct approach group, the number (n) and percentage (%) of patients experiencing an adverse event. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each study conduct approach group.

Sorting within tables ensures the same presentation for the set of all adverse events within the observation period (pretreatment, treatment-emergent, and post-treatment). For that purpose, the table of all treatment-emergent adverse events presented by SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. Sorting will be based on results for the Virtual arm.

Analysis of all treatment-emergent adverse events

The following treatment-emergent adverse event summaries will be generated for the safety population.

- Overview of treatment-emergent adverse events, summarizing number (%) of patients with any
 - Treatment-emergent adverse event
 - Serious treatment-emergent adverse event

- Treatment-emergent adverse event leading to death
- Treatment-emergent adverse event leading to permanent treatment discontinuation
- All treatment-emergent adverse event by primary SOC, HLG, HLT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLG, HLT, PT) will be presented in alphabetical order.
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables, unless otherwise specified.
- All common treatment-emergent adverse event (HLT incidence $\geq 2\%$ in any study conduct approach group) by primary SOC, HLT, and PT, showing number (%) of patients with at least 1 common treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLT, PT) will be presented in alphabetical order.
- All treatment-emergent adverse events regardless of relationship and related to IMP by primary SOC, HLG, HLT and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLG, HLT, PT) will be presented in alphabetical order.
- All treatment-emergent adverse events by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event by severity (ie, mild, moderate, or severe), sorted by the sorting order defined above.

Analysis of all treatment emergent serious adverse event(s)

- All treatment-emergent serious adverse events by primary SOC, HLG, HLT, and PT, showing the number (%) of patients with at least 1 serious treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLG, HLT, PT) will be presented in alphabetical order,
- All treatment-emergent serious adverse events regardless of relationship and related to IMP, by primary SOC, HLG, HLT, and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order. The other levels (HLG, HLT, PT) will be presented in alphabetical order.

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

- All treatment-emergent adverse events leading to treatment discontinuation, by primary SOC, HLG, HLT, and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLG, HLT, PT) will be presented in alphabetical order.

Analysis of injection site reactions and hypersensitivity reaction TEAE(s)

- All treatment-emergent adverse events related to injection site reactions or hypersensitivity reactions, by PT, showing the number (%) of patients sorted by decreasing incidence of PTs in Virtual arm.

Analysis of adverse events of special interest

- A listing of patients with symptomatic overdose with IMP/NIMP, pregnancy and unusual lack of efficacy of IMR (Canada only) will be provided separately.

Analysis of pretreatment and post-treatment adverse events

- All pre-treatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 pre-treatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs in Virtual arm within each SOC. (If more relevant a listing will be performed instead of table).
- All pre-treatment adverse events leading to study discontinuation by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs Virtual arm within each SOC. (If more relevant a listing will be performed instead of table).
- All post-treatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 post-treatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs Virtual arm within each SOC.
- All post-treatment serious adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 posttreatment serious adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs Virtual arm within each SOC.
- Listing of SAE.
- Listing of AEs leading to permanent treatment discontinuation.

2.4.5.3 Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients who died by study period (on-study, pre-study, on-treatment, post-study).
- Deaths in non-randomized patients or randomized but not treated patients.
- Treatment-emergent adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC, HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC.
- All pre-treatment adverse events leading to death by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC,
- All post-treatment adverse events leading to death by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC,
- Listing of deaths.

2.4.5.4 Analyses of laboratory variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all laboratory variables (central laboratory values) will be calculated at baseline by study conduct approach group. This section will be organized by biological function as specified in [Section 2.1.4.4](#).

2.4.5.5 Analyses of vital sign variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all vital signs variables blood pressure, heart rate and body weight (and changes from baseline) will be calculated for each visit or study assessment (baseline, each post baseline time point, last on-treatment) by study conduct approach group.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by study conduct approach group irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing.
- Abnormal according to PCSA criterion or criteria.

The change in body weight from baseline to Week 24 will be analyzed in the safety population using a similar MMRM model as described in [Section 2.4.4.1.1](#).

2.4.5.6 Analyses of electrocardiogram variables

Not applicable

2.4.6 Analyses of pharmacokinetic and pharmacodynamic variables

Not applicable

2.4.7 Analyses of PRO and ClinRO variables

The analysis of the following endpoints will be conducted on the ITT population, on the 24-week randomized period, ie, using all available post-baseline data, regardless of IMP discontinuation.

No p-value will be provided.

For interpretation of results, Effect Sizes (ES) using Cohen's definition will be calculated in order to interpret changes from baseline to Week 24 in PRO scores.

- Within ES: calculated at the study conduct approach group level, when focusing on changes from baseline
- Between ES: Calculated when comparing study conduct approach groups

The calculation and interpretation of ES is described on [Section 2.5.1](#).

To help the interpretation of PROs and ClinRO, plots will be provided if relevant.

2.4.7.1 Study methodology endpoints: Patient satisfaction with trial experience (WIWI)

Descriptive statistics (mean, median, SD, minimum and maximum) for each score will be presented by study conduct approach group at Week 24.

WIWI scores (1 score for each item) will be compared between approach groups using an ANOVA. This model will include fixed categorical effects of study conduct approach group, of randomization strata of screening HbA1c (<7.6%, ≥7.6%) and randomization strata of sites.

2.4.7.2 Study methodology endpoints: Impact of trial participation patient reported outcome (WPAI-SP)

Descriptive statistics (mean, median, SD, minimum and maximum) for each score and combined scores will be presented by study conduct approach group at baseline and Week 24.

The change in WPAI-SP scores from baseline to Week 24 will be analyzed using an ANCOVA. This model will include fixed categorical effects of study conduct approach group, on randomization strata of screening HbA1c (<7.6%, ≥7.6%) and randomization strata of sites as well as continuous fixed covariates of corresponding baseline score.

2.4.7.3 Study methodology endpoints: Patient burden with trial participation (OSEP)

Descriptive statistics (mean, median, SD, minimum and maximum) for each score and combined scores will be presented by study conduct approach group at baseline (OSEP (Part 1)) and Week 24 (OSEP (Part 1), OSEP (Part 2)).

The change in OSEP (Part 1) score from baseline to Week 24 will be analyzed using an ANCOVA. This model will include fixed categorical effects of study conduct approach group, on randomization strata of screening HbA1c (<7.6%, ≥7.6%) and randomization strata of sites as well as continuous fixed covariates of corresponding baseline score.

OSEP (Part 2) score will be compared between study conduct approach groups using an ANOVA. This model will include fixed categorical effects of study conduct approach group, on randomization strata of screening HbA1c (<7.6%, ≥7.6%) and randomization strata of sites.

2.4.7.4 Study methodology endpoints: Resource use (RUQ)

Descriptive summary (mean, median, SD, minimum and maximum) will be provided for each study conduct approach group at baseline and for each applicable on-treatment visit on the following items:

- Total number of visits (overall and per healthcare professional type)
- Total money spent
- Total time spent

In addition, the total and average resource utilization per patient will be calculated on all on-treatment questionnaires. The change between baseline and this on-treatment average will be calculated.

A plot will be provided for each 3 above items.

2.4.7.5 Diabetes control endpoints: Diabetes-related patient reported outcomes (DTSQs, DTSQc, HFS-II, DDS)

For each PRO questionnaire total and domain scores:

A graphical presentation will be used to illustrate trends over time per study conduct approach group, by visit on mean scores $\pm\sqrt{2}$ SE and on change from baseline values $\pm\sqrt{2}$ SE.

Cumulative distribution functions of PRO changes from baseline to Week 24 will be plotted by study conduct approach group.

The Diabetes Treatment Satisfaction Questionnaire Status Version (DTSQs)

Descriptive summary (mean, median, SD, minimum and maximum) at each visit (baseline and Week 24) and change from baseline to Week 24 will be provided including:

- “total treatment satisfaction” score (sum of items 1, 4, 5, 6, 7 and 8), score ranging is from 0 (no satisfaction) to 36 (high satisfaction with treatment).
- “perceived frequency of hyperglycemia” score (Item 2), score ranging is from 0 (none of the time) to 6 (most of the time).
- “perceived frequency of hypoglycemia” score (Item 3), score ranging is from 0 (none of the time) to 6 (most of the time).

The change for each DTSQs scores from baseline to Week 24 will be analyzed using an ANCOVA. This model will include fixed categorical effects of study conduct approach group, randomization strata of screening HbA1c (<7.6%, \geq 7.6%) and randomization strata of sites as well as continuous fixed covariates of corresponding baseline score.

The change for each DTSQs scores from baseline to Week 24 will be analyzed using cumulative distribution functions of scores. Changes from baseline will be displayed by study conduct approach group, for each the 3 DTSQs scores and a graphical presentation will be used to illustrate trends over time per study conduct approach group by visit on mean scores $\pm\sqrt{2}$ SE and on change from baseline values $\pm\sqrt{2}$ SE.

The Diabetes Treatment Satisfaction Questionnaire Change Version (DTSQc)

Descriptive summary (mean, median, SD, minimum and maximum) at Week 24 will be provided including:

- “total treatment satisfaction” score (sum of items 1, 4, 5, 6, 7 and 8), score ranging is from -18 to 18. Positive scores are indicative of improvement in treatment satisfaction, whereas negative scores are indicative of deterioration in treatment satisfaction. A score of 0 represents no change.
- “perceived frequency of hyperglycemia” score (Item 2), score ranging is from -3 (‘much less of the time now’) to +3 (‘much more of the time now’), meaning negative scores indicate fewer problems with blood glucose levels and positive scores indicate more problems than before. A score of 0 represents no change.

- “perceived frequency of hypoglycemia” score (Item 3), score ranging is from -3 (‘much less of the time now’) to +3 (‘much more of the time now’), meaning negative scores indicate fewer problems with blood glucose levels and positive scores indicate more problems than before. A score of 0 represents no change.

Average scores at Week 24 in total treatment satisfaction score, hyperglycemia perception and hypoglycemia perception score from DTSQc will be analyzed using an ANCOVA model. This model will include fixed categorical effects of study conduct approach group, randomization strata of screening HbA1c (<7.6%, ≥7.6%), randomization strata of site, as well as continuous fixed covariates of corresponding baseline score from DTSQs.

Hypoglycemia Fear Survey-II (HFS-II)

Fear of hypoglycemia will be measured with the Hypoglycemia Fear Survey-II (HFS-II) at baseline and Week 24 (Visit 12). The HFS-II comprises 33 items:

- The hypoglycemia fear survey-behavior subscale [HFS-B] determined by computing the mean of the 15 items measuring behavior (score from 0 to 4).
- The hypoglycemia fear survey-worry subscale [HFS-W] determined by computing the mean of the 18 items measuring worry (score from 0 to 4).
- The total score determined by computing the mean of all 33 items (score from 0 to 4)

The change in HFS-II scores from baseline to Week 24 will be analyzed using an ANCOVA. This model will include fixed categorical effects of study conduct approach group, on randomization strata of screening HbA1c (<7.6%, ≥7.6%) and randomization strata of sites as well as continuous fixed covariates of corresponding baseline score.

Diabetes Distress Scale (DDS)

Descriptive summary (mean, median, SD, minimum and maximum) at each visit (baseline and Week 24) and change from baseline to Week 24 will be provided including the total score and the 4 domains scores determined by computing the mean of item responses:

- Emotional burden score: mean of items 2, 4, 7, 10 and 14 (score from 0 to 6).
- Physician distress score: mean of items 1, 5, 11 and 15 (score from 0 to 6).
- Regimen distress score: mean of items 6, 8, 3, 12 and 16 (score from 0 to 6).
- Interpersonal distress score: mean of items 9, 13 and 17 (score from 0 to 6).
- Total DDS score: mean of the 17 items (score from 0 to 6).

The change in DDS scores from baseline to Week 24 will be analyzed using an ANCOVA. This model will include fixed categorical effects of study conduct approach group, on randomization strata of screening HbA1c (<7.6%, ≥7.6%) and randomization strata of sites as well as continuous fixed covariates of corresponding baseline score.

The incidence of patients experiencing a score ≥ 3 (in DDS total score and domain scores) as well as responder patients (in DDS total score and domain scores) will be determined, during the 24-week randomized period.

2.4.7.6 Investigator (clinician) reported outcome (ClinRO) endpoints

Overall Study Experience-sites (OSES) questionnaire

For OSES Part 1 (study-specific resource requirements), a descriptive summary will be provided for each approach group at each applicable visit, and a total time will be calculated for each patient and averaged within each approach group. Overall Study Experience-Sites Part 1 scores will be compared between approach groups using the same approach as the one used for primary endpoint (MMRM model) as described in [Section 2.4.4.1.1](#). This model will include fixed categorical effects of approach group, on randomization strata of screening HbA1c (<7.6%, $\geq 7.6\%$) and randomization strata of sites as well as continuous fixed covariates of corresponding baseline score.

For OSES Part 2 (relationship and satisfaction), a descriptive summary will be provided for each item for each approach group at Week 24. Item scores will be compared between approach groups using an ANOVA. This model will include fixed categorical effects of approach group, on randomization strata of screening HbA1c (<7.6%, $\geq 7.6\%$) and randomization strata of sites.

2.4.8 Patient interviews

Exit interviews with a subset of patient from the virtual group is described in [Section 2.1.10](#). Data will be analyzed via an expert qualitative research analysis group using standardized qualitative methods (eg, thematic analysis, grounded theory). No details of analysis will be provided in this SAP, but will be developed by expert.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Reference day

The reference day for the calculation of extent of exposure, time to onset and relative days is the day of the first administration of IMP, denoted as Day 1.

Demographic formulas

Body Mass Index (kg/m^2) = (Weight in kg)/(Height in meters)².

Disease characteristics formulas

Duration of diabetes (years) = (Date of informed consent – date of diagnosis of diabetes +1)/365.25.

Age at onset of diabetes (years) = (Date [DD-MM-YYYY] of diagnosis of diabetes – date [DD-MM-YYYY] of birth +1) /365.25. In case of unavailable date of birth, only the year of the date of diabetes diagnosis and the year of the date of birth (retrieve using the age recorded at screening) will be considered in the age at onset calculation.

Duration of previous mealtime insulin treatment (years) = Duration of mealtime insulin treatment in patient life (years) = (Date of informed consent – Date of first intake of mealtime Anti-hyperglycemic therapy in patient life +1)/365.25.

Duration of basal insulin treatment (years) = (Date of informed consent – Date of first intake of Basal Anti-hyperglycemic therapy +1)/365.25

HbA1c transformation

To transform HbA1c in % to mmol/mol, the following formula is used:

$$\text{IFCC} = (10.93 \times \text{NGSP}) - 23.50$$

NGSP (National Glycohemoglobin Standardization Program network) corresponds to HbA1c (%) and IFCC (International Federation of Clinical Chemistry network) to HbA1c (mmol/mol)

FPG and SMPG conversion

From mg/dL to mmol/L: x 0.0555

From mmol/L to mg/dL: x 18.0148

Renal function formulas

Conversion for serum creatinine:

From mg/dL to $\mu\text{mol/L}$: x 88.402

Conversion for total bilirubin:

From mg/dL to $\mu\text{mol/L}$: x 17.104

Creatinine clearance (CL_{Cr}) value will be derived using the equation of Cockcroft and Gault (2), using weight assessed at the same visit:

- For Male:

$$\text{CL}_{\text{Cr}} (\text{mL/min}) = \frac{[(140 - \text{age}(\text{years})) \times \text{weight}(\text{ kg})]}{[0.814 \times \text{serum creatinine} (\mu\text{mol/L})]}$$

- For Female: result above multiplied by 0.85.

eGFR will be derived using MDRD formula (3):

$$eGFR \text{ (mL/min/1.73m}^2\text{)} = \left[\begin{array}{l} 175 \times \text{Serum Creatinine (mg/dL)}^{-1.154} \times \text{Age}^{-0.203} \times 1.212 \text{ (if black)} \\ \times 0.742 \text{ (if female)} \end{array} \right]$$

2.5.2 Data handling conventions for secondary efficacy variables

Fasting condition

FPG measurement not collecting in fasting condition will not be used in the analyses.

Invalid laboratory data

HbA1c or FPG measurements flagged as invalid by the laboratory will not be used in the analyses.

Handling of missing data in the calculation of SMPG variables

At least 4 measurements from the 7 points profile are required for analyzing the profile by timepoint, the 24-hour mean SMPG and the corresponding variability.

At least 3 measurements from the 5 points profile are required for analyzing the profile by timepoint.

At least 3 fasting (prebreakfast) SMPG values in the last 7 days are required for calculating the mean of the fasting SMPG.

Patient Reported Outcomes and Clinician Reported Outcomes

Was It Worth It (WIWI)

No total score is calculated. Each item will be analysed separately with all available data ie. with no imputation

Work Productivity and Impairment (WPAI) Questionnaire

See [Appendix D](#)

Overall Study Experience-Participation (OSEP) Questionnaire

For OSEP (Part 1), no total score is calculated. Each item will be analysed separately with all available data ie. with no imputation. For participants with data at one timepoint only – for example, Visit 2-Step 2 but not Visit 12 - they will be excluded from the analysis.

For OSEP (Part 2), no total score is calculated. Each item will be analysed separately with all available data ie. with no imputation.

Resource Use Questionnaire (RUQ)

No total score is calculated. For analysis of average on-treatment RUQ score, all available data will be used and no imputation will be completed. For a participant with only 3 post-baseline RUQ completions, the average for each item will be taken of these 3 scores. For a participant with 10 post-baseline RUQ completions, the average for each item will be taken of these 10 scores.

Overall Study Experience-sites (OSES) Questionnaire

For OSES (Part 1), no total score is calculated. For analysis of average on-treatment OSES (Part 1) time score, all available data will be used and no imputation will be completed. For a participant with only 3 post-baseline OSES-Part 1 completions, the average will be taken of these 3 scores. For a participant with 10 post-baseline OSES-Part 1 completions, the average will be taken of these 10 scores.

For OSES (Part 2), no total score is calculated. Each item will be analysed separately with all available data ie. with no imputation.

Diabetes Treatment Satisfaction Questionnaire DTSQs and DTSQc)

The total treatment satisfaction score is the sum of items 1, 4, 5, 6, 7 and 8.

If no more than 2 out of the 6 questions comprising the total treatment satisfaction score are missing, the total treatment satisfaction score is imputed by calculating the average of the scores from the answered questions, dividing this sum by the number of answered questions and multiplying the average by six.

If items 2 or 3 are not answered, frequency of hypoglycemia or hyperglycemia scores is considered as missing.

Hypoglycemia Fear Survey (HFS-II)

Using an item mean score also makes handling missing data more sensible. Instead of dividing by the entire scale or subscale to compute the item mean, only divide by the number of questions answered. This allows a more reasonable comparison between respondents. However, it is recommended that this technique be used only if more than 75% of the items have responses. This equates to having responses for 25 items if scoring the whole HFS-II, for 12 items if scoring the HFS-B, and for 14 items if scoring the HFS-W. If less than 75% of the data is available, the score for that scale or subscale should be counted as missing as it may not be a true reflection of the participants' behaviors and/or worries.

The Diabetes Distress Scale (DDS)

Minimum number of items required for score calculation (at least 2/3).

Table 1 - PROs: Diabetes related - Missing Data Handling

PRO scales	Score	Number of items included in score derivation	Minimum number of items required for score calculation
DTSQs	Total treatment satisfaction score	6	4
	Perceived frequency of hyperglycemia score	1	1
	Perceived frequency of hypoglycemia score	1	1
DTSQc	Total treatment satisfaction score	6	4
	Perceived frequency of hyperglycemia score	1	1
	Perceived frequency of hypoglycemia score	1	1
HFS-II	total score	33	25
	HFS-B score	15	12
	HFS-W score	18	14
DDS	Emotional Burden score	5	4
	Physician distress score	4	3
	Regimen distress score	5	4
	Interpersonal distress score	3	2
	Total DDS score	17	12

Effect Size

The effect size is defined as: $ES = \text{difference} / SD$ where SD is the standard deviation. Note that there are two main types of effect size:

- Within ES: Calculated at the group level, when focusing on change from baseline.
- Between ES: Calculated when comparing treatments groups.

The within-group ES (WES) indicates if the changes from baseline to the end of treatment are clinically meaningful for each group.

$$WES = \frac{LS \text{ mean change from baseline at timepoint } t}{\text{pooled baseline standard deviation}}$$

The between-group ES (BES) indicates if the mean changes from baseline to the end of treatment are clinically meaningful between groups.

$$BES = \frac{\text{difference in LS means between groups at timepoint } t}{\text{pooled baseline standard deviation}}$$

Cohen's rules for Effect Size (ES) and interpretation

ES < 0.2 : Negligible

0.2 ≤ ES < 0.5 : Small

0.5 ≤ ES < 0.8 : Moderate

ES ≥ 0.8 : Important

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

For example, if either a baseline assessment or an endpoint assessment is missing for a particular patient, then the change from baseline at endpoint is missing. Depending upon the assessment, analyses may not include all patients in the analysis population, because certain patients in the intended population may have missing data.

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the end-of-treatment e-case report form page. If this date is missing, the exposure duration should be left as missing.

The last dose intake should be clearly identified in the e-case report form and should not be approximated by the last returned package date.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

Handling of adverse events/hypoglycemia with missing or partial date/time of onset

No imputation of adverse event/hypoglycemia dates/times will be performed.

By default all adverse events/hypoglycemia are emergent except if additional information allows to classify otherwise.

Handling of adverse events/hypoglycemia, laboratory data, vital signs when date and time of first investigational medicinal product administration is missing

When the date and time of the first IMP administration is missing, all adverse events/hypoglycemia that occurred on or after the day of randomization should be considered as treatment-emergent adverse events/hypoglycemia. The exposure duration should be kept as missing.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category “normal/missing at baseline.”

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

Handling of hypoglycemia event classification when some classification items are missing

Rule for handling missing data in classification items for hypoglycemia event will be provided in ADaM metadata.

Handling of missing data in the calculation of 7-point SMPG variables

For a given 7-point SMPG profile, at least 4 available measurements in the last 7 days are required to be taken into account in the statistical analyses (including the descriptive analyses at each time-point).

Handling of missing data in the calculation of average pre-breakfast SMPG,

At least 3 pre-breakfast (fasting) SMPG values in the last 7 days are required to be taken into account in the statistical analyses (including descriptive analyses at each time-point).

Handling of missing data in the calculation of insulin doses

At each visit, the average daily insulin doses (basal, mealtime, and total) will be calculated as the average of the daily insulin doses available in the week (7 days) before the visit.

No minimum number of available doses will be required.

For insulin doses in U/kg, if the body weight measurement is missing at a given visit, the last available measurement from previous visit will be used.

2.5.4 Windows for time points

The following process will be applied for visit re-allocation. Re-allocated visits will be used in all statistical analyses (descriptive statistics, plots, and statistical models).

No re-allocation will be performed for nominal visits already provided in the clinical database (Visit 1 to Visit 20).

SMPG

In the clinical database, SMPG profiles transferred from the e-diary will not be assigned to a protocol visit. For the analysis, they will be assigned to the next visit actually performed by the patient after the date/time of data collection (Visit 3 to Visit 12, or Visit 700).

In the clinical database, SMPG assessments which do not correspond to a 7-point profile transferred from the e-diary will not be assigned to a protocol visit. For the analysis, they will be assigned to the next visit after the date/time of data collection.

Insulin doses

In the clinical database, insulin doses transferred from the e-diary will not be assigned to a protocol visit. For the analysis, they will be assigned to the next on-site visit actually performed by the patient after the date/time of data collection.

PROs and ClinRO

In the clinical database, PROs and ClinRO transferred from the e-diary will not be assigned to a protocol visit. For the analysis, they will be assigned to the video chat/phone call/ on-site visit using the date/time of data collection and the date of first IMP taken (or Randomization date if no IMP taken) as reference for derivation of the Study day .

Table 2 - Reallocation time windows definition

Scheduled visit post baseline	Targeted study day	Analysis window in study days
DTSQs, DDS, HFS-II, WPAI-SP, OSES Part 1		
Day 1 (Visit 2 Step 2)	1	-28 to 1
Week 24 (Visit 12)	169	141 to 196
DTSQc, WIWI, OSES Part 2, OSEP Part 2		
Week 24 (Visit 12)	169	141 to 196
OSES Part 1		
Day 1 (Visit 2 Step 2)	1	-28 to 1
Week 1 (Visit 3)	8	5 to 11
Week 2 (Visit 4)	15	12 to 18
Week 3 (Visit 5)	22	19 to 25
Week 4 (Visit 6)	29	26 to 32
Week 6 (Visit 7)	43	36 to 49
Week 8 (Visit 8)	57	50 to 63
Week 12 (Visit 9)	85	71 to 98
Week 16 (Visit 10)	113	99 to 126
Week 20 (Visit 11)	141	127 to 154
Week 24 (Visit 12)	169	155 to 196

Scheduled visit post baseline	Targeted study day	Analysis window in study days
RUQ		
Day 1 (Visit 2 Step 2)	1	-28 to 1
Week 4 (Visit 6)	29	15 to 42
Week 8 (Visit 8)	57	43 to 70
Week 12 (Visit 9)	85	71 to 98
Week 16 (Visit 10)	113	99 to 126
Week 20 (Visit 11)	141	127 to 154
Week 24 (Visit 12)	169	155 to 196

Study days are calculated from the day of first IMP, the day of first IMP injection being Day 1. For randomized but not treated patients, Day 1 is the day of randomization.

End of treatment visit

The following analysis windows will be applicable to re-allocate the premature end of treatment assessments (premature EOT visit) for HbA1c and FPG assessments.

Table 3 - Reallocation time windows definition

Scheduled visit post baseline	Targeted study day	Analysis window in study days
HbA1c and FPG		
Week 16 (Visit 10)	113	85 to 140
Week 24 (Visit 12)	169	141 to 196

Study days are calculated from the day of first IMP, the day of first IMP injection being Day 1. For randomized but not treated patients, Day 1 is the day of randomization.

Study days are calculated from the day of first IMP injection; the day of first IMP injection being Day1.

To retrieve all safety and other assessments performed at the end of treatment visit, the following process will be followed: if a patient discontinues the treatment prematurely, end of treatment assessments will be re-allocated to the next scheduled visit for the patient. The next scheduled visit for each patient will be determined as the next visit that should be performed as per protocol, following the last visit actually performed by the patient before end of treatment visit.

For a given parameter, the value will not be re-allocated in the following cases:

- If the parameter is not planned to be collected at the re-allocation visit.
- If a value is already available for the parameter at the re-allocation visit.

2.5.5 Unscheduled visits

The analysis windows mentioned in [Section 2.5.4](#) will be applicable to re-allocate the unscheduled assessments (measurements from the central laboratory only) for HbA1c and FPG assessments.

After applying the time windows as mentioned in [Section 2.5.4](#), if two assessments are associated to the same time point, the closest from the targeted study day is used. In case of equality, the earliest measurement is used.

The determination of baseline for HbA1c and FPG variables is based on all measurements from both scheduled and unscheduled visits (measurements from the central laboratory only). The determination of baseline for safety parameters is based on all assessments from both scheduled and unscheduled visits too. The determination of the last on-treatment value for safety parameters is also based on all assessments from both scheduled and unscheduled visits. Measurements from the unscheduled visits (including results from local laboratory when no corresponding central laboratory results are available) are also considered for PCSA summary of safety parameters.

Unscheduled visit measurements are not included in the by-visit summaries.

2.5.6 Pooling of centers for statistical analyses

No pooling of centers is planned for statistical analyses.

2.5.7 Statistical technical issues

None.

3 INTERIM ANALYSIS

No interim analysis will be performed during the study.

4 DATABASE LOCK

The database is planned to be locked at approximately between 5 and 7 weeks after last patient last visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS Enterprise Guide version 5.1 or higher.

6 REFERENCES

1. American Diabetes Association Workgroup on Hypoglycemia. Defining and Reporting Hypoglycemia in Diabetes: a report from the American Diabetes Association Workgroup on Hypoglycemia. *Diabetes Care*. 2005;28(5):1245-9.
2. Cockcroft DW, Gault MH. Prediction of CLcr from serum creatinine. *Nephron*.1976;16(1):31-41.
3. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A More Accurate Method To Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation. *American College of Physicians–American Society of Internal Medicine-Annals of Internal Medicine*.1999;130(6):461-70.

7 LIST OF APPENDICES

- Appendix A: Potentially clinically significant abnormalities criteria
- Appendix B: Study flochart
- Appendix C: PRO: Was It Worth It (WIWI)
- Appendix D: PRO: Work Productivity And Impairment (WPAI)
- Appendix E: PRO: Overall Study Evaluation – Participation (OSEP)
- Appendix F: PRO: Ressources Use Questionnaire (RUQ)
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Appendix A Potentially clinically significant abnormalities criteria

CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES for phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis : >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in $\mu\text{mol/L}$ or mg/L . Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI>1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.

**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)**

Parameter	PCSA	Comments
ALT and Total Bilirubin	ALT>3 ULN and TBILI>2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurements.
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
CLcr (mL/min) (Estimated creatinine clearance based on the Cockcroft-Gault equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - <60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m2) (Estimate of GFR based on an MDRD equation)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - <60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥ 90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.
Uric Acid Hyperuricemia Hypouricemia	>408 µmol/L <120 µmol/L	Harrison- Principles of internal Medicine 17 th Ed., 2008.
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L >115 mmol/L	
Sodium	≤129 mmol/L ≥160 mmol/L	
Potassium	<3 mmol/L ≥5.5 mmol/L	FDA Feb 2005.
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.

**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)**

Parameter	PCSA	Comments
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose		
Hypoglycaemia	≤3.9 mmol/L and <LLN	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black); <1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN ≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17 th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female) ≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.

**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)**

Parameter	PCSA	Comments
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	To be applied for all positions (including missing) except STANDING.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension		
Orthostatic SDB		
Orthostatic DBP	≤-20 mmHg ≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.

**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
for phase 2/3 studies (oncology excepted)**

Parameter	PCSA	Comments
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)
HR	<50 bpm <50 bpm and decrease from baseline \geq 20 bpm <40 bpm <40 bpm and decrease from baseline \geq 20 bpm <30 bpm <30 bpm and decrease from baseline \geq 20 bpm >90 bpm >90 bpm and increase from baseline \geq 20bpm >100 bpm >100 bpm and increase from baseline \geq 20bpm >120 bpm >120 bpm and increase from baseline \geq 20 bpm	Categories are cumulative Categories are cumulative
PR	>200 ms >200 ms and increase from baseline \geq 25% >220 ms >220 ms and increase from baseline \geq 25% >240 ms >240 ms and increase from baseline \geq 25%	Categories are cumulative
QRS	>110 ms >110 msec and increase from baseline \geq 25% >120 ms >120 ms and increase from baseline \geq 25%	Categories are cumulative
QT	>500 ms	

**CRITERIA for POTENTIALLY CLINICALLY SIGNIFICANT ABNORMALITIES
 for phase 2/3 studies (oncology excepted)**

Parameter	PCSA	Comments
QTc	<u>Absolute values (ms)</u>	To be applied to any kind of QT correction formula.
	>450 ms	Absolute values categories are cumulative
	>480 ms	
	>500 ms	
	<u>Increase from baseline</u>	QTc >480 ms and Δ QTc >60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.
	Increase from baseline]30-60] ms	
Increase from baseline >60 ms		

Appendix B Study flowchart

(☎) = virtual visits; ☎ = phone call visits; P = on-site in-person visits)

Visits	Screening		Randomization		Treatment period										Follow-up
	1 Step-1 ^a	1 Step-2 ^b	2 Step-1 ^c	2 Step-2 ^d	3	4	5	6	7	8	9	10	11	12 EOT ^g	13 EOS
Traditional group	(☎) (Digital screening)		☎	P	☎	☎	☎	P	☎	P	☎	P	☎	P	☎
Virtual group	(☎) (Digital screening)		☎	P & (☎)	(☎)	(☎)	(☎)	(☎)	(☎)	(☎)	(☎)	(☎)	(☎)	(☎)	(☎)
Weeks	-3	-2	-1	0	1	2	3	4	6	8	12	16	20	24	1 week
Window (day)			-/+ 4		-/+ 3	-/+ 3	-/+ 3	-/+ 4	-/+3	-/+ 4	-/+ 3	-/+ 4	-/+ 3	-/+ 3	+/-2
Informed Consent (eConsent)	X														
Schedule Homecare visit	X														
Interactive response technology (IRT) calls	X		X				X		X		X		X		
Inclusion	X	X													
Exclusion		X													
Demography	X	X													
Video chat with Investigator and site staff	X	X													
Medical and surgical history; diabetes history		X													
Concomitant medication(s)		X		X	X	X	X	X	X	X	X	X	X	X	X
Physical examination ^d				X											
Vital signs ^h and body weight		X		X				X		X		X		X	
Height		X													
Virtual material/device shipment (Bluetooth devices) ^e			X												
Dispensation/collection of e-diary				X	X	X	X	X	X	X	X	X	X	X	

Visits	Screening		Randomization		Treatment period										Follow-up
	1 Step-1 ^a	1 Step-2 ^b	2 Step-1 ^c	2 Step-2 ^d	3	4	5	6	7	8	9	10	11	12 EOT ^g	13 EOS
Traditional group	☎ (Digital screening)		☎	P	☎	☎	☎	P	☎	P	☎	P	☎	P	☎
Virtual group			☎	P & ☎	☎	☎	☎	☎	☎	☎	☎	☎	☎	☎	☎
Weeks	-3	-2	-1	0	1	2	3	4	6	8	12	16	20	24	1 week
Window (day)			-/+ 4		-/+ 3	-/+ 3	-/+ 3	-/+ 4	-/+ 3	-/+ 4	-/+ 3	-/+ 4	-/+ 3	-/+ 3	+/-2
Randomization via IRT call			X												
Video chat with investigator and site staff via the virtual device ^e				X	X	X	X	X	X	X	X	X	X	X	X
Allocation of study medication (IMP)				X				X		X		X			
First IMP (Toujeo) injection ^e				X											
Documentation and review of IMP and NIMP doses ^f				X	X	X	X	X	X	X	X	X	X	X	
IMP compliance check; collecting & counting used & unused pens								X		X		X		X	
Diet and lifestyle counselling		X		X	X	X	X	X	X	X	X	X	X		
Glucose meter shipment ^c			X												
7-Point SMPG ⁱ				X								X		X	
5-point SMPG ⁱ				X	X	X	X	X	X	X	X	X	X	X	
Upload SMPG to PC ^j				X				X		X		X		X	
AE/SAE	To be assessed and reported (if any) since consent throughout the study (report SAE to the sponsor within 24 hours)														
Hypoglycemia recording	To be assessed and reported (if any) since randomization throughout the study														
Injection site reactions, PTCs	To be assessed and reported (if any) since randomization throughout the study														
Central Laboratory^{k,e}															
HbA1c, FPG		X										X		X	
Hematology, clinical biochemistry ^l		X													

Visits	Screening		Randomization		Treatment period										Follow-up
	1 Step-1 ^a	1 Step-2 ^b	2 Step-1 ^c	2 Step-2 ^d	3	4	5	6	7	8	9	10	11	12 EOT ^g	13 EOS
Traditional group	☎ (Digital screening)		☎	P	☎	☎	☎	P	☎	P	☎	P	☎	P	☎
Virtual group			☎	P & ☎	☎	☎	☎	☎	☎	☎	☎	☎	☎	☎	☎
Weeks	-3	-2	-1	0	1	2	3	4	6	8	12	16	20	24	1 week
Window (day)			-/+ 4		-/+ 3	-/+ 3	-/+ 3	-/+ 4	-/+ 3	-/+ 4	-/+ 3	-/+ 4	-/+ 3	-/+ 3	+/-2
Urine analysis ^m		X													
Pregnancy test (WOCBP only) ⁿ		X		X				X		X		X		X	
PROs and other questionnaires^o															
Diabetes related PROs: DTSQs, DDS, HFS-II				X										X	
Diabetes related PRO: DTSQc														X	
Was it Worth It (WIWI) Questionnaire														X	
Work Productivity and Impairment Study Participation (WPAI-SP)				X										X	
Overall Study Experience - Participation (OSEP) Part 1				X										X	
Overall Study Experience - Participation (OSEP) Part 2														X	
Resource Use Questionnaire (RUQ)				X			X		X	X	X	X	X	X	
Overall Study Experience - Sites (OSES) – Part 1 (resource requirements)				X	X	X	X	X	X	X	X	X	X	X	
Overall Study Experience – Sites (OSES) – Part 2 (relationship, satisfaction)														X	
Qualitative exit interview ^p														X	

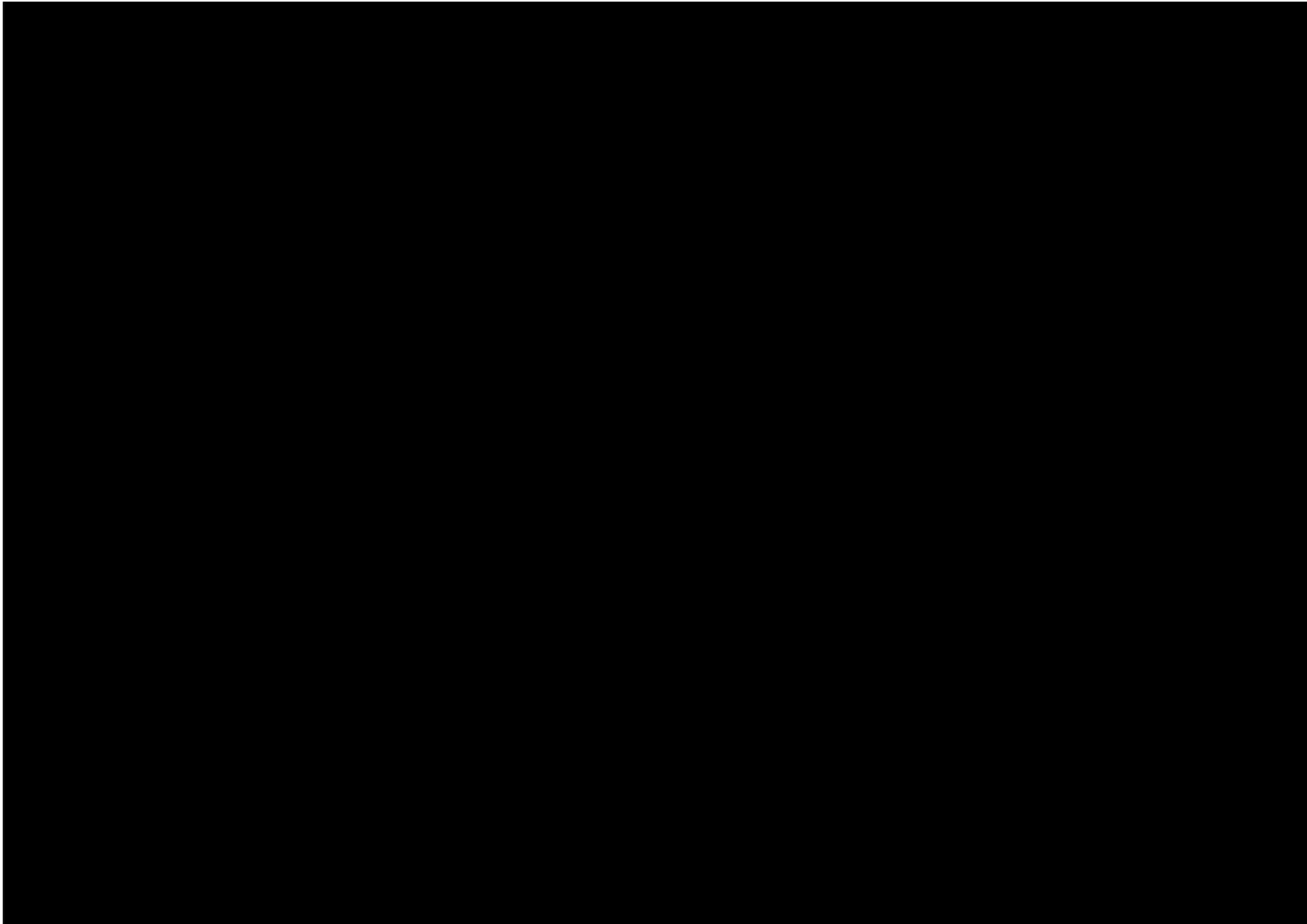
^a Prior to Visit 1, patients will be contacted by the sites or guided by the multi-channel digital recruiters to the eConsent web portal (Parallel 6 Website). Informed consent process will be completed electronically by the candidate trial patients. During the eConsent process, the study purpose, virtual tools for participation, and other protocol requirements will be introduced and discussed with the patients in the text or audio/video manner. After eSigning and counter-eSigning by the patient and the investigator, the enrolment IRT call will be made and the patient ID assigned.

- b* Assessments at Visit 1- Step 2 will be performed in-person by Homecare health professional (The MRN) in corporation with the study investigators and designees. This visit can occur at the patient's home, at work, or at any location providing the adequate space and level of privacy. Patient identification will be further verified and confirmed.
- c* At the end of screening, investigators will determine the eligibility of the screened patients for participation. The randomization IRT call will be made at the Visit 2- Step 1. Patients will be informed by the study sites of their randomization group and Visit 2- Step 2 will be scheduled for the baseline assessments within 1 week (+/- 4 days).
Glucose meters with Bluetooth access and associated accessories (lancet, control solutions, test strips, etc), e-diaries features, and instructions will be shipped to all eligible patients. Patients will use the study provided glucose meters throughout the study.
- d* Physical examination will be performed at the in-person visit in the traditional group. In the virtual group, physical examination will be performed on-site, in-person, between randomization IRT call and the first IMP administration. All other assessments will occur remotely on the day of the first IMP administration (Day 1).
- e* Only for patients randomized in virtual group:
- They will receive the Bluetooth devices for their remote participation and the IMP (Toujeo®) before Visit 2-Step 2.
 - Shortly after randomization (IRT call), they will be scheduled for an in-person visit to allow for the initiation physical examination performed by the investigator.
 - They will be further trained on the Bluetooth devices utilization.
 - The IMP starting date and dose will be instructed by the investigator at the time of Visit 2-Step 2. The first IMP (Day 1) data will be documented with the dose in the e-CRF.
 - All study assessments, including vital signs and weight, will be done via the Bluetooth devices by the patients at home.
 - Patients located in the United States (US) will receive a laboratory requisition and have their blood drawn at any local Quest®. For patients located in Canada, blood draw will be performed by the Homecare via The MRN.
 - Unscheduled on-site visits or Homecare physician visits (depending on the patient's location) only for safety assessment could be scheduled as deemed necessary by the investigator (ie, performance of physical examinations is critical to determine a diagnosis or further evaluation procedure for an AE).
- f* IMP dose will be titrated at the investigator's discretion to achieve the fasting glycemic target while avoiding hypoglycemia
- g* EOT assessments will also be performed for any patients who prematurely discontinue the study treatment. Patients should continue the study procedure as planned up to the EOS after IMP discontinuation.
- h* Heart rate and blood pressure (sitting position)
- i* 7-point SMPG profile (before [preinjection after randomization] and 2 hours after breakfast, lunch and dinner, and at bedtime): at least ONE day during the weeks before Visit 2-Step 2 (Week 0), Visit 10 (Week 16), and Visit 12 (Week 24)
5-point SMPG profile (before breakfast, lunch and dinner; 2 hours after a main meal [or as per investigator's instruction] and at bedtime): at least 3 days during the week before each visit
The SMPG before breakfast should be measured in the fasting status, ie, after the patient wakes up, before breakfast, and before injection of any insulin; preferably no food should have been taken overnight. A note should be made in the diary if the SMPG is not tested in fasting status (eg, if food was taken to cope with a hypoglycemic episode)
- j* Only for patients randomized in the traditional group
- k* Blood samples will be sent to and analyzed by Quest® central lab
- l* Hematology: erythrocytes, hemoglobin, hematocrit, leukocytes and platelets. Clinical chemistry: total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), AST, ALT, ALP, plasma glucose, creatinine, estimated creatinine clearance, uric acid, sodium, and potassium
- m* Urine analysis by dipstick: pH, glucose, ketones, leucocytes, blood/hemoglobin, protein
- n* For women of child-bearing potential (WOCBP): serum pregnancy test for screening; urine pregnancy test for subsequent monitoring and it can be confirmed with a serum test if needed. For WOCBP in virtual group, the urine pregnancy test kit will be provided by the study.
- o* For patients randomized to the virtual group, all questionnaires will be performed remotely via the mobile technology at home. For patients randomized in the traditional group, the questionnaires will be completed electronically (via the mobile technology) at the study site (before visiting the study site for baseline assessment on Visit 2 Step 2).
- p* In a subset of patients (approximately 30) in the virtual approach group.

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; DDS = Diabetes Distress Scale; DTSQc = Diabetes Treatment Satisfaction Questionnaire change; DTSQs = Diabetes Treatment Satisfaction Questionnaire status; e-CRF = electronic case report form; EOS = end of study; EOT = end of treatment; FPG = Fasting plasma glucose; HbA1c = glycated hemoglobin A1c; HFS = Hypoglycemia Fear Survey; ID = identification; IMP = investigational medicinal product; IRT = interactive response technology; MRN = medical research network; NIMP = noninvestigational medicinal product; OSEP = overall study experience – participation; OSES = overall study experience – sites; PC = personal computer; PRO = patient reported outcome; PTC = product technical complaints; RUQ = resource use questionnaire; SAE = serious adverse event; SMPG = self-monitoring of plasma glucose; US = United States; WIWI = was it worth it; WPAL-SP = work productivity and impairment study participation; WOCBP = women of child-bearing potential;

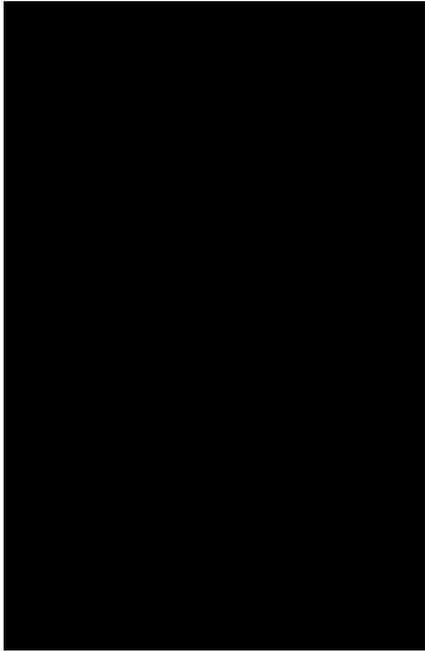
Appendix C





Appendix D 





1. General Guidelines

In the general health version (WPAI:GH), respondents are asked questions about work and activity impairment due to health problems. In the specific health problem version (WPAI:SHP), respondents are asked questions concerning impairment due to the target health problem (eg, arthritis). In the combination version, WPAI:GH/SHP respondents are asked about impairment due to a specified health problem and impairment due to other health reasons. The sum of impairment due to the specified problem and other health reasons is considered impairment due to all health problems. The WPAI:GH/SHP, therefore, measures impairment due to the specified problem and all health problems.

The WPAI elicits hours worked (all versions), hours missed due to the target condition (WPAI:GH/SHP, WPAI:SHP, WPAI:AS), hours missed due to other health problems (WPAI:GH/SHP) and hours missed for any other reasons (WPAI:SHP, WPAI:GH, WPAI:GH/SHP). Hours missed for "other reasons" is not used in the scoring, but only as a prompt to the respondent to exclude those hours from the count of actual hours worked. In the WPAI:AS, respondents are asked about usual hours worked, not actual hours worked.

2. Coding Rules for Interviewers

The coding rules below apply to the WPAI:GH, WPAI:SHP, WPAI:GH/SHP and the WPAI:AS, as noted.

Are you currently employed? (All versions)

Yes: works part-time or full-time; self-employed; works in family business; on vacation from paid employment, eg, schoolteachers on leave for the summer. No: does not work for pay; only does volunteer work; usually works, but has been laid-off or unemployed during past seven days; seasonal workers not currently working.

Work time missed due to specified health problem (WPAI:SHP, WPAI:GH/SHP and WPAI:AS only)

Include: any time taken off from work due to problem; doctor visits for problem; trip to pharmacy to get medication for problem; side effect of medication for problem; reason was partly problem and partly something else. Exclude: if it happened today; if the respondent is not sure, ie, can't say if it was problem or something else.

Work time missed due to other health reasons (WPAI:GH/SHP only)

Include: time taken off from work for health reasons unrelated to target disease; visits to doctor, dentist, and pharmacy. Partly health, partly something else, eg, couldn't shovel snow to get car out because of back problem. Says no health problem, just had a pain, cold, fatigue, etc. Exclude: hours missed due to specified problem; non-health reasons.

Work time missed due to any other reasons (WPAI:GH and WPAI:GH/SHP only)

Include: time taken off from work for vacations, holidays, compensatory time; time missed because of required study visits. Exclude: hours missed for any health reason.

Work time missed due to any other reasons (WPAI:SHP only)

Include: time taken off from work for vacations, holidays, compensatory time; time missed because of required study visits; hours missed due to health that is unrelated to specified problem. Exclude: hours missed due to specified problem.

Actual hours worked (WPAI:GH, WPAI:SHP, WPAI:GH/SHP only)

Include: actual hours worked, including overtime (paid, unpaid). Exclude: vacation, holidays, sick time, personal leave; any paid hours not actually worked, eg. compensatory time.

Productivity

Respondent is asked for overall productivity on days actually went to work. If productivity differed greatly from day to day, for example, one day was 0 and one day was 10, ask him to respond for all days, on average. Probe: "Thinking of all the days together, what was the average effect on your work?"

Regular daily activities

Regular activities are expected to be different for every respondent. Regular activities could be exercising, watching television, gardening, sewing, etc. The intention of the question is to have the respondent think of his activities and then make a global evaluation of how difficult it was to do these activities. If impairment differed greatly from day to day or from activity to activity, probe: "Thinking of all the days together, and all of your usual activities, what was the average effect on your daily routine?"

3. Coding Rules for Self-Administration

Employment status:

If Q1 = YES or Q1 = NO or missing and hours missed or worked >0, then employed.

If Q1 = missing and hours missed and worked = 0, then not employed.

Hours missed

If hours worked = 0, then productivity while at work is not applicable.

If the line or box is slashed through or there is a response of NA, code as zero. If respondent enters a range of hours, enter the midpoint. If respondent records "+" after the number of hours, ignore the "+"..

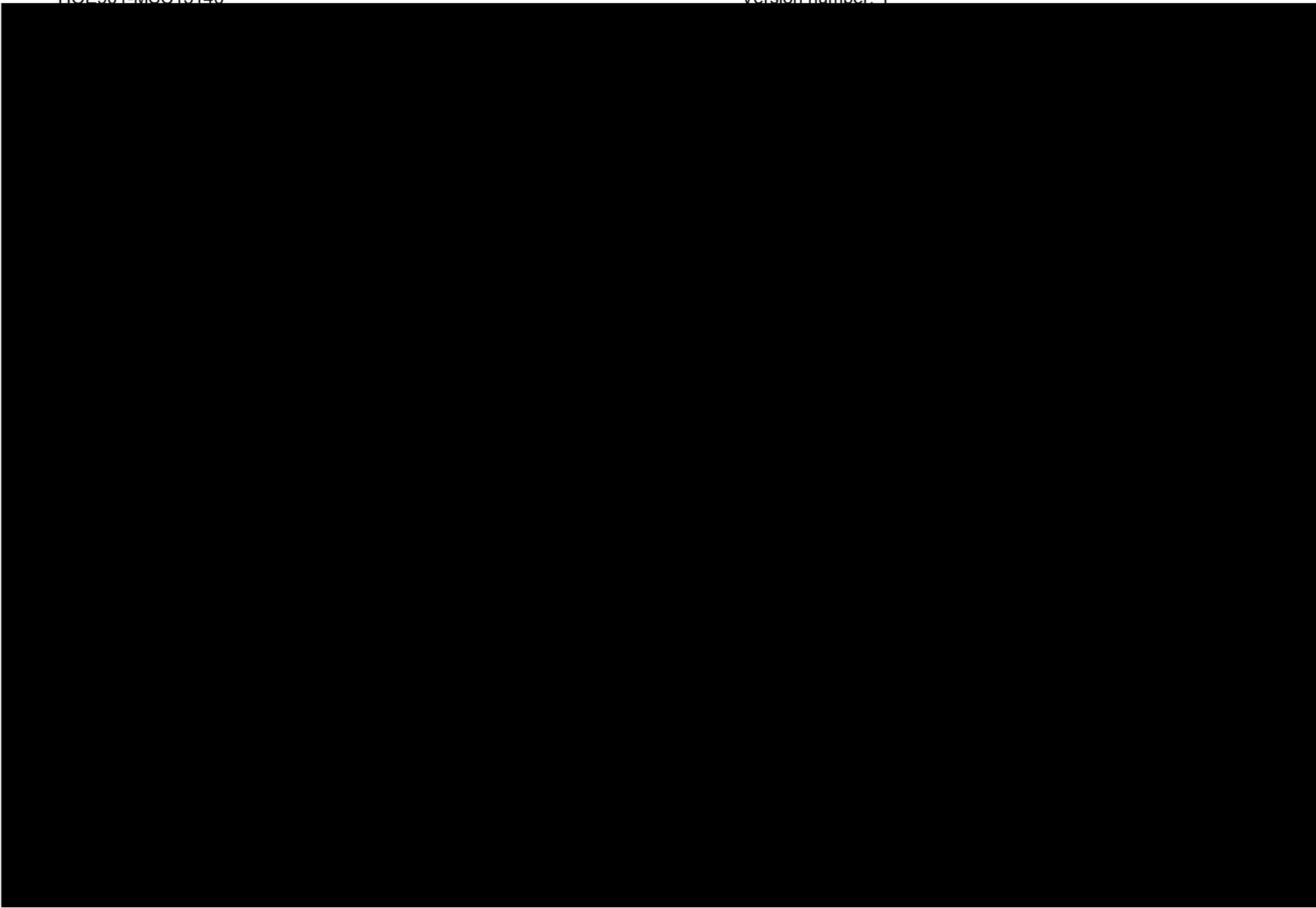
Missing or unreadable response

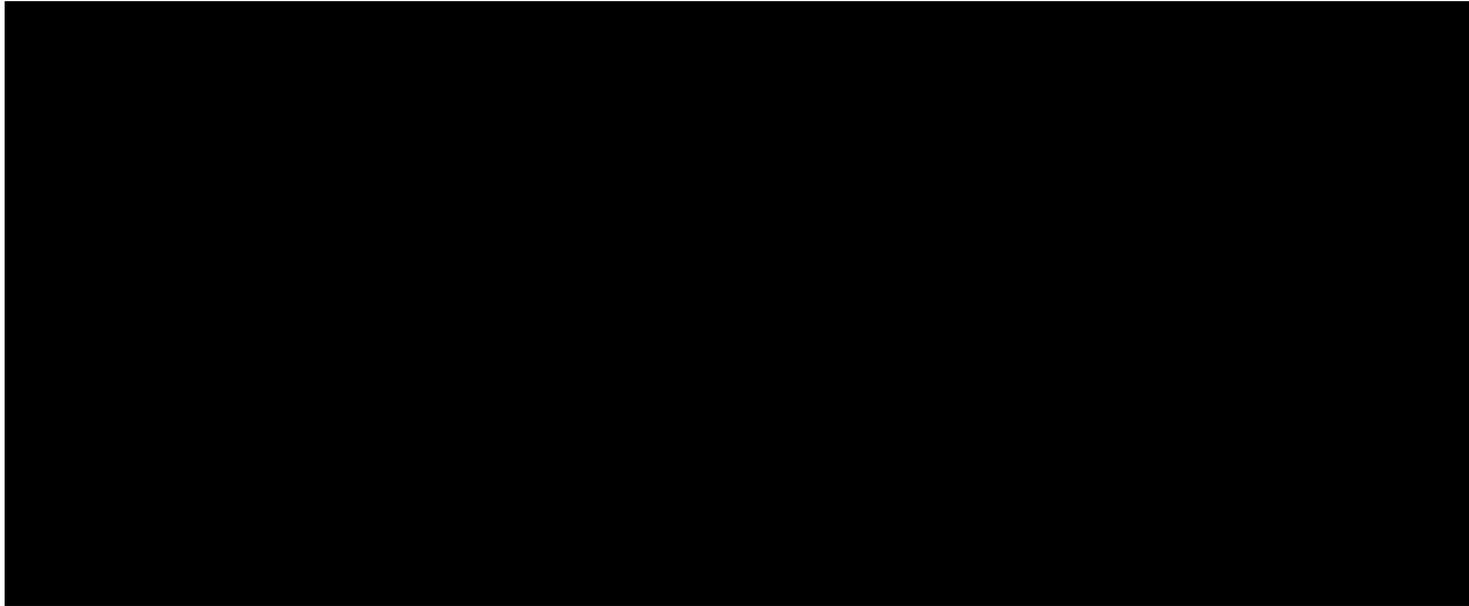
Responses from other assessments should not be used to eliminate missing data. For example, if a subject indicates he works 40 hours at one assessment, but leaves that question blank on a subsequent assessment, the blank response is coded missing.

Productivity questions

If the words at the end of the scale are circled, enter the corresponding number, ie, a "0" or "10".

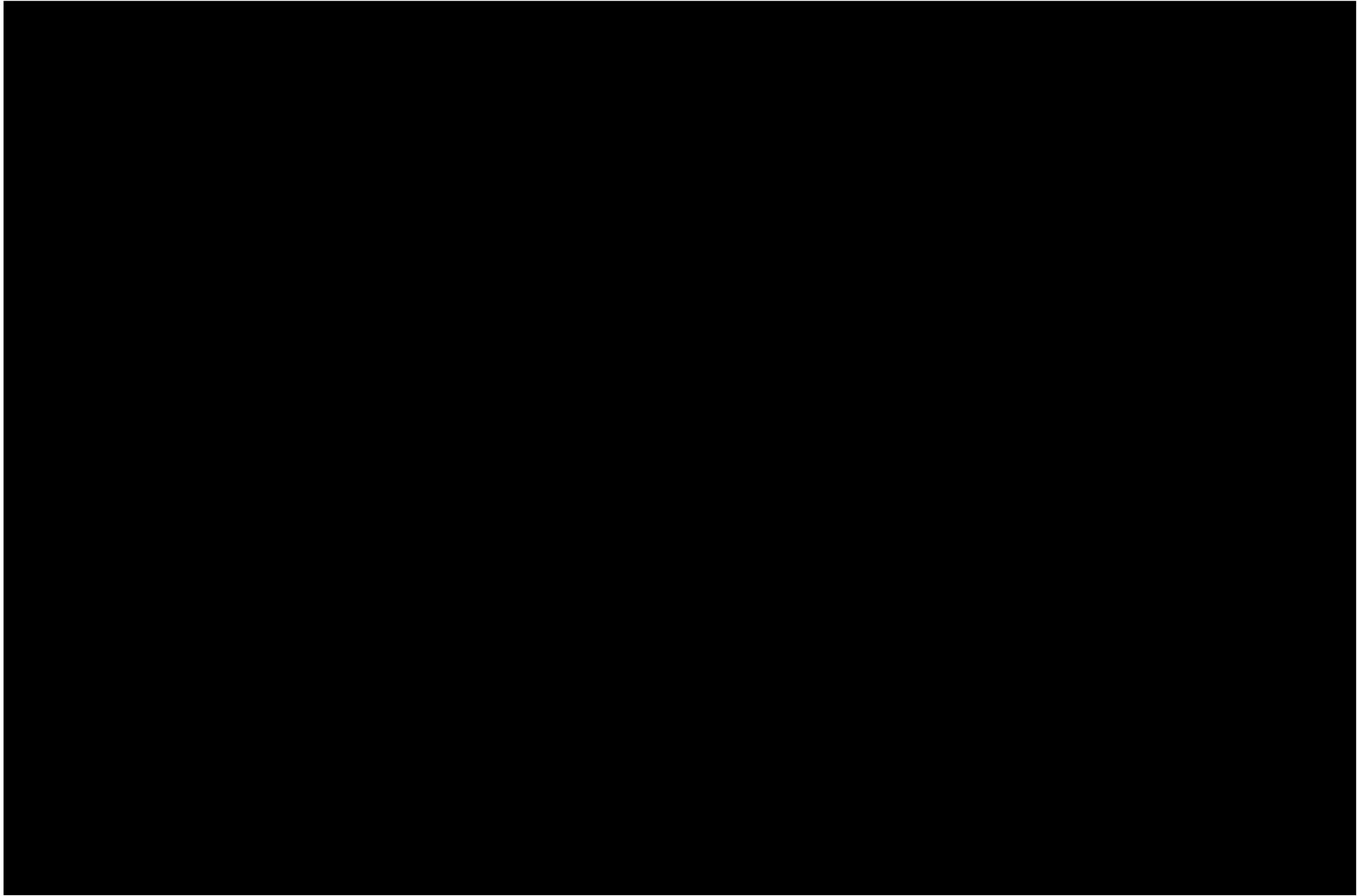
Appendix E 





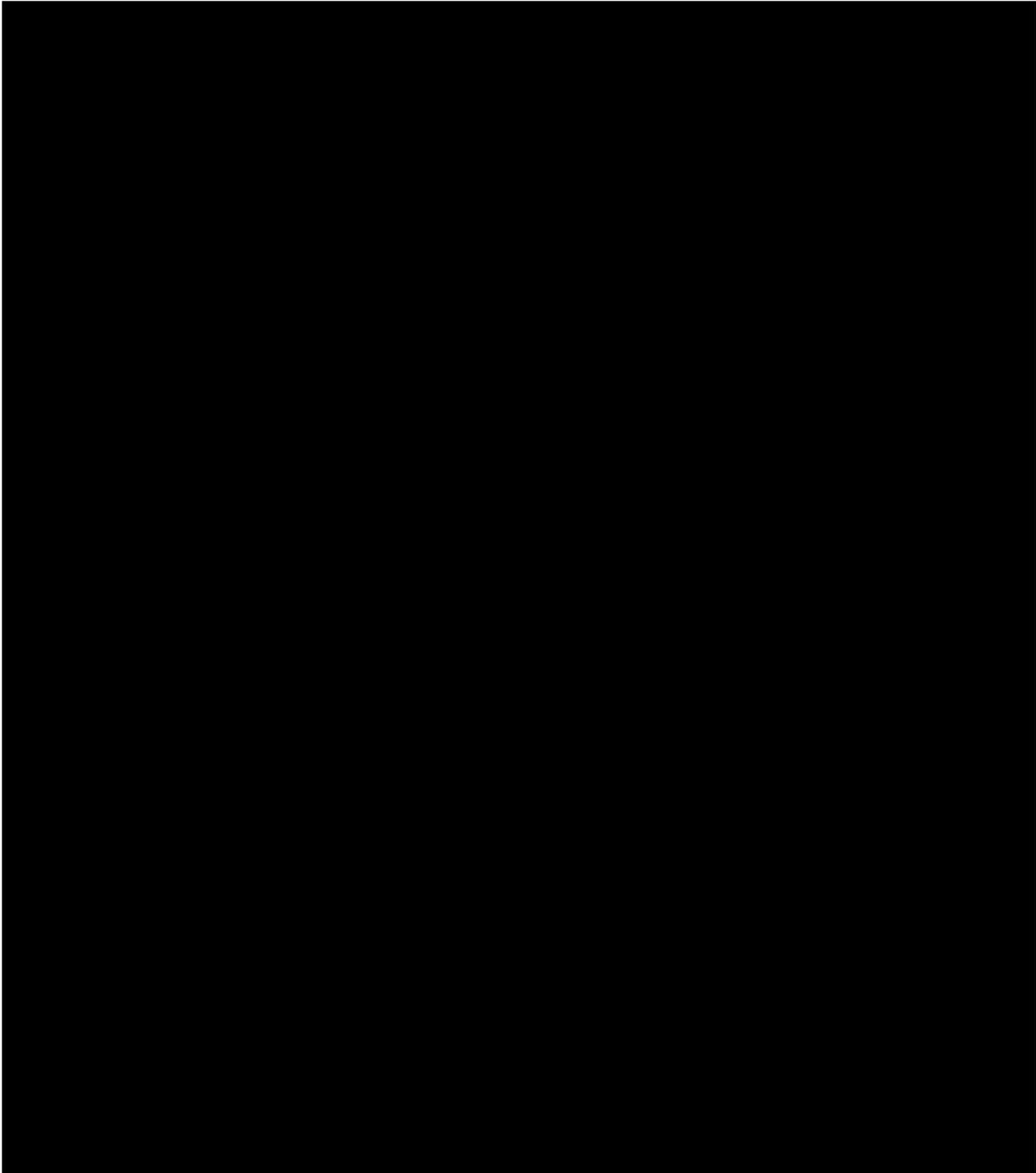
Appendix F





Appendix G





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DTSQs © Prof Clare Bradley 9/93. English for UK and USA (rev. 7/94)
Health Psychology Research, Dept of Psychology, Royal Holloway, University of London, Egham, Surrey, TW20 0EX, UK.

[Redacted]

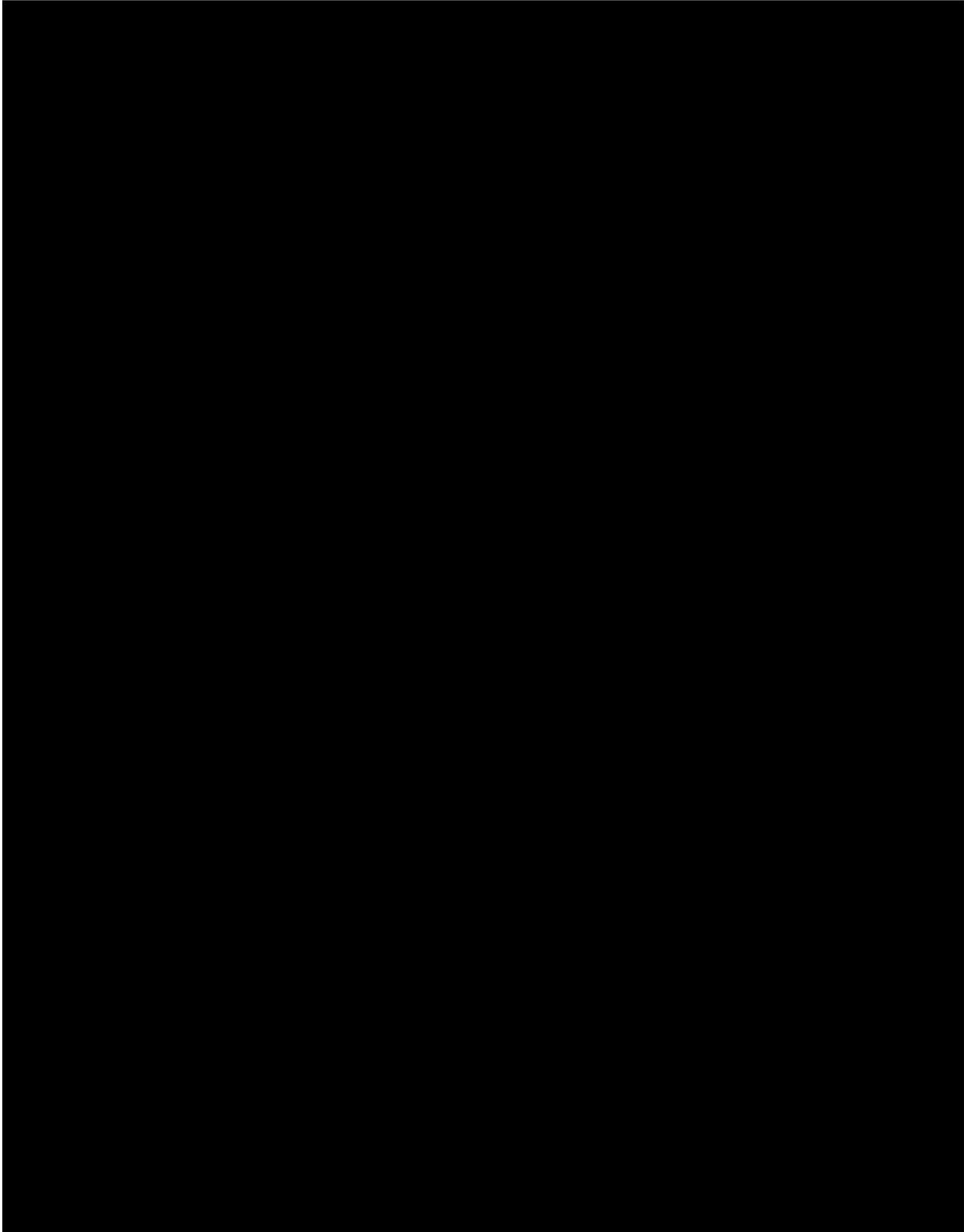
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Appendix H





FOR USE by SANOFI in study LPS 14966 under license HPR 1924
DTSQc © Prof Clare Bradley 11.9.96. English for UK & USA (rev. 4.3.98; generic intro. rev. 28.2.02)
Health Psychology Research, Dept of Psychology, Royal Holloway, University of London, Egham, Surrey, TW20 0EX, UK.

[Redacted]

[Redacted]

[Redacted]

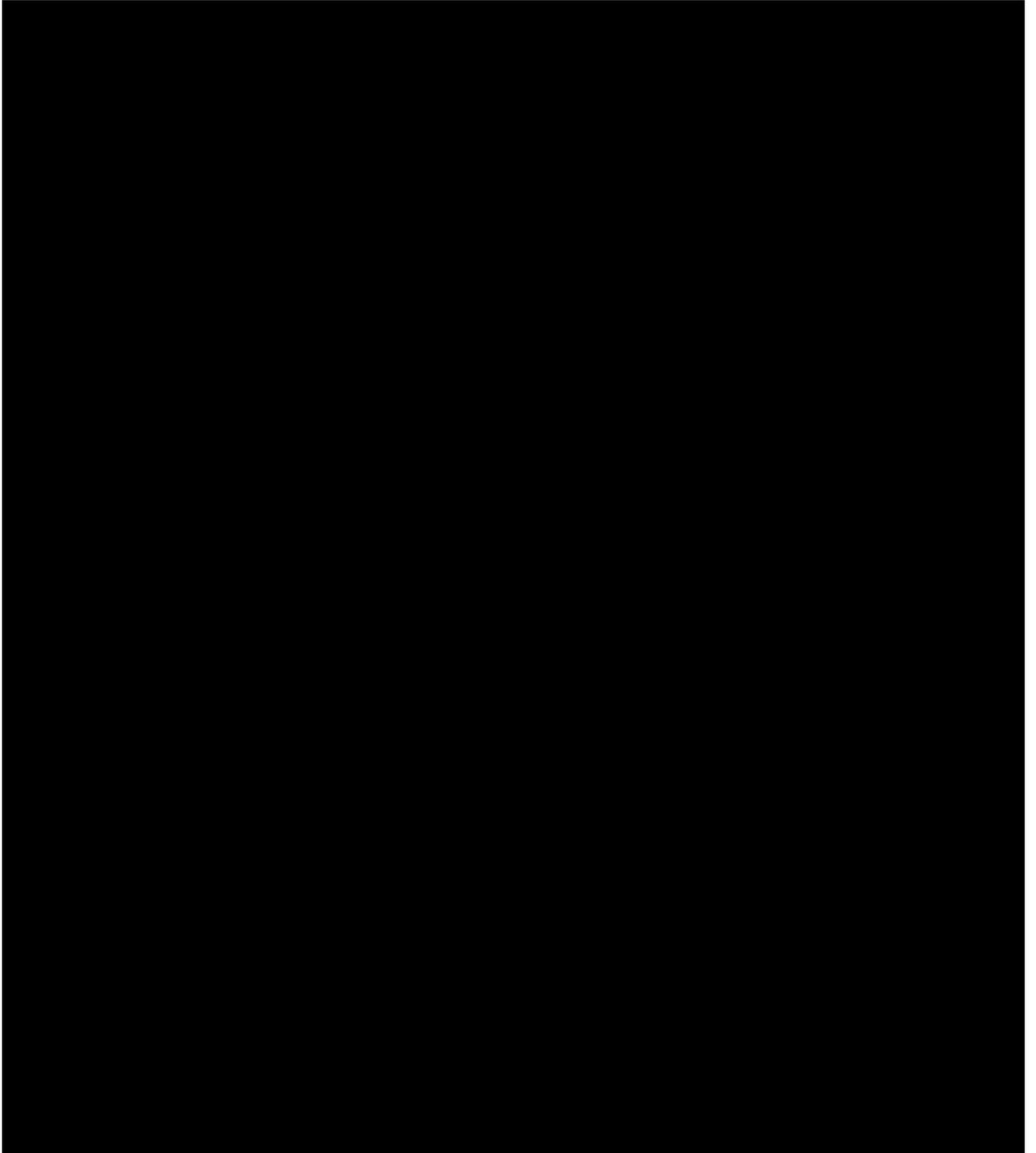
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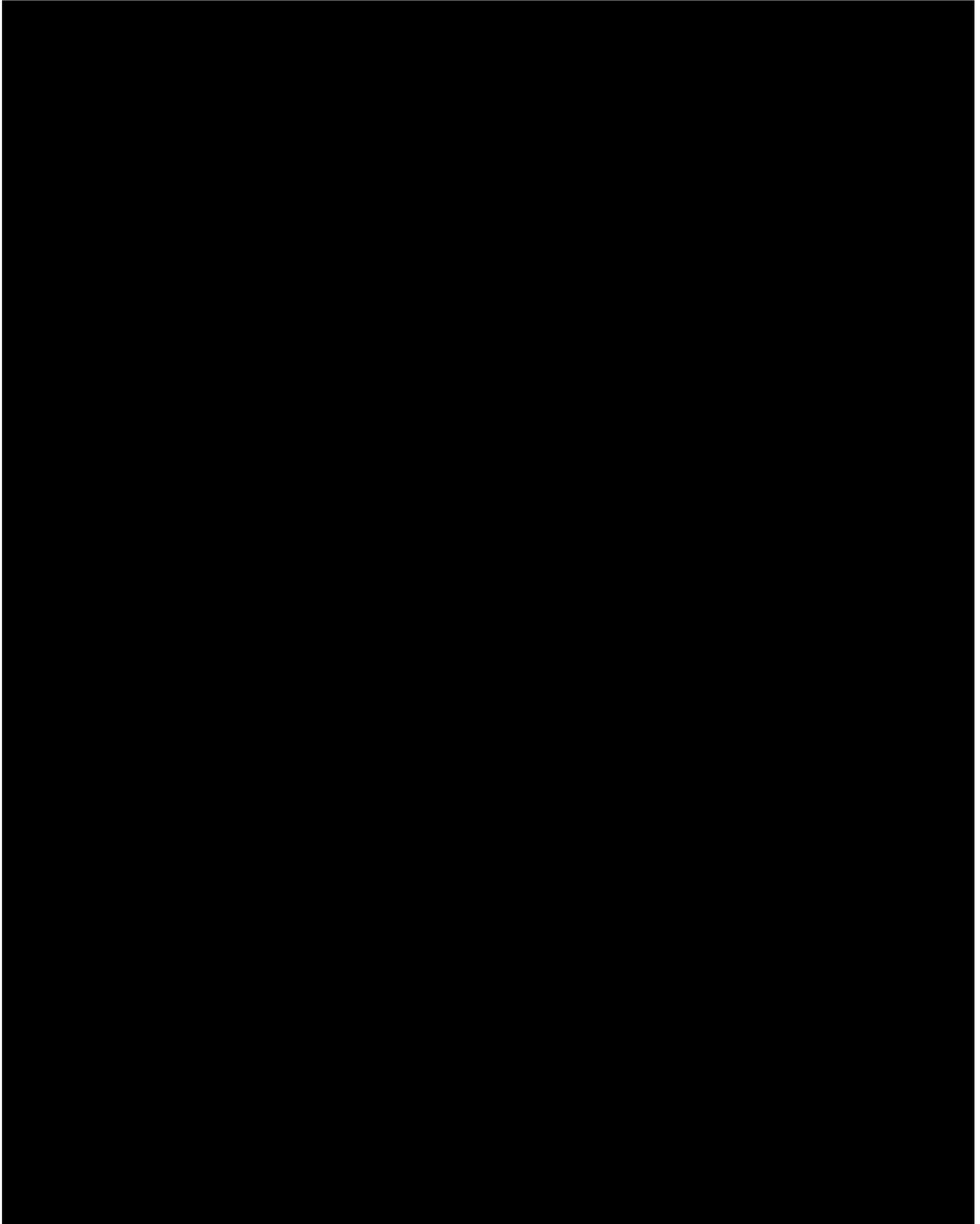
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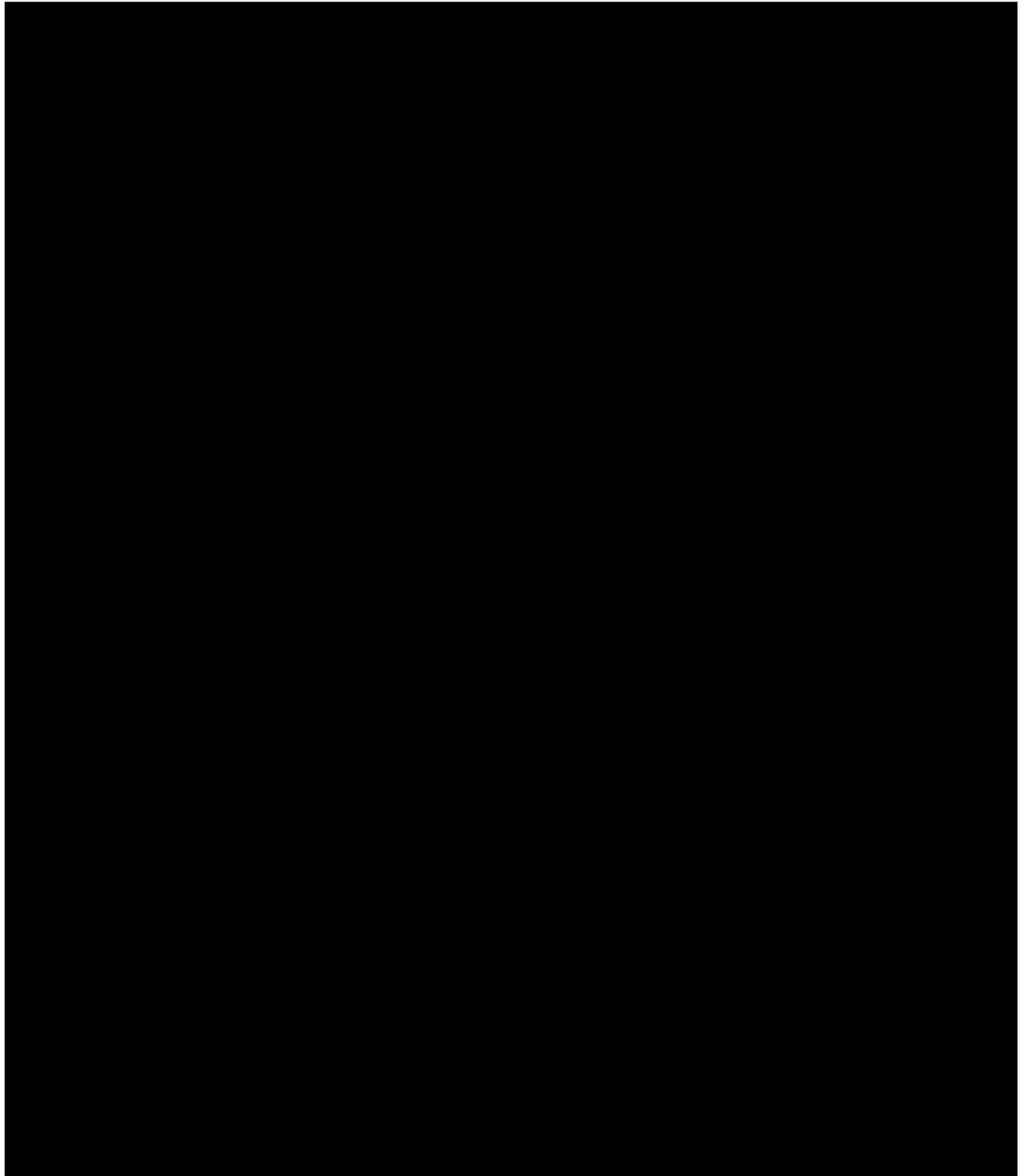


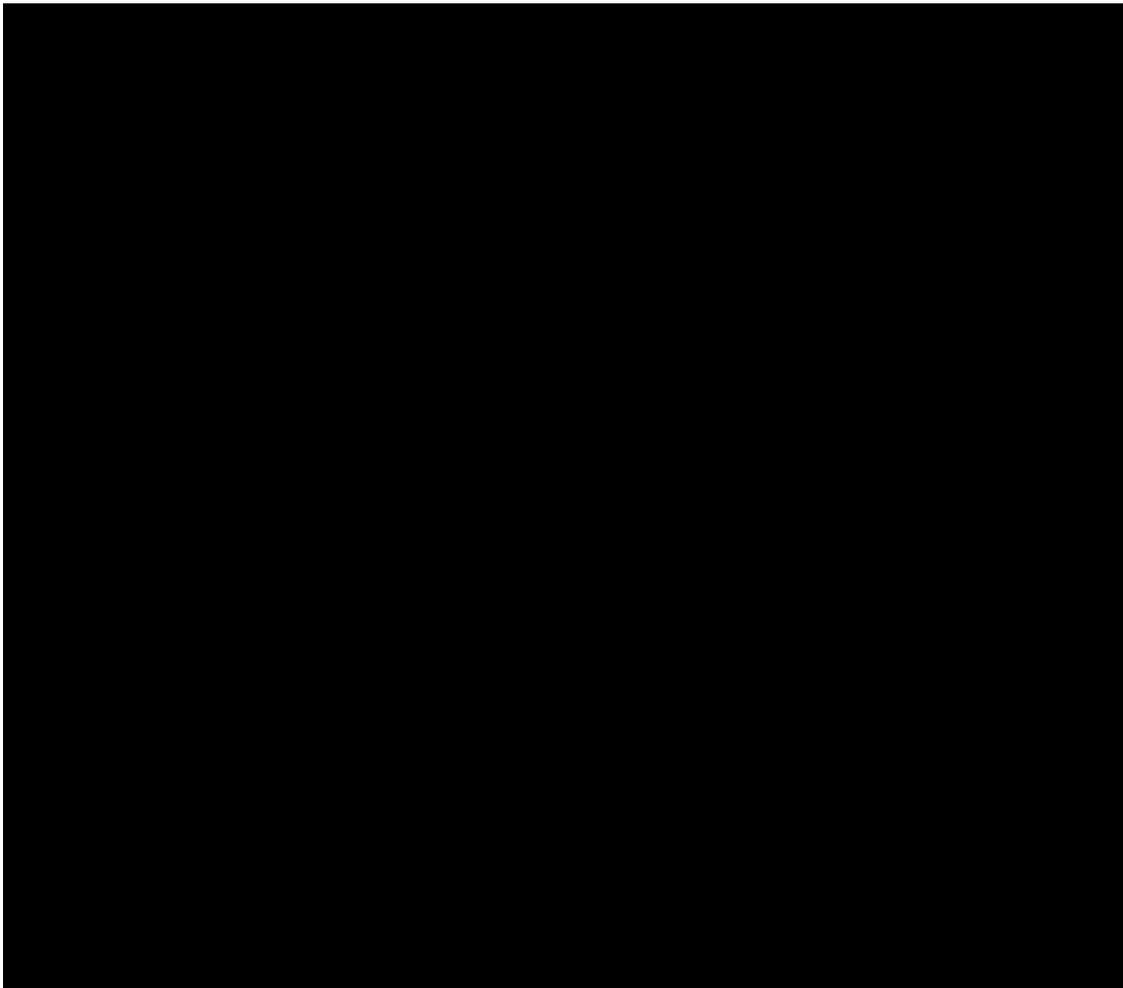
Appendix I











THANK YOU FOR YOUR TIME!

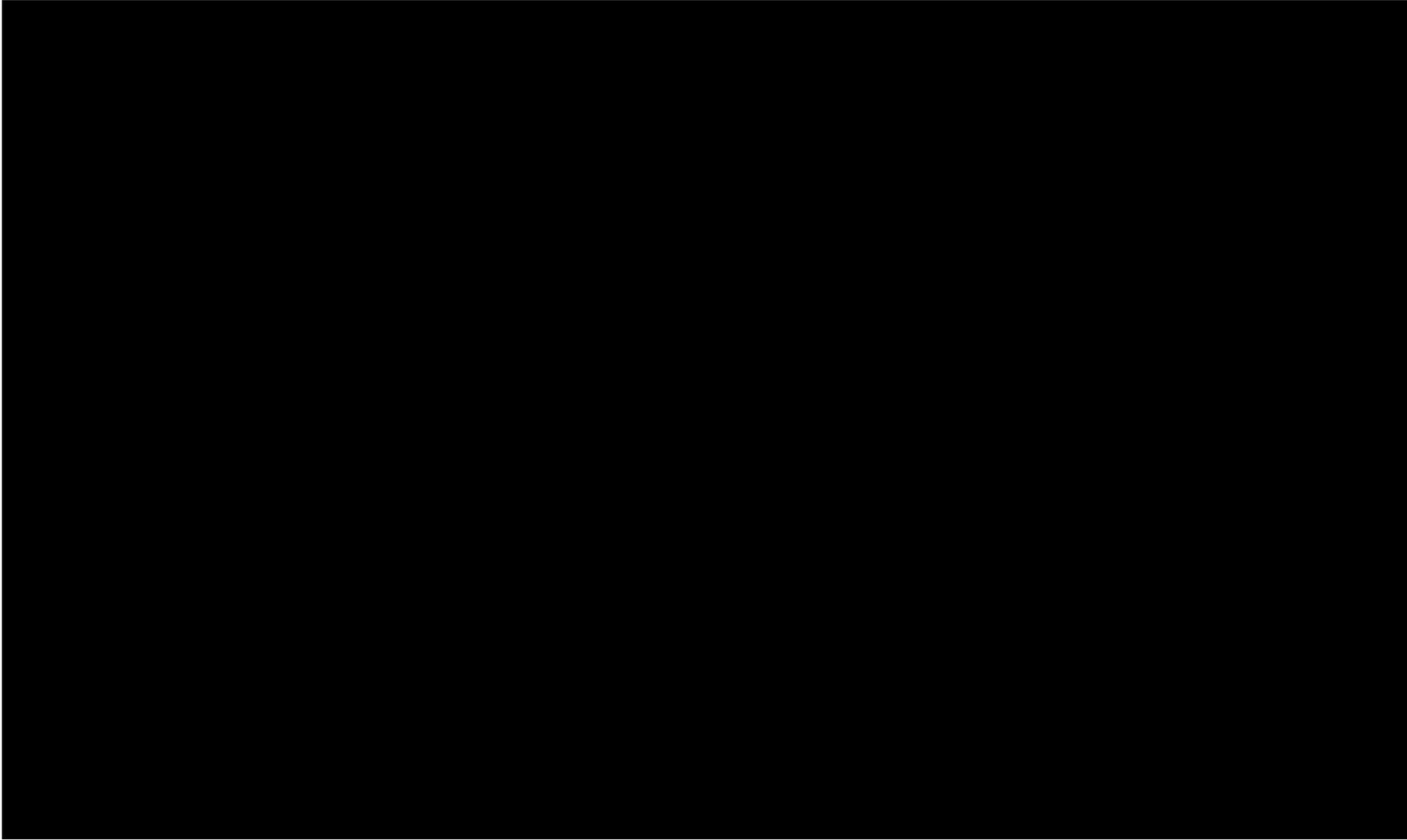
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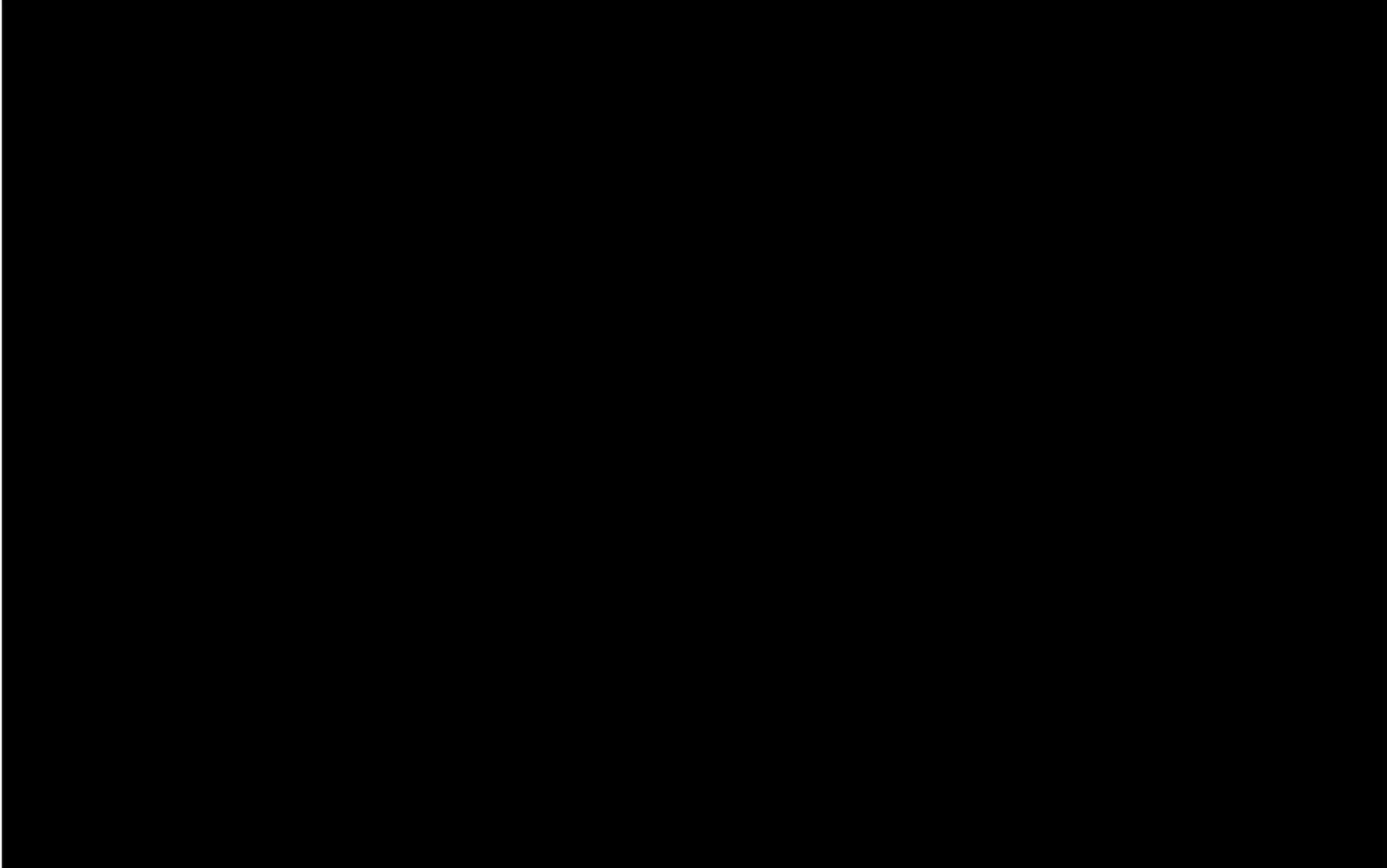
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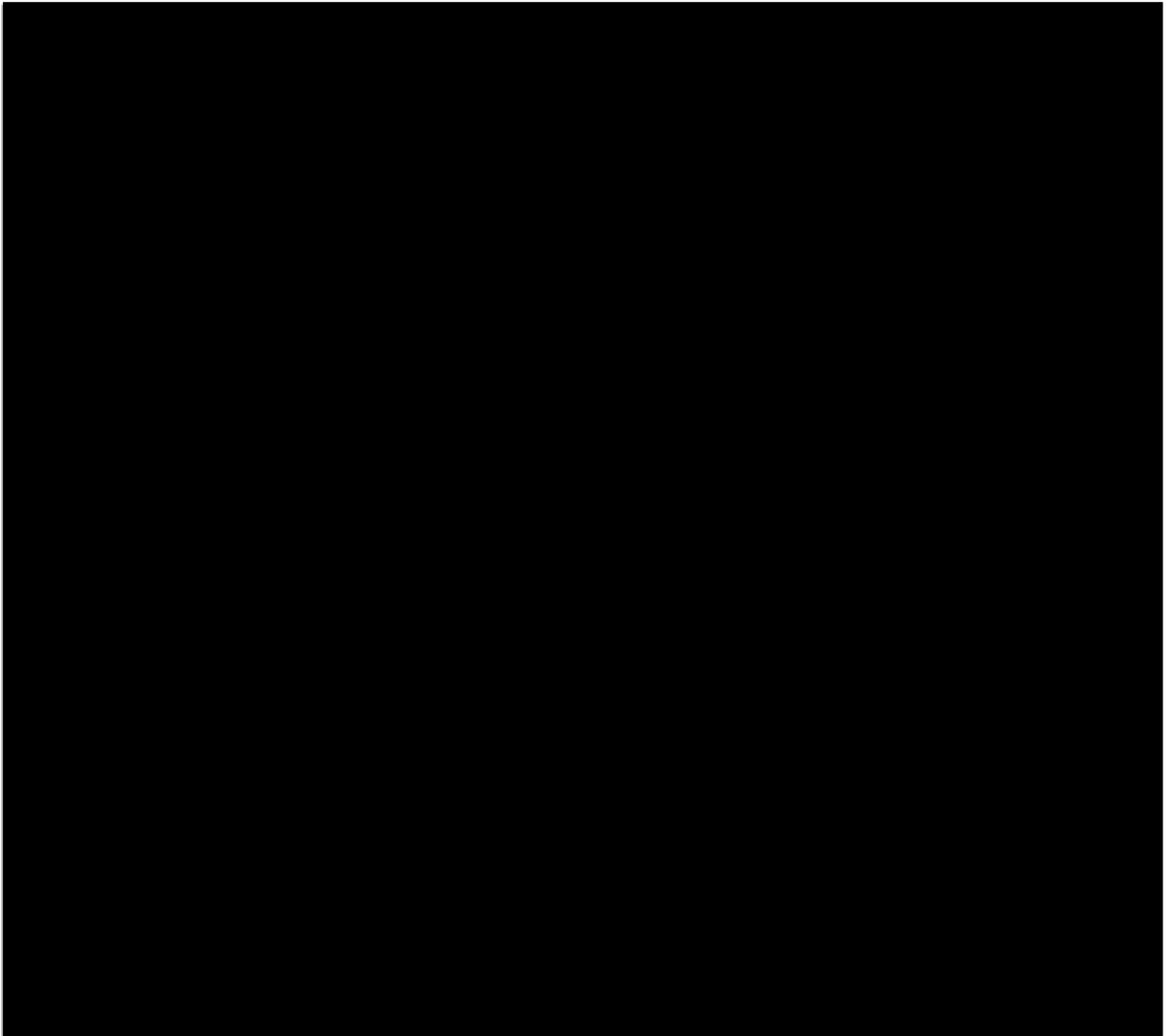
Appendix J

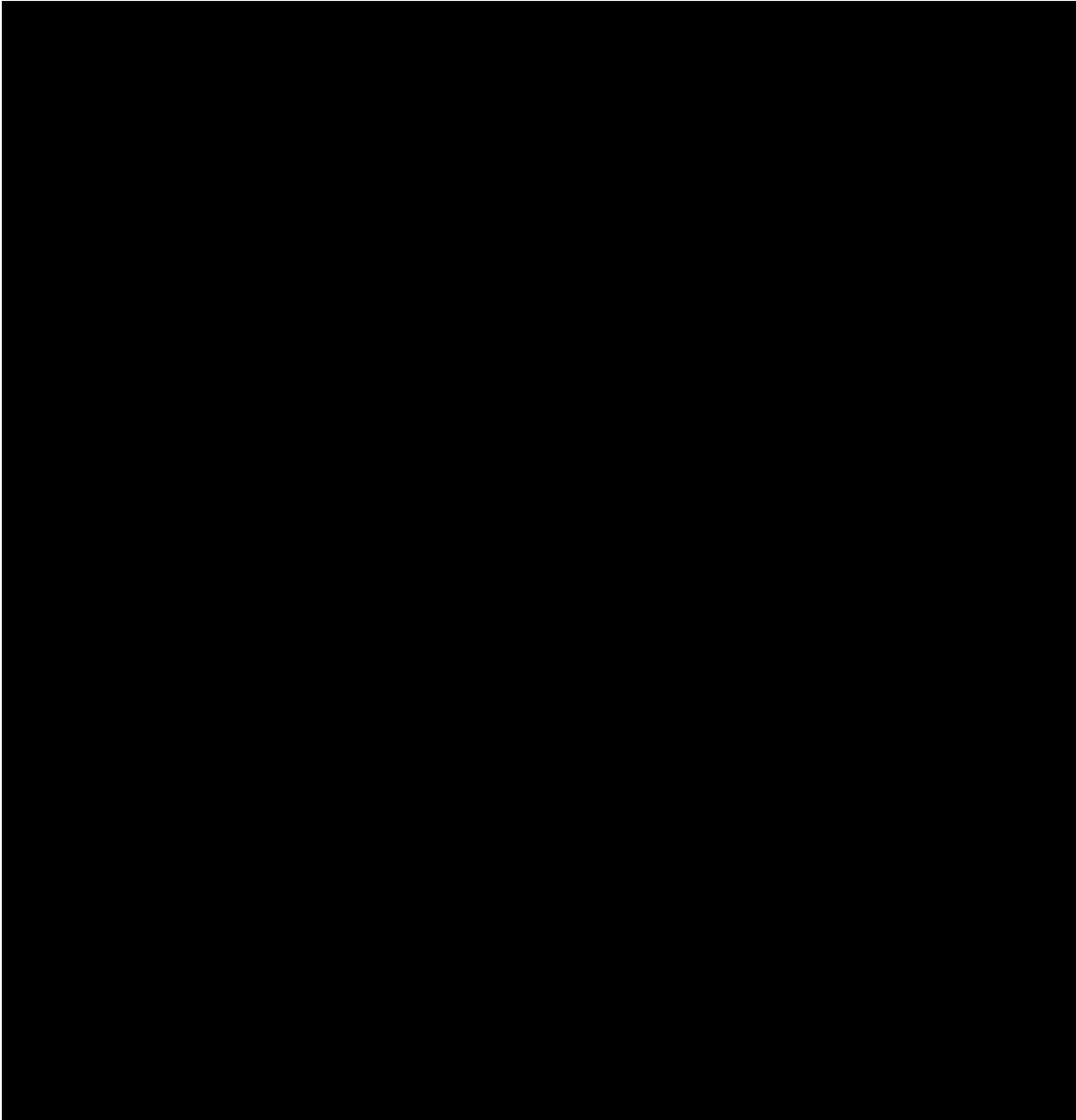


DDS

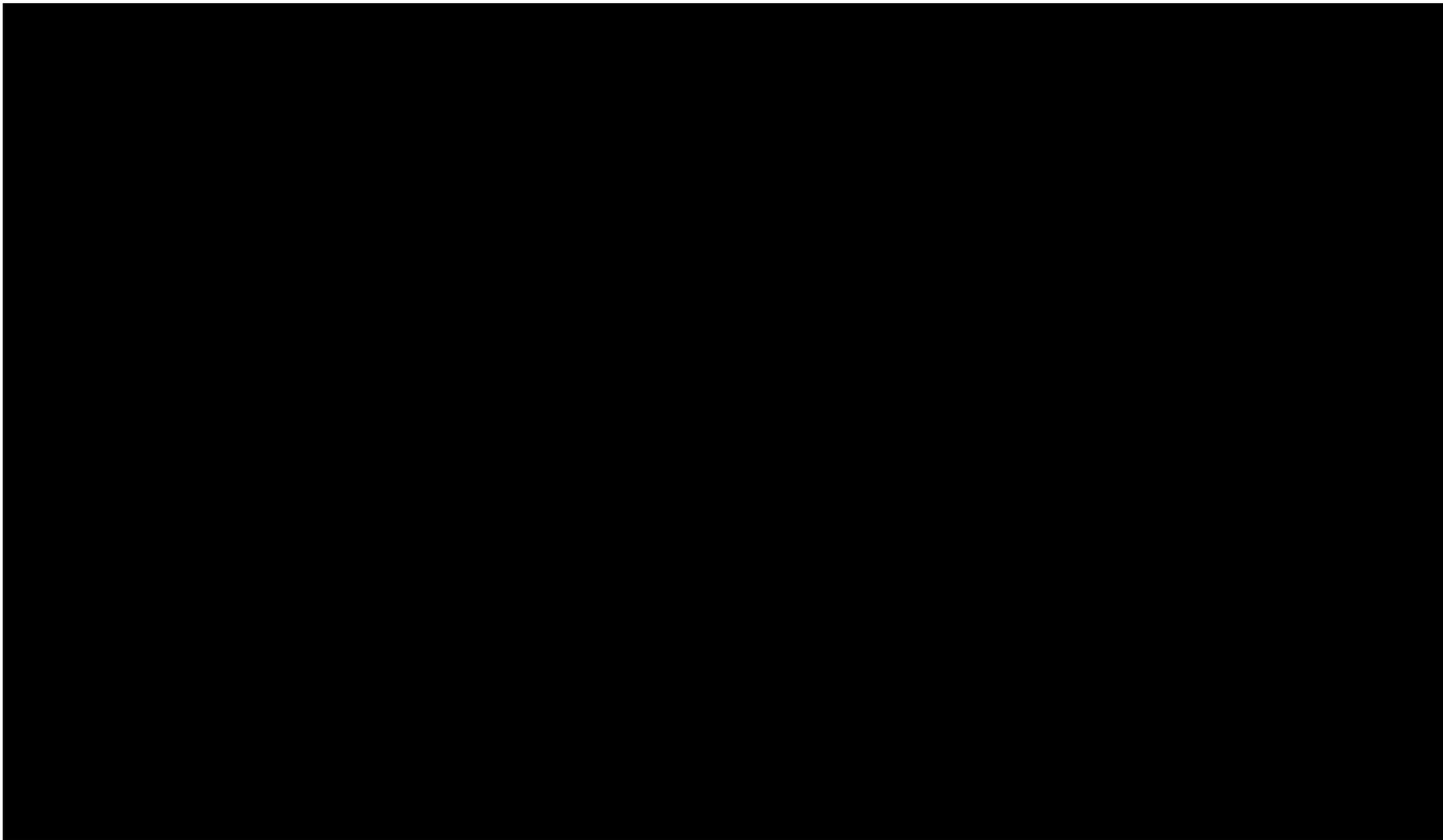
DIRECTIONS: Living with diabetes can sometimes be tough. There may be many problems and hassles concerning diabetes and they can vary greatly in severity. Problems may range from minor hassles to major life difficulties. Listed below are 17 potential problem areas that people with diabetes may experience. Consider the degree to which each of the 17 items may have distressed or bothered you DURING THE PAST MONTH and circle the appropriate number.

Please note that we are asking you to indicate the degree to which each item may be bothering you in your life, NOT whether the item is merely true for you. If you feel that a particular item is not a bother or a problem for you, you would circle "1". If it is very bothersome to you, you might circle "6".





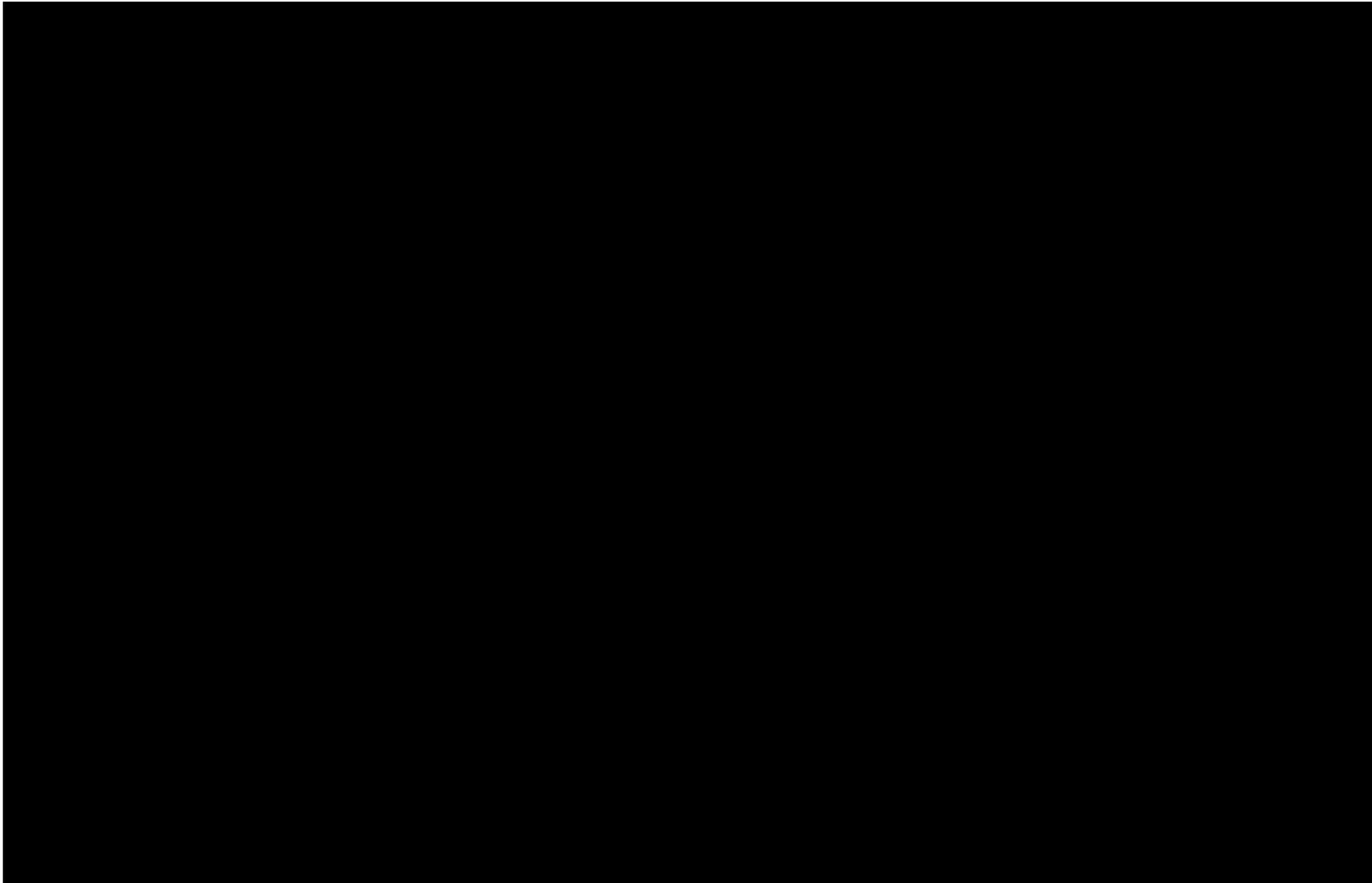






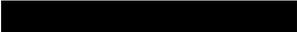
Appendix K





Signature Page for VV-CLIN-0544978 v1.0
MSC15146-16-1-9-sap

Approve & eSign	 Clinical 15-Jul-2019 14:25:47 GMT+0000
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Approve & eSign	 Clinical 17-Jul-2019 08:38:27 GMT+0000
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