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Protocol

Protocol for a randomized controlled study comparing the efficacy and safety of daily versus alternate day teneligliptin 20 mg in type 2 diabetes mellitus patients

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ABSTRACT

Background: For effective management of type 2 diabetes mellitus (T2DM), in addition to efficacy, safety, compliance and cost play a considerable role. Teneligliptin has long elimination half-life (24 hours) and offers a potential to be administered on alternate days. But there is paucity of robust clinical evidence. This study seeks to compare efficacy and safety of daily and alternate day teneligliptin therapy.
Methods: This is a single-center, open label, parallel group, randomized controlled study. A total of 60 adults suffering from T2DM with HbA1c 7 to 9 %, who received at least 3 months of metformin (≥1000 mg), will be enrolled. The participants will be randomized in 1:1 ratio into two groups (30 participants per group) receiving daily or alternated day teneligliptin 20 mg over and above standard of care for a duration of 3 months. The primary end point is change in HbA1c levels from baseline after 3 months of initiating teneligliptin 20 mg therapy. Data analysis will be done using SYSTAT software (13.2 version for windows, San Jose, CA: Inpixon Inc.) and the Intention-to-Treat approach will be employed for the analysis.
Conclusions: If alternate day teneligliptin add on therapy proves to have comparable efficacy with daily therapy, it will provide us with a safe, efficacious and cost-effective alternative in T2DM patients. This study has potential to bring down the public health and economic burdens associated with management of T2DM.
Trial registration: CTRI number: CTRI/2024/06/068564.

Keywords: DPP-4-inhibitor, Metformin, Type 2 diabetes mellitus, Teneligliptin

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder of global health concern, with increased morbidity, mortality and economic cost. It acts as an important risk factor for cardiovascular disorders, chronic kidney disease (CKD), retinopathy and neuropathy etc.[1-4] Diabetes rates have surged in low- and middle-income countries, but treatment availability continues to be severely inadequate.[5] In individuals with T2DM, the requirement of lifelong therapy makes it important to find an oral anti diabetic agent (OAD) which is efficacious, has good safety profile and is cost effective. Majority of the newly diagnosed patients are treated with metformin along with lifestyle modification.[1]

Dipeptidyl peptidase 4 inhibitors (DPP4Is) are a class of OADs commonly used either as monotherapy or in combination with other agents.[6] They are a favorable alternative to conventional therapies as adjunctive treatment for patients with uncontrolled hyperglycemia on metformin, as their action on glycemic control mimics the physiological mechanism. Additionally, they are safe to use without dose adjustments in elderly, and in mild

renal impairment.[7] Among the available DPP4Is, teneligliptin has been found to be equally efficacious with the added benefit of lower cost making it a cost-effective treatment alternative.[8,9] An expert review by Chowdhary et al, revealed that teneligliptin when used alone or in combination with other OADs (including metformin), contribute to lower incidence of hypoglycemia, is weight neutral, and require once daily dosing and is priced lower than other gliptins.[10] In case of elderly patients, DPP-4 inhibitors including teneligliptin have shown better treatment satisfaction and efficacy compared to other OADs and were found to be well tolerated. It was found to have sustained beneficial effects over long term in elderly population without any significant safety concerns.[11,12]

Based on the scientific evidence we can establish that in case of T2DM patients with uncontrolled hyperglycemia, daily dose of teneligliptin 20 mg as add on therapy is effective and safe.[13-15] Furthermore, recent studies and literature have assessed the possibility of using teneligliptin at lower doses i.e. 10 mg or as alternate day therapy. Owing to its favorable pharmacokinetic properties, including long elimination half-life (24 hours), and clinical evidence, alternate day treatment with teneligliptin 20 mg may provide a feasible alternative.[16-18]

However, currently, there is a paucity of robust clinical evidence evaluating effectiveness and safety profile of teneligliptin 20 mg as an alternate day therapy. There is only one such study to the best of our knowledge done by Kamiko et al on Japanese patients. In this non-inferiority RCT, involving 51 T2DM patients, it was observed that therapy with teneligliptin 20 mg taken on alternate day basis was not inferior to its daily dosing. At the completion of 12 weeks treatment, glycated hemoglobin (HbA1c) levels declined significantly in both groups ($p \leq 0.05$). Moreover, both groups were similar in terms of adverse events, treatment satisfaction and adherence.[17]

Alternate day therapy with teneligliptin will help in reducing the economic burden of the disease to society. It might also contribute to improved patient compliance in taking medication due to reduced pill burden. It may lead to a decrease in incidence of adverse effects as cumulative dose will decrease with alternate day dosing. Thus, evaluating efficacy and safety of teneligliptin 20 mg as an alternate day therapy will provide us with a safe, efficacious and cost-effective alternative in T2DM patients.

By comparing the two dosage schedules, this study aims to provide much-needed, robust evidence that may help determine whether an alternate dosing schedule can offer similar efficacy with fewer adverse events or improved patient compliance, ultimately guiding future clinical recommendations for optimal dosing strategies.

To address the gap, we aim to carry out a single-center, open-label, randomized controlled study within the Indian context.

Study objectives and outcome measures

The primary objective of this study is to determine the efficacy of teneligliptin 20 mg administered as add on therapy on daily versus alternate day in T2DM patients having inadequate glycemic control. Efficacy will be measured by the change in HbA1c levels from baseline to 3 months in both the groups. The secondary objective is to evaluate the safety profile of Teneligliptin 20 mg with both the dosing schedules by assessing and comparing the incidence of adverse events (AEs) in both groups during 3-month treatment period. In addition, the secondary efficacy measure will focus on the change in fasting blood sugar (FBS) level from baseline to 3 months in both groups. The primary efficacy outcome will be the change in HbA1c levels, while the secondary outcomes will include both the change in FBS and the monitoring of AEs.

METHODS

Study design and setting

This is a single-center, open label, parallel group, randomized controlled study. The study will be conducted in the Departments of Pharmacology, General medicine (Endocrinology) and Biochemistry of Government Medical College and Hospital (GMCH), Chandigarh. This study is investigating the equivalence of alternate day Teneligliptin 20 mg compared to its daily dosing for primary outcome. This will be conducted over a period of 18 months from June 2024 to December 2025.

Study protocol development and conduct

The study protocol was approved by the Institutional Ethics Committee (IEC), GMCH, Chandigarh on April 19, 2024 (Reference number: GMCH/IEC/2024/1196R). The protocol adheres to the SPIRIT 2013 checklist (Appendix I). This study will abide by the principles outlined in the Declaration of Helsinki (modified 2000) and National Ethical Guidelines for Biomedical and Health Research Involving Human Participants given by the Indian Council of Medical Research (New Delhi) in 2017. The study has been registered under clinical trials registry of India (CTRI) prospectively on June 7, 2024. The study will be reported in accordance with CONSORT (consolidated standards of reporting trials) recommendation. During the trial if any amendment required, amended protocol will be submitted with permission of IEC.

Study participants

The study sample will be obtained by visiting Medicine/Endocrinology Outpatient Department (OPD) / Inpatient Department (IPD) of the institute on specific days and the study population (T2DM fulfilling the inclusion criteria) will be drawn from the source population (patients of T2DM visiting the OPD/Ward).

Sample size

We referred to a previous estimate where alternate day therapy achieved a significant decline in baseline HbA1c.[17] In this study, the baseline HbA1c was 7.6±0.5 and we assumed at least 5% decrease in this value at the end of 3 months of therapy with alternate day teneleglipti̇n given as add on therapy. Power was set at 80% and alpha error was set at 5% (0.05). This will require a sample size of 54 (27 in each group). Clin Calc sample size calculator was used to calculate the sample size for difference in means (continuous data) of two independent groups.[19] Further, considering a dropout rate of 10%, a total sample of 60 (n=30 in each arm) would be needed for this study (adjusted sample size=original sample size/ (1−dropout rate).

Inclusion criteria

Patients diagnosed with T2DM; age 18-59 years; with HbA1c levels between 7-9 % and history of treatment with metformin (dose ≥1000 mg) for at least three months, will be enrolled in this study.

Exclusion criteria

Following patients will be excluded from this study. Patients diagnosed with type 1 diabetes; pregnant and lactating women; patients with less than three months history of treatment with metformin; patients with co morbidities like uncontrolled cardiovascular disorder, renal dysfunction (defined as (serum creatinine 1.5 times more than the upper normal limit range), hepatic dysfunction (defined as SGOT and/ or SGPT levels 3-fold > than upper limit range), recent history of diabetic ketoacidosis and/or any other severe life-threatening diseases; those with known allergy to any of the study drugs; patients who are unwilling / unable to give written informed consent.

Recruitment procedure

The study objective and method will be explained to the patients along with their role in it, after which, a written informed consent will be obtained from them if they are willing to participate in the study. To elicit their eligibility, a thorough history along with clinical examination and biochemical parameters will be assessed. This will also serve as baseline data for the enrolled participants and will be recorded in a case report form (CRF). Baseline investigations include HbA1c; FBS; Aspartate aminotransferase (AST); Alanine aminotransferase (ALT); and serum creatinine. HbA1c will be estimated by high performance liquid chromatography methods. Commercial kits will be used to determine FBS, AST, ALT and Serum creatinine levels. We will collect 5 ml blood sample, under aseptic conditions at baseline, 1 month and 3 months for specific laboratory investigations. The biochemical investigations will be conducted in the Department of Biochemistry, GMCH, Chandigarh.

Randomization and allocation concealment method

Enrolled participants will be randomized into two groups A and B with an allocation ratio of 1:1. This will ensure that every patient will have an equal chance of receiving daily and alternate day therapy. An independent individual, not involved in the recruitment and allocation process, will generate a random number sequence using computer-based system. This will ensure an unbiased and transparent randomization. Allocation sequence will be concealed by using sequentially numbered sealed envelopes until the participant enrollment, to prevent allocation bias.

Blinding

This is an open label trial and hence, no blinding will be done.

Intervention

Participants in both groups will receive Tablet Teneleglipti̇n 20 mg for 3 months. Group A will receive the drug orally once daily, while group B will receive the same dose orally on alternate days. In addition, all participants will receive standard of care (SoC) as determined by the attending physician. All the participants will be encouraged to follow adequate lifestyle modifications along with medication.

Safety considerations

Participants will be warned about the hypoglycemia symptoms (palpitations, sweating, tremors, dizziness) and instructed on managing it by taking glucose, sugar, juice or a meal. Patient will be instructed to report this immediately to the investigator, and this will be recorded as an adverse drug event in the CRF. Instructions will be provided to consult the treating specialist, in case of abnormally elevated or low blood sugar levels or any emergency. Necessary treatment or rescue therapy with the advice of consulting physician / endocrinologist will be provided. Other adverse events like – nasopharyngitis, headache, GI adverse events (nausea, diarrhea, constipation etc.), allergic reactions etc. will be recorded.

Method of follow up

Each patient will be asked to report their FBS value after 1 month of starting teneligliptin therapy (either self-reported or by visiting the OPD). This is to check any abnormal fluctuations in blood glucose levels. At this point, If FBS levels are found to be >212 mg/dl (according to the eAG/A1C conversion calculator given by the American diabetes association, it corresponds to HbA1c of 9%) then the participant will be dropped out

from the study and rescue therapy will be provided at the discretion of attending physician.[20]

The data of these patients will be retained and analyzed according to intention to treat analysis. One follows up visit in the OPD will be at 3 months after start of therapy with teneligliptin. The following biochemical parameters will be estimated in the department of Biochemistry, GMCH Chandigarh–HbA1c value and FBS. Along with it, data regarding history and clinical examination for adverse events (if any) will be recorded in the CRF.

End point

Primary end point is change in HbA1c levels from baseline after 3 months of initiating teneligliptin 20 mg therapy in T2DM patients having inadequate glycemic control with metformin. Secondary end point is difference in incidence of adverse drug events among T2DM patients receiving daily versus alternate day teneligliptin 20 mg therapy.

Data management

We will collect the data using CRF during OPD / IPD visits at baseline and at 3 months after initiating teneligliptin therapy. Data regarding history, clinical examination, biochemical investigation and adverse drug events (if any) will be recorded in the CRF. Patient hospital records and OPD cards will also be reviewed for history, biochemical parameters. The collected data will be entered into a Microsoft spreadsheet and data will be coded and cleaned for the purpose of analysis. The information gained from the participant will be kept confidential and will be accessible only to the investigators.

Statistical analysis

The data will be analyzed using SYSTAT software (13.2 version for windows, San Jose, CA: Inpixon Inc.). Data will be represented in numerical form, including percentages, Mean Standard deviation (mean±SD), and Median and range wherever applicable. Categorical data will be analyzed by using Chi-square test and/or Fisher exact test.

Parametric data (for continuous variables) will be subjected to t-test, while non-parametric data will be analyzed using the Mann-Whitney test. A p value <0.05 will be deemed statistically significant. The Intention to Treat approach will be employed for the analysis, encompassing all patients initially included in the study regardless of whether they completed the intervention or not. Missing data will be addressed by using imputation analysis. A sensitivity analysis will be considered for analyzing data with and without missing data (if applicable).

RESULTS

The study aims to evaluate the efficacy and safety of daily (group A) versus alternate day (group B), add on therapy with Teneligliptin in T2DM patients. A total of 60 patients will be recruited and randomly assigned to both group (30 in each group). The data for all the 60 participants, initially enrolled in this study, will be analyzed as described in the methodology (Intention to treat approach) (Figure 1). To ensure comparability between two groups at the start of study, we will compare their baseline characteristics. This includes demographic, clinical, and laboratory variables, which could influence the intervention outcome (as summarized in Table 1). The primary outcome of this study includes the change in HbA1c levels from baseline after 3 months of teneligliptin therapy. To assess the impact of teneligliptin on HbA1c we will compare the change in HbA1c from baseline, between group A and group B. The secondary outcomes will include change in FBS level from baseline to 3 months in both groups, incidence of adverse events in both groups and their comparison. As described previously, in the sample size calculation, we hypothesize that alternate day teneligliptin therapy will lead to a statistically significant reduction in HbA1c comparable to its daily dosing. This hypothesis was based on previous studies indicating such effects.

Table 1: Baseline characteristics.

Characteristics	Group A (Daily teneligliptin)	Group B (Alternate day teneligliptin)	P value
Age (years)	Mean±SD	Mean±SD	
Gender (% of Males & Females)	Males=x %	Males=y %	
	Females=x %	Females=y %	
Height (cm)	Mean±SD	Mean±SD	
Weight (Kg)	Mean±SD	Mean±SD	
Duration of T2DM (years)	Mean±SD	Mean±SD	
Metformin treatment			
Metformin dose	Mean±SD	Mean±SD	
Metformin duration	Mean±SD	Mean±SD	
% on Sulfonylurea (SU) treatment	x %	y %	

Continued.

Characteristics	Group A (Daily teneligliptin)	Group B (Alternate day teneligliptin)	P value
Other medications	Antihypertensive medication (x %), Statins=x %	Antihypertensive medication (y %), Statins (y %)	
Comorbidities	Hypertension =x % Dyslipidemia =x % Others=	Hypertension =y % Dyslipidemia =y % Others=	
Systolic blood pressure (mmHg)	Mean±SD	Mean±SD	
Diastolic blood pressure (mmHg)	Mean±SD	Mean±SD	
Baseline HbA1c (%)	Mean±SD	Mean±SD	
Baseline FBS (mg/dl)	Mean±SD	Mean±SD	
AST (SGOT) (IU/l)	Mean±SD	Mean±SD	
ALT (SGPT) (IU/l)	Mean±SD	Mean±SD	
Serum creatinine (mg/dl)	Mean±SD	Mean±SD	

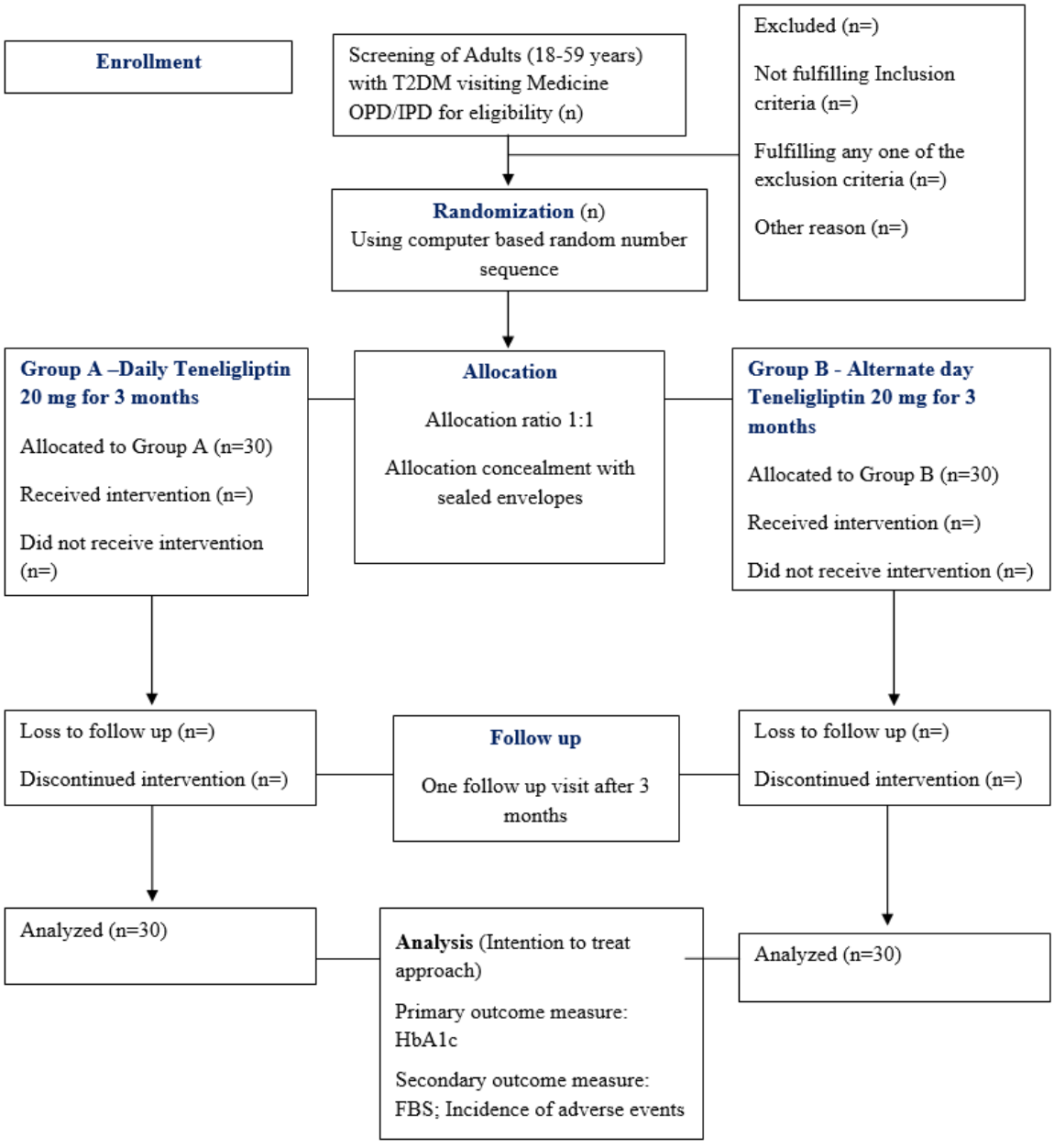

Figure 1: CONSORT flow chart.

DISCUSSION

Diabetes mellitus is a significant global health concern leading to considerable morbidity and mortality. According to International Diabetes Federation data, prevalence of diabetes was approximately 9.8% in 2021 which is expected to increase to 11.2% (Age adjusted comparative prevalence) in 2045.[1] Recommended management includes lifelong therapy with oral anti diabetic agents (OADs).[21] Adherence to treatment in T2DM can be affected by various drug factors like its tolerability, efficacy, dosing frequency and cost.[4] Teneligliptin is an efficacious, safe and cost-effective treatment option in T2DM. In India, it is included in the national list of essential medicine and thus comes under drug price control order, making it more affordable and accessible and thus improving adherence.[22,23] It has been found to be effective when given alone or in combination with other OADs (including metformin). When combined with other OADs its safety profile is similar as compared with other commonly used combinations and is found to be better than sulfonylureas in terms of incidence of hypoglycemia.[14] A post-marketing surveillance study on elderly Japanese patients with T2DM aimed to evaluate the efficacy and safety of teneligliptin over a span of 3 years in a real-world scenario. Authors observed no difference in the occurrence of adverse drug reactions (ADRs) and a significant decline in HbA1c levels, with these lowered levels being sustained throughout the subsequent 3 years. It is also observed to be safe and effective in patients with renal dysfunction. Thus, they can be used in patients with renal impairment without any dose adjustment.[11,12] It is also found to be efficacious at lower doses i.e. 10 mg per day and well tolerated even at a higher dose of 40 mg per day. It offers the potential to be administered on alternate days because of its long elimination half-life (24 hours) but there is very less evidence available on its efficacy as alternate day therapy.[11,16-18]

In patients diagnosed with T2DM experiencing uncontrolled hyperglycemia despite treatment with metformin, incorporating teneligliptin 20 mg on alternate days may not exhibit a significant variation in effectiveness when compared to daily administration of teneligliptin 20 mg as an additional therapy. This approach could potentially offer a safer and more cost-efficient strategy, potentially enhancing patient compliance. By reducing the frequency of dosing, there is a prospect of alleviating pill burden, decreasing the occurrence of adverse effects, and ultimately providing a better adherence to treatment. Consequently, this could lead to a reduction in the public health and economic burdens associated with managing T2DM. At present, there is insufficient evidence to conclusively support this hypothesis. So far there is only one study to the best of our knowledge conducted by Kamiko et al in Japan evaluating alternated day therapy with teneleglipti n.[17] Therefore, this randomized controlled study aims to assess the efficacy and safety of incorporating teneligliptin 20 mg as an alternate day add on treatment in the Indian population.

CONCLUSION

If efficacy of alternate day therapy with teneligliptin is proven to be comparable to daily therapy, then it could potentially offer a safer and more cost-efficient strategy, potentially enhancing patient compliance. By reducing the frequency of dosing, there is a prospect of alleviating pill burden, decreasing the occurrence of adverse effects, and ultimately providing a better adherence to treatment. Consequently, this may be favorable option for individuals with T2DM while reducing healthcare costs and economic strain.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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APPENDIX I

SPIRIT 2013 checklist: recommended items to address in a clinical trial protocol and related documents.*

Section/item	Description	Page number #
Administrative information		
Title	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	Trial identifier and registry name. If not yet registered, name of intended registry	2
	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	Date and version identifier	1
Funding	Sources and types of financial, material, and other support	3
Roles and responsibilities	Names, affiliations, and roles of protocol contributors	1
	Name and contact information for the trial sponsor	NA
	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA
	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	NA (Single center study)
Introduction		
Background and rationale	Description of research question and justification for undertaking the trial including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	1,2
	Explanation for choice of comparators	1,2
Objectives	Specific objectives or hypotheses	2
Trial design	Description of trial design including type of trial (e.g., parallel group, crossover, factorial, single group), allocation ratio, and framework (e.g., superiority, equivalence, noninferiority, exploratory)	2,3
Methods: Participants, interventions, and outcomes		
Study setting	Description of study settings (e.g., community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	2
Eligibility criteria	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (e.g., surgeons, psychotherapists)	3
Interventions	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	3
	Criteria for discontinuing or modifying allocated interventions for a given trial participant (e.g., drug dose change in response to harms, participant request, or improving/worsening disease)	3
	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (e.g., drug tablet return, laboratory tests)	3,4
	Relevant concomitant care and interventions that are permitted or prohibited during the trial	3
Outcomes	Primary, secondary, and other outcomes, including the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	2,4
Participant timeline	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	2-4
Sample size	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	3
Recruitment	Strategies for achieving adequate participant enrolment to reach the target sample size	3
Methods: Assignment of interventions (for controlled trials)		
Allocation		
Sequence generation	Method of generating the allocation sequence (e.g., computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (e.g., blocking) should be provided in a separate document that is unavailable to those who enroll participants or assign interventions	3
Allocation concealment mechanism	Mechanism of implementing the allocation sequence (e.g., central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	3
Implementation	Who will generate the allocation sequence, who will enroll participants, and who will assign participants to interventions	3

Continued.

Section/item	Description	Page number #
Blinding (masking)	Who will be blinded after assignment to interventions (e.g., trial participants, care providers, outcome assessors, data analysts), and how	NA
	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis		
Data collection methods	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (e.g., duplicate measurements, training of assessors) and a description of study instruments (e.g., questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	4
	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	4
Data management	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (e.g., double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	4
Statistical methods	Statistical methods for analyzing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	4
	Methods for any additional analyses (e.g., subgroup and adjusted analyses)	4
	Definition of analysis population relating to protocol non-adherence (e.g., as randomized analysis), and any statistical methods to handle missing data (e.g., multiple imputation)	4
Methods: Monitoring		
Data monitoring	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, explanation of why DMC is not needed	NA
	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions/trial conduct	3,4
Auditing	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination		
Research ethics approval	Plans for seeking research ethics committee/institutional review board (REC/IRB)	2
Protocol amendments	Plans for communicating important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) to relevant parties (e.g., investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	2
Consent or assent	Who will obtain informed consent or assent from potential trial participants or authorized surrogates, and how (see Item 32)	3
	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	4
Declaration of interests	Financial and other competing interests for principal investigators for the overall trial and each study site	6
Access to data	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	4
Ancillary and post trial care	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (e.g., via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	NA
	Authorship eligibility guidelines and any intended use of professional writers	NA
	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices		
Informed consent materials	Model consent form and other related documentation given to participants and authorized surrogates	Appendix II
Biological specimens	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 explanation and elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT group under the creative commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license. #Please note: Page numbers refer to the original version of this manuscript and may differ in the final published article.

APPENDIX II

Informed Consent Form

Patient ID----------

I_____Age_____years, S/o, D/o, W/o _____

Resident of_____voluntarily and of my own free will, consent to participate in the research project titled "Efficacy and Safety of daily versus alternate day add-on therapy with teneligliptin in type 2 diabetes mellitus patients: An open label, parallel group, randomized controlled study" being conducted by Dr. Suave, Post graduate Junior Resident, Department of Pharmacology, Dr. Harmanjit Singh, Assistant professor, Department of Pharmacology, GMCH, Sector 32, Chandigarh, Dr. Mandeep Singla, Assistant professor, Department of General Medicine, GMCH, Sector 32, and their team.

The principal investigator has given me a full explanation of the nature, purpose and the likely duration of the study and what I will be expected to do. The information sheet given to me is also in a language familiar to me.

I have been given the opportunity by the Principal Investigator to question all aspects of the study and have understood the advice/information given; as a result, I agree to cooperate fully with the Principal Investigator. I understand that the Principal Investigator of the study may stop the study or stop my participation in the study any time, for any reason, without my consent.

I have been informed that the study may or may not be of direct benefit to me but will enhance the medical knowledge in the field and be of benefit in medical care/for the benefit of the society by improving health care, monitoring, health policies or filling the gap in existing knowledge.

The nature and purpose of the study and its potential risks/ benefits and expected duration of the study have been explained to me in detail. I understand that my participation is voluntary. There is no extra cost involved in participating in this study. I am aware that I am free to withdraw at any time, without giving any reason. If I do so I will not be denied further hospital care and will continue to receive the best available facilities at GMCH, Sector 32, Chandigarh.

I have been assured that my medical records will be treated with utmost confidentiality and will be revealed only to other doctors/scientists involved in the study. The results of this study may be published in a scientific journal, but I will not be identified by name/image unless I give written informed consent or if it is required by the law/ enforcement agencies/ privileged communication.

The above has been explained to me in the language I understand. I have been informed that I can contact the study investigators Dr. Suave at any time on the mobile no. 8209858645, Dr. Harmanjit Singh, mobile no. 9968118472, Dr. Mandeep Singla, mobile no. 9815990985 and in any other case of other case the Director-Principal or Chairman, Institutional Ethics Committee, GMCH, Sector 32, Chandigarh.

Signature/ Thumb impression of the Participant with Date and place

Signatures of impartial witness with Date and place

Name and address of the witness

Signature of the investigator with Date and place