PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Molidustat for the treatment of renal anaemia in patients with dialysis-dependent chronic kidney disease: design and rationale of three phase 3 studies
AUTHORS	Akizawa, Tadao; Taguchi, Megumi; Matsuda, Yoshimi; Iekushi, Kazuma; Yamada, Takashi; Yamamoto, Hiroyasu

VERSION 1 - REVIEW

REVIEWER	Matthew Roberts Eastern Health Clinical School, Monash University, Australia
REVIEW RETURNED	02-Nov-2018

GENERAL COMMENTS	This protocol manuscript applies to three studies so again, the reader needs to be clear what applies to all studies and what applies to the individual studies. The “MIYABI” acronym is slightly misleading in that there is no assessment of symptoms in any of these studies (or the MIYABI ND ones). The objectives are stated generally on pp 5 (Introduction) for the suite of “MIYABI” trials. The Abstract provides more detail of what is meant by efficacy for the three studies. Also in the Introduction – the risks of ESAs are stated quite strongly in the second paragraph. Pure red cell aplasia is now exceedingly rare and the tumour progression is a potential risk that needs to be weighed against the benefits. In the 3rd paragraph of the Introduction (line 46, p4), the “undesirable conditions” should be expanded upon. In referring to the phase 2 studies on p5, this should be referred to as “unpublished data” until the manuscript under consideration has been accepted. The abbreviation “PD” is used for pharmacodynamics on p5 and for peritoneal dialysis in the Abstract, on p6 and possibly elsewhere – different (or no) abbreviations should be used for these terms. Methods Table 2 should be a supplementary table, consistent with the other manuscript. The randomised trial MIYABI HD-M is an appropriate design. The design of MIYABI HD-C and MIYABI PD seems to be based more on the concern about limited numbers of patients. A single arm study should only be chosen if it can answer the research question. Without a control arm, it will be difficult to know if the Hb improved because of the drug or because of some other reason. These two studies have a much weaker study design. The Screening period is not adequately described. How often will patients be seen during the screening period? Is eligibility based on two measurements of Hb within the stated ranges? If so, how

	far apart will the measurements be? With patients in MIYABI HD-M, will there be a period of time after switching from their pre-study ESA to darbepoetin? There may be a period of instability after switching and it may take time to fine tune the darbepoetin dose. A rationale for doing this, or not doing this, should be provided. Reference is made to a pharmacokinetic study is made in the middle of p8. Will this be for all patients or an optional substudy? How many samples are required to calculate AUC? Will this enrol patients from all three studies? What is the specific aim of doing this and what is the main outcome of interest? Where two primary outcomes are listed (MIYABI HD-C), how will the rate of rise be assessed statistically? As in the non-dialysis studies, requiring the upper and lower bounds of each individual patients mean Hb from 4 measures to be within range may prove too stringent. Why has this approach been taken? Why do previous ESA dose and previous thromboembolic events need to be included in the ANCOVA model for change in Hb? As stated, the sample sizes for MIYABI HD-C and MIYABI PD are determined on “feasibility” and the purpose of these trials, and whether to conduct them at all, should be reconsidered. The sample size for MIABI HD-M gives two levels of power. The non-inferiority to molidustat assumptions are given. However, the “>=98% power” to establish that mean Hb levels are within target range is not explained. This should be expanded upon. Is this based on mean levels or on the proportion of patients within the target? What assumptions were used for this power calculation? Discussion: Om p10, line 22 – “It is anticipated that the three phase three trials described here” – are MIYABI HD-C and MIYABI PD really phase 3 trials (and also p11, line 22)? It is stated that Ethics approval has been obtained. The name of the Ethics Committee and the application number should be provided. A timeline for the actual study would be helpful. Has the study commenced recruiting? When is recruiting anticipated to finish? The SPIRIT checklist is not specifically referred to.

REVIEWER	Bruce Spinowitz New York Presbyterian Queens Weill Cornell School of Medicine USA
REVIEW RETURNED	20-Nov-2018

GENERAL COMMENTS	1- The trials are not adequately powered to assess safety issues related to major atherosclerotic CV events- which is a significant issue for ESA use in the esrd population. 2- What is the frequency of VEGF level testing 3- Based on cited reference 22, any increase in EPO level , cannot be presumed to be of renal origin as stated in discussion(page 11) 4- A brief description of supplemental iron use should be stated , not simply reference on page 7(ref # 31)

REVIEWER	Titi Chen University of Sydney Australia
REVIEW RETURNED	07-Jan-2019

GENERAL COMMENTS	The manuscript entitled “Molidustat for the treatment of renal anaemia in patients with dialysis-dependent chronic kidney disease: design and rationale of three phase 3 studies” reports the methodologies of three Japanese trials investigating the efficacy of HIF-PHI Molidustat in dialysis patients. Molidustat is one of four HIF-PHI, which have completed phase 2 trial and are currently undergoing phase 3 clinical trials. The current manuscript consists of 3 trials, with the first being a non-inferiority RCT (MIYABI HD-M) comparing Molidustat with Darbepoetin alfa. Compared with a previous open-label phase 2b trial, (DIALOGUE 4), the current study has a larger sample size and longer follow up period. The other two trials in the manuscript are single armed with relatively small sample size. These two trials, for the first time, investigated Molidustat in PD (MIYABI PD) patients and HD (MIYABI HD-C) patients not on ESA. The studies are well designed. For phase 3 studies, one of the limitations of the trials was the relatively small sample size of the two single armed trials and the single armed design, which are due to feasibility and limited available patients. Could the authors please kindly clarify the following : 1. For MIYABI HD-M, please detail the type of randomization and method used to randomize sample. 2. For MIYABI HD-M, please clarify who was blinded and how? 3. Please specify the role of study funder (Bayer) plays in the study design and data collection, analysis and interpretation. 4. Page 3 strengths and limitations of the studies – only strengths are discussed; limitations are not discussed.

VERSION 1 – AUTHOR RESPONSE

Response to reviewer comments

Reviewer comment	Response	Revision
Reviewer #1		
This protocol manuscript applies to three studies so again, the reader needs to be clear what applies to all studies and what applies to the individual studies.	Several sentences and paragraphs have been revised as suggested.	‘Methods and planned analysis’ section
The “MIYABI” acronym is slightly misleading in that there is no assessment of symptoms in any of these studies (or the MIYABI ND ones).	Thank you for the comment. Upon reflection, the MIYABI acronym might be slightly misleading but the acronym has been described in the protocol which has been approved by the Japanese Pharmaceuticals and Medical Devices Agency.	No change
The objectives are stated generally on pp 5 (Introduction) for the suite of “MIYABI” trials. The Abstract	We have added some text to the Abstract to clarify the primary objective in the MIYABI HD-M trial. We have	Abstract (lines 40 and 41),

provides more detail of what is meant by efficacy for the three studies.	also added some text to the Introduction to clarify the objectives in the three MIYABI trials covered in this paper, rather than for the whole MIYABI programme. Further details about objectives and variables in the three studies are in the Methods section (lines 131–134 and 212–265).	Introduction (lines 121 and 122)
Also in the Introduction – the risks of ESAs are stated quite strongly in the second paragraph. Pure red cell aplasia is now exceedingly rare and the tumour progression is a potential risk that needs to be weighed against the benefits.	We agree that pure red cell aplasia (PRCA) is rare and have revised the sentence accordingly. We also deleted the text about tumour progression and made is clearer that thrombosis was in patients with cancer.	Line 80–83.
In the 3rd paragraph of the Introduction (line 46, p4), the "undesirable conditions" should be expanded upon.	We agree and have revised the sentence.	Lines 95 and 96
In referring to the phase 2 studies on p5, this should be referred to as "unpublished data" until the manuscript under consideration has been accepted.	We have included the recently published DIALOGUE studies paper (Macdougall et al, 2019) and refer to the DIALOGUE extension studies paper as "unpublished data".	Lines 114 and 115
The abbreviation "PD" is used for pharmacodynamics on p5 and for peritoneal dialysis in the Abstract, on p6 and possibly elsewhere – different (or no) abbreviations should be used for these terms.	We agree. We now use the word "pharmacodynamics" instead of "PD".	Lines 119, 121 and 133
Table 2 should be a supplementary table, consistent with the other manuscript.	We agree.	New supplementary table 1
The randomised trial MIYABI HD-M is an appropriate design. The design of MIYABI HD-C and MIYABI PD seems to be based more on the concern about limited numbers of patients. A single arm study should only be chosen if it can answer the research question. Without a control arm, it will be difficult to know if the Hb improved because of the drug or because of some other reason. These two studies have a much weaker study design.	We appreciate the reviewer's concerns on this point. We understand the concern about the design of MIYABI HD-C and MIYABI PD and sample sizes, therefore we have highlighted these limitations further in the paper.	Line 311–316
The Screening period is not adequately described. How often will patients be seen during the screening period? Is eligibility based	We have now included a description of the screening periods in the text.	Line 136–141

on two measurements of Hb within the stated ranges? If so, how far apart will the measurements be? With patients in MIYABI HD-M, will there be a period of time after switching from their pre-study ESA to darbepoetin? There may be a period of instability after switching and it may take time to fine tune the darbepoetin dose. A rationale for doing this, or not doing this, should be provided.	The time period after switching from the pre-study ESAs takes into account the half-life of the ESA. Further details relating to this are specified in table 1. "Treated with the same ESA for ≥8 weeks before randomisation (weekly or biweekly dose of darbepoetin alfa, monthly or biweekly dose of epoetin beta pegol, OR weekly, biweekly, twice or three times per week dose of epoetin alfa/beta, and having had no more than one dose change during the 8 weeks before randomisation)." We have also included a description the time period for patients washed out from ESAs in a footnote under table1. "*For patients washed out from ESAs, the mean Hb level before dialysis (at least two measurements taken ≥2 days apart, assessed by the central laboratory) must have decreased by ≥0.5 g/dL after the last ESA administration, AND the interval from the last ESA administration to study drug assignment should be >1 week for epoetin alfa, >2 weeks for darbepoetin alfa or >4 weeks for epoetin beta pegol."	Table 1
Reference is made to a pharmacokinetic study is made in the middle of p8. Will this be for all patients or an optional substudy? How many samples are required to calculate AUC? Will this enrol patients from all three studies? What is the specific aim of doing this and what is the main outcome of interest?	In the following sentence, which includes the aim of the PK work, we have made some revisions to clarify that this will be done as part of each study and that all patients will be involved: "In each study, to investigate systemic exposure to molidustat and the relationship between molidustat exposure and response, sparse sampling from all patients will be conducted for pharmacokinetics and pharmacodynamics". With regard to the number of samples required to access pharmacokinetics, it's stated in the paper that "If possible, molidustat exposure parameters (eg, C_{max}, AUC) and the relationship between molidustat exposure and treatment effects will be evaluated".	Line 224–226

	The intention is to investigate the impact of intrinsic and extrinsic covariates on molidustat exposure. The magnitude of effect of selected covariates will be reported, if any.	
Where two primary outcomes are listed (MIYABI HD-C), how will the rate of rise be assessed statistically?	Thank you for the comment. We have described in the following sentence: “In MIYABI HD-C, the primary efficacy variables (rate of rise in Hb and responder rate) and their two-sided 95% confidence intervals (CI) will be estimated using one-sample t-statistics and the Clopper–Pearson method, respectively”.	No change (relevant lines are 240–242)
As in the non-dialysis studies, requiring the upper and lower bounds of each individual patients mean Hb from 4 measures to be within range may prove too stringent. Why has this approach been taken?	The analysis for primary efficacy in MIYABI HD-M is that the mean of the mean Hb levels per patient is within target range, not all of 4 measurements of each patient Hb.	No change
Why do previous ESA dose and previous thromboembolic events need to be included in the ANCOVA model for change in Hb?	The ANCOVA model requires inclusion of thromboembolic events and previous ESA dose because the randomization will be stratified by previous ESA dose and previous thromboembolic events.	No change
As stated, the sample sizes for MIYABI HD-C and MIYABI PD are determined on “feasibility” and the purpose of these trials, and whether to conduct them at all, should be reconsidered.	We appreciate the reviewer’s concerns on this point. As we mentioned above, we understand the concern about the design of MIYABI HD-C and MIYABI PD and sample sizes, therefore we have highlighted these limitations further in the paper.	Line 311–316
The sample size for MIABI HD-M gives two levels of power. The non-inferiority to molidustat assumptions are given. However, the “>=98% power” to establish that mean Hb levels are within target range is not explained. This should be expanded upon. Is this based on mean levels or on the proportion of patients within the target? What assumptions were used for this power calculation?	We have revised the sample size paragraph, which now includes the following explanation: “If 150 patients are randomised to the molidustat group, the power to establish that mean Hb levels are within target levels during the evaluation period is ≥98%, assuming a standard deviation of 1.3–1.5g/dL from the previous phase 2b studies”.	Line 267–278
Om p10, line 22 – “It is anticipated that the three phase three trials described here” – are MIYABI HD-C and MIYABI PD really phase 3 trials (and also p11, line 22)?	We appreciate the reviewer’s concerns on this point. As we mentioned above, we understand the concern about the design of MIYABI HD-C and MIYABI PD and sample sizes, therefore we	Line 311–316

	have highlighted these limitations further in the paper.	
It is stated that Ethics approval has been obtained. The name of the Ethics Committee and the application number should be provided.	The MIYABI HD-C has been approved by the institutional review board of All Tohoku Clinical Trial Review and Audit Organization (application number: 20171204) and another 20 sites. The MIYABI PD has been approved by the institutional review board of Kyushu University Hospital (application number: 20180221) and another 26 sites. The MIYABI HD-M has been approved by the institutional review board of Ibaraki Prefectural Central Hospital (application number: 20180524), Asahikawa-Kosei General Hospital (20180806) and another 51 sites.	No change
A timeline for the actual study would be helpful. Has the study commenced recruiting? When is recruiting anticipated to finish?	We have included in the text that "The three trials commenced in the first half of 2018 and have finished recruiting".	Line 134–135
The SPIRIT checklist is not specifically referred to.	The protocols for all three studies were written in accordance with SPIRIT guidelines, with the exception of item number 15 (strategies for achieving adequate participant enrolment to reach target sample size) and 31b (authorship eligibility guidelines and any intended use of professional writers).	No change
Reviewer #2		
1- The trials are not adequately powered to assess safety issues related to major atherosclerotic CV events which is a significant issue for ESA use in the esrd population.	We agree with the reviewer and have added text accordingly in the Discussion.	Line 309–311
2- What is the frequency of VEGF level testing	VEGF level will be tested at baseline (week 0) in each study and: in MIYABI HD-C, end of treatment (week 24) and end of follow-up (week 28); in MIYABI PD end of treatment (week 36) and end of follow-up (week 40); in MIYABI HD-M, end of the efficacy evaluation period (week 36), end of treatment (week 52) and end of follow-up (week 56).	No change
3- Based on cited reference 22, any increase in EPO level , cannot be	We agree. We have added "predominately in the kidney".	Line 324–325

presumed to be of renal origin as stated in discussion(page 11)		
4- A brief description of supplemental iron use should be stated , not simply reference on page 7(ref # 31)	We agree with the reviewer and have updated the manuscript accordingly. The following sentence has been added: “Iron supplementation will be administered to reach with a target serum ferritin level of at least 100 ng/mL or transferrin saturation of at least 20%”.	Line 207–209
Reviewer #3		
1. For MIYABI HD-M, please detail the type of randomization and method used to randomize sample.	The following sentence has been added: “Allocation to treatment arms will be achieved using an interactive voice/web response system (IxRS) at the first (baseline) visit”.	Line 163–164
2. For MIYABI HD-M, please clarify who was blinded and how?	We have revised and added to the following text: “All investigators and patients in MIYABI HD-M will be blinded to treatment allocation. In cases of emergency, such as occurrence of a suspected, unexpected, serious AE, when the investigator needs to know which drug has been allocated, unblinding will occur by entering the emergency key code for the relevant patient into the IxRS”.	Line 167–168
3. Please specify the role of study funder (Bayer) plays in the study design and data collection, analysis and interpretation	We have revised the funding statement as: “FUNDING These trials are funded by Bayer Yakuhin. The trials were designed and are being conducted by employees of Bayer Yakuhin, in consultation with healthcare professionals including TA and HY”. Relevant information is also in the Acknowledgements, Author Contributions and Competing Interests sections.	Line 355–357
4. Page 3 strengths and limitations of the studies – only strengths are discussed; limitations are not discussed.	We agree. We’ve added a new paragraph in the Discussion.	Line 307–318

VERSION 2 – REVIEW

REVIEWER	Matthew Roberts Eastern Health Clinical School, Monash University, Australia
REVIEW RETURNED	27-Feb-2019

GENERAL COMMENTS	Overall, the manuscript has been improved and most of the changes made appear appropriate. My residual concerns are listed below: An acronym indicating that the study is about symptoms when the "sYmptoms of renal Anaemia:" are not assessed at all still sits very uncomfortably with me, regardless of whether the protocol was approved by another agency. The main outcomes are related to haemoglobin levels. I find this problematic as the acronym is referred to throughout the protocol. The SPIRIT Guideline is listed but not as a checklist showing how and where each point is covered in the protocol.

REVIEWER	bruce spinowitz new york presbyterian queens flushing ny usa research support from fibrinogen,gsk and akebia
REVIEW RETURNED	19-Feb-2019

GENERAL COMMENTS	ine 199 re: Hgb goal of 11-13. Is that the treatment goal for PD in Japan? If yes, so state. Why is EQ-5D-SL only noted in supplement? Mention it's use in Methods.

VERSION 2 – AUTHOR RESPONSE

Reviewer #1 comments		
Overall, the manuscript has been improved and most of the changes made appear appropriate. My residual concerns are listed below: An acronym indicating that the study is about symptoms when the "sYmptoms of renal Anaemia:" are not assessed at all still sits very uncomfortably with me, regardless of whether the protocol was approved by another agency. The main outcomes are related to haemoglobin levels. I find this problematic as the acronym is referred to throughout the protocol.	Thank you for your feedback. We understand your concern that the MIYABI acronym expansion is potentially misleading and therefore have changed it to the following: "MolIdustat once dailY improves renal Anemia By Inducing EPO".	Line 25–26 Line 119–120
The SPIRIT Guideline is listed but not as a checklist showing how and where each point is covered in the protocol.	The completed SPIRIT checklist is included below.	No change
Reviewer #2 comments		
line 199 re: Hgb goal of 11-13. Is that the treatment goal for PD in Japan? If yes, so state.	Japanese clinical guidelines suggest target Hb levels between 11–13 g/dL for patients on peritoneal dialysis. This has been added to the text, as follows: "…and ≥11.0 to <13.0 g/dL in	Line 183–184

	MIYABI PD, as per Japanese guideline recommendations.[31]"	
Why is EQ-5D-SL only noted in supplement? Mention it's use in Methods.	This has been added to the methods as follows: "…and assessment of health-related quality of life using the EuroQol 5-dimension 5-level questionnaire ."	Line 221–222

SPIRIT 2013 Checklist

Section/item	Item No	Description	Page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 13
	2b	All items from the World Health Organization Trial Registration Data Set	Not included[a]
Protocol version	3	Date and version identifier	Not included[a]
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Not included[a]
	5b	Name and contact information for the trial sponsor	13
	5c	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	13

	5d	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)	Not included[a]
Introduction			
Background and rationale	6a	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	4–5
	6b	Explanation for choice of comparators	11[b]
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	6, Table 1
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	17–18, Supplementary Table 1
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7–8, Table 1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Not included[a]
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Not included[a]

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	8–9, Table 2
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	None
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6–7[b]
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6–7[b]
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6–7[b]

Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Not included[a]
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	7[b]
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, 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	8–9, Table 2
	18b	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	Not included[a]
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Not included[a]
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9–10
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Not included[a]
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			

Data monitoring	21a	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, an explanation of why a DMC is not needed	7
	21b	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	Not included[a]
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Table 2
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not included[a]
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	12
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Not included[a]
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Not included[a]
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	n/a
Confidentiality	27	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	Not included[a]

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Not included[a]
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Not included[a]
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13
	31b	Authorship eligibility guidelines and any intended use of professional writers	None
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not included[a]
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not included[a]
Biological specimens	33	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	n/a

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

[a]Not included in published article, but present in full protocol document.

[b]For MIYABI HD-M only, as MIYABI HD-C and MIYABI PD are single arm, open-label trials.