Supplementary Online Content 3


Data and Safety Monitoring Committee (DSMC) Charter
Therapeutic Evaluation of STeroids in IgA Nephropathy Global study
TESTING Study
Protocol Number: GI-R-01-2011

Data Safety Monitoring Committee (DSMC) Charter

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1. BACKGROUND
This study aims to evaluate the long-term efficacy and safety of a 6-8 month regimen of tapering corticosteroid therapy i.e. oral methylprednisolone/matching placebo on a background of routine RAS inhibitor therapy in 1300 patients with IgA nephropathy and features suggesting a high risk of progression. The primary objective will be to determine if adding oral methylprednisolone to best available standard care for 6-8 months reduces the risk of the composite outcome of persistent 50% reduction in eGFR, end stage kidney disease and death due to kidney disease, in patients with progressive IgA nephropathy.

The DSMC will report to the TESTING study Executive Committee and will receive technical support from the independent Statistics Group.

2. OBJECTIVES OF THE DATA SAFETY MONITORING COMMITTEE (DSMC)
The objectives for the DSMC will be to:

- protect the safety of the study participants
- review the research protocols, plans for data and safety monitoring
- review the progress of the study and monitor adherence to the protocol, participant recruitment, outcomes, data quality, complications, and other issues related to participant safety
- monitor the assumptions underlying sample size calculations for the study and alert the investigators if they see substantial departures as the data accumulate
- ensure the confidentiality of the study data and the results of monitoring

The DSMC will consist of physicians and a statistician experienced in clinical studies. The committee will be supported by an unblinded statistician at The George Institute for Global Health. The independent DSMC will review safety data on an on-going basis and may recommend the TESTING study Executive Committee to stop or amend the study based on safety findings.
3. MEMBERS OF THE DSMC
The DSMC includes experts in clinical medicine, nephrology, clinical trials, and statistics. The names of the DSMC members and the consultants to the DSMC, their voting rights, affiliations, and contact information are listed in Attachment 1. The DSMC may call upon other experts to attend DSMC meetings to provide information and/or advice regarding unanticipated findings or issues. They are not considered DSMC members and cannot vote in DSMC meetings.

4. RESPONSIBILITIES OF THE DSMC CHAIRPERSON AND MEMEBERS
The DSMC serves as an independent expert advisory group for the TESTING study. The DSMC is responsible for determining its operational procedures and acting in accordance with its approved DSMC charter. If changes to the charter are required, amendments will be prepared and agreed to by the DSMC and the TESTING study Executive Committee.

Throughout its tenure, the DSMC will undertake TESTING study data reviews while maintaining the scientific integrity of the trials. The Institute of Nephrology Peking University and The George Institute for Global Health and investigators will retain ultimate responsibility for the safety of all subjects enrolled in the TESTING study.

Following each DSMC meeting, the DSMC will provide the TESTING study Executive Committee with a written DSMC Meeting Report summarising their recommendations, which will not include references to unblinded data.

**DSMC Chairperson:** The TESTING study Executive Committee have appointed David Jayne as the chairperson of the DSMC. The chairperson will:

- Sign off on the DSMC charter (and any subsequent amendments), indicating the agreement of the DSMC to conduct its operations in accordance with the charter.
- Ensure that DSMC meetings are scheduled.
- Work with the Statistics Group to ensure that the Data Monitoring Report, consisting of unblinded data listings and summaries, is received by the DSMC members within the given timeframes
- Chair the DSMC meetings.
- Act as the contact between the DSMC and the TESTING study Executive Committee by discussing the issues and representing the views of the DSMC without jeopardising the integrity of the data
- Record minutes of conversations with the TESTING study Executive Committee.
- Approve the DSMC meeting minutes and sign the DSMC Meeting Report summarising the conclusions and recommendations of the DSMC from each meeting.
- Inform the TESTING study Executive Committee Chairpersons of the need for additional DSMC meetings and identified issues, proposed meeting date(s), and specifications for data review.
- Ensure that the DSMC meeting minutes and other documentation are maintained appropriately.

The DSMC Chairperson will receive administrative support from the Statistics Group as required.

**DSMC Members:** Each member is responsible for maintaining strict confidentiality of the study data. Members will not share any study data or information about the study with any individual external to the DSMC. The DSMC statistician may contact the statistician in the Statistics Group (see below) directly with questions regarding the operational details associated with the data analyses and summary tables.

Each member will review the Data Monitoring Report thoroughly prior to each DSMC meeting. A member who believes he or she may have a potential intellectual or financial conflict of interest during the course of review of the data must inform the chairperson of the DSMC. In such cases, the DSMC meeting
minutes must document the disclosure of the potential conflict of interest and the outcome of the discussion, e.g., abstention of member from voting.

5. RESPONSIBILITIES OF STATISTICS GROUP

The Statistics Group is based at The George Institute for Global Health. Their names, roles in the project, and contact information are included in Attachment 2. The Statistics Group will have primary responsibility for:

- Ensuring that the Data Monitoring Report provided to the DSMC is complete and accurate.
- Storing copies of the Data Monitoring Reports until after the completion of the TESTING study and database lock.
- After database lock sending to the TESTING study Executive Committee a copy of each Data Monitoring Report along with any other applicable documentation.
- Performing additional analyses that are requested by the DSMC, which may have the potential to unblind individuals to the results of the study. All such additional analyses will be similarly archived and made available at study termination.

In addition, the Statistics Group will assist the DSMC chairperson with the following responsibilities:

- Ensure that DSMC meetings are scheduled via ICC PM’s coordinating.
- Oversee the preparation of the Data Monitoring Report, ensuring that it includes the required unblinded data listings and summaries, and that it is received by the DSMC members within the given timeframes
- Record and finalise minutes of closed sessions meeting with the DSMC and the TESTING study Executive Committee, review and help finalise other meeting minutes prepared by TESTING project team.
- Ensure that the DSMC meeting minutes and other documentation are maintained appropriately.
6. RESPONSIBILITIES OF THE TESTING EXECUTIVE COMMITTEE

The TESTING study Executive Committee is responsible for:

- constituting the DSMC
- appointing the DSMC chairperson
- agreeing to the DSMC charter
- coordinating resources and procedures to support DSMC operations
- providing the DSMC with relevant information regarding the drug and conduct of the clinical trial including protocol amendments
- communicating the DSMC recommendations
- communicating to the DSMC the action taken based on DSMC recommendations
- reviewing unblinded information from the DSMC in the event that the DSMC recommends to stop the trial prior to scheduled closure

The names of the TESTING study Executive Committee, their roles, and contact information are included in Attachment 3.

7. DSMC MEETINGS

An initial meeting of the DSMC will be held prior to receipt of any safety or efficacy data from TESTING. The purpose of the meeting will be to:

- Familiarize DSMC members with the TESTING study, and the therapeutic area.
- Review and approve the content and format of the Data Monitoring Reports
- Develop more specific operational guidelines, i.e. frequency of meetings, logistics of meetings.
- Review the DSMC charter and complete the procedural sections of the DSMC charter.

Subsequent meetings will be scheduled at regular intervals (approximately every 6 months). DSMC members are expected to participate in each meeting.
Meetings may be held in person, by videoconference or teleconference. On occasion, the DSMC may require consultants with additional expertise in the review of safety or efficacy data. These consultants will be bound by the same confidentiality requirements as regular DSMC members. The TESTING study Executive Committee must agree to the objectives and the presence of additional participants at DSMC meetings. This information must also be documented in the DSMC meeting minutes and the DSMC Meeting Report.

The DSMC may deem it necessary to hold additional, unscheduled, meetings. The DSMC chairperson will ensure that the request for additional analyses and meetings are consistent with the objectives of the DSMC as outlined in the charter. The DSMC chairperson must inform the TESTING study Executive Committee Chairperson of the issues, proposed meeting date(s), and specifications for data review and obtain agreement.

**Meeting format**

The DSMC meeting will begin with an open session followed by a closed session. George Institute or Peking University First Hospital project team members may present pertinent study information to the DSMC members during the open session. Investigators or experts serving as ad hoc advisors may be requested to attend an open session of the meeting. The closed session will be limited to the DSMC members, consultants to the DSMC if needed, and designated staff from Statistics for presentation of the unblinded data. An executive session can be called with DSMC members only if required. George Institute and Peking University First Hospital representatives and TESTING study Executive Committee members are excluded from participating in any closed or executive session of the DSMC.

**Meeting reports**

DSMC meeting minutes and the DSMC Meeting Report (Attachment 4) summarising the conclusions and recommendations of the DSMC will be drafted after each meeting. The DSMC Chairperson will oversee the finalisation of the
DSMC meeting minutes and the DSMC Meeting Report and sign both documents. The DSMC meeting minutes should include important considerations that led to the DSMC recommendations. The DSMC meeting minutes will not be sent to The George Institute, Peking University First Hospital or the TESTING Study Executive Committee until after the completion of the study and database lock. The DSMC Meeting Report, which will be sent to the TESTING study Executive Committee, will include DSMC conclusions and recommendations without reference to unblinded data.

**Meeting schedule**

To ensure ongoing safety surveillance the DSMC will review un-blinded data periodically, two of these reviews will be interim analyses. The review will be based upon the best available data, which may include events adjudicated by the EAC and un-adjudicated investigator-reported data.

8. PREPARATION AND DISTRIBUTION OF DATA FOR DSMC REVIEW

The TESTING study database is held and maintained by The George Institute. Likewise, the randomisation codes have been prepared and are held by The George Institute. The preparation of DSMC reports will be done on the basis that only the independent Statistics Group and the DSMC will have access to unblinded data.

The unblinded statistician will obtain unblinded data extracts one month prior to the planned DSMC meeting. The data will be saved in an access-restricted folder; the unblinded statistician is the only person has the access to randomization code.

The preparation of the Data Monitoring Reports will be done to an agreed standard analysis and reporting format developed by the independent Statistics Group with the support of the project statistician at The George Institute and
under the direction of the DSMC. The format will be signed off by the TESTING study Executive Committee.

The independent Statistics Group will send DSMC members Data Monitoring Reports at least 5 working days prior to scheduled meetings in a password-encrypted PDF file.

9. GUIDELINE FOR REGULAR MONITORING OF SAFETY AND EFFICACY

DSMC review will be conducted approximately every 6 months after enrollment commences. The DSMC will also respond to specific requests made by the TESTING study Executive Committee.

At the conclusion of each regular review the DSMC will recommend to the TESTING Executive Committee in the DSMC Meeting Report/ Letter from the committee one of the following:

1. To continue TESTING unchanged
2. To discontinue TESTING
3. To modify TESTING
4. To request additional expert review after which a recommendation will be made
5. To request additional analyses of the Statistics Group after which a recommendation will be made

The DSMC will base the primary review on the entire randomised trial population although additional analyses of subgroups may be done as requested by the DSMC.

A recommendation to discontinue the TESTING study prematurely will be based upon their being clear evidence that the agent provides protection or causes harm for an important clinical outcome. O'Brien Fleming method will be used to define the stopping boundaries for efficacy. The final recommendation to the TESTING study Executive Committee will remain at the discretion of the DSMC but will be based upon agreed standards for the interpretation of interim analyses in clinical trials. The TESTING study Executive Committee will subsequently
have the responsibility of evaluating and implementing as they consider appropriate the recommendations provided by the DSMC.

A recommendation to modify the TESTING study will be accompanied by the maximum possible information that the DSMC can provide to the TESTING trial Executive Committee without affecting the integrity of the trial. Once again, the TESTING study Executive Committee will have the responsibility of evaluating and implementing the recommendations as they consider appropriate.

If additional expert opinion is to be sought or additional analyses are required prior to making a recommendation, the DSMC will work to schedule another meeting at the earliest possible opportunity.

10. GUIDELINE FOR REVIEW OF DATA FROM THE INTERIM ANALYSIS

The trial DSMC will monitor safety data on an ongoing basis, and will also perform two unblinded interim analyses for the primary outcome, based on a comparison of the primary endpoint in the two treatment groups with the use of a normal approximation for a two-sided test, when one third and two thirds of the events have occurred. A group sequential approach (O'Brien Fleming method) will be utilised.

The analyses will be performed by an independent statistician from the George Institute for Global Health, who is not involved in managing the trial. The DSMC can recommend the Central Executive Committee of the TESTING-Trial should
Adjust the duration of follow-up;
Terminate the study early if there is clear and substantial evidence of benefit;
Terminate the study early if the data suggests the risk of adverse events substantially outweighs the potential benefits
11. MAINTENANCE OF DOCUMENTATION
The DSMC chairperson with the support of the Statistical Group will compile and maintain the following documents:

- copy of the charter (and all amendments to the charter) and associated attachments and addenda
- a copy of the Investigator's Brochure
- protocols and protocol amendments for the TESTING study
- curriculum vitae for each DSMC member
- copies of the Data Monitoring Reports provided to the DSMC members
- minutes of each DSMC meeting, including conclusions or recommendations concerning the conduct or evaluation of the trial and any important considerations that led to the conclusions/recommendations
- DSMC reports provided to the TESTING study Executive Committee containing conclusions or recommendations without reference to unblinded data
- copies of key correspondence related to this DSMC

Upon completion of the trial and closure of the relevant clinical database(s), the documents will be forwarded to the TESTING Executive Committee for archiving.

12. LINES OF COMMUNICATION
All communication from the DSMC will be by the DSMC chairperson to the TESTING Executive Committee chair/deputy chair. The TESTING study Executive Committee chairperson/deputy will then further disseminate information to the TESTING study Executive Committee, The George Institute and Peking University First Hospital as required. The DSMC Chairperson will send to the TESTING study Executive Committee Chairperson a DSMC Meeting Report within 5 working days of each meeting, containing the committees’ recommendation, thereby documenting that the DSMC has reviewed the data. The report will divulge no details of DSMC discussions and especially no information regarding unblinded data. The TESTING study Executive Committee
chairperson will inform the DSMC chairperson of any decisions about changes to
the conduct of the trial within 5 days of receipt of the DSMC Meeting Report.

13. CONFIDENTIALITY
All materials and information are strictly confidential and may not be discussed or
disclosed with anyone external to the DSMC unless specifically authorised in this
charter.
Appendix 1: DSMC Members and Non-Voting Consultants to DSMC

<table>
<thead>
<tr>
<th>Members</th>
<th>Voting Rights</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name: David Jayne</td>
<td>Yes X No</td>
</tr>
<tr>
<td>Position and Affiliation: Reader in Vasculitis, University of Cambridge, UK</td>
<td></td>
</tr>
<tr>
<td>Phone: +44 1223 586796 Fax: +44 1223 586796</td>
<td></td>
</tr>
<tr>
<td>E-mail address: <a href="mailto:dj106@cam.ac.uk">dj106@cam.ac.uk</a></td>
<td></td>
</tr>
</tbody>
</table>

| Name: Tom Greene | Yes X No |
| Position and Affiliation: Professor of Epidemiology, Statistician and Director of the University of Utah School of Medicine, Salt Lake City, USA | |
| Phone: +1 801.585.5667 Fax: +1 801.581.3623 | |
| E-mail address: Tom.Greene@hsc.utah.edu | |

| Name: Mike Walsh | Yes X No |
| Position and Affiliation: A/Professor Department of Nephrology, Joint Member of the Department of clinical and biostatistics at McMaster university, Ontario, Canada | |
| Phone: +1 905 522 1155 Fax: +1 905 521 6153 Ext: 35016 | |
| E-mail address: lastwalsh1975@gmail.com | |

| Name: Angela Wang | Yes X No |
| Position and Affiliation: Associate Professor and Consultant, University of Hong Kong, Queen Mary Hospital. | |
| Phone: +852 22554949 Fax: +852 22555411 | |
| E-mail address: aymwang@hku.hk | |
Consultants to DSMC: will be amended if appointed by DSMC.
Appendix 2: Statistics Group Members

**Study Biostatistician - Blinded**
Name: Qiang Li
Phone: +61 2 9993 4516  Fax: +61 2 9993 4501 
E-mail address: qli@georgeinstitute.org

**Biostatistician - Unblinded**
Name: Laurent Billot
Phone: +61 2 9993 4581  Fax: +61 2 9993 4501
E-mail address: lbillot@georgeinstitute.org

**Programmer – Unblinded**
Name: Jayanthi Mysore
Phone: +61 2 8507 2540  Fax: +61 2 9993 4501
E-mail address: jravikumar@georgeinstitute.org
Appendix 3: TESTING study Central Executive Committee Members

CENTRAL EXECUTIVE COMMITTEE

Co-Chair: Hong Zhang (Peking University Institute of Nephrology, China)
Co-Chair: Vlado Perkovic (The George Institute for Global Health, Australia)

Members

Alan Cass (The George Institute for Global Health, Australia; Menzies School of Health Research, Charles Darwin University, Australia.)
Daniel Cattran (University Health Network, Canada)
Tak Mao Chan (University of Hong Kong, China)
John Feehally (University of Leicester, UK)
Jürgen Floege (University of Aachen, Germany)
Richard J. Glassock (UCLA David Geffen School of Medicine, USA.)
Vivek Jha (the Postgraduate Institute of Medical Education and Research, India)
David Johnson (Australasian Kidney Trials Network, Australia)
Adeera Levin (the University of British Columbia, Canada)
Zhihong Liu (Nanjing University School of Medicine, China)
Giuseppe Remuzzi (Mario Negri Institute for Pharmacological Research & Clinical Research Centre for Rare Diseases, Italy)
David Wheeler (Royal Free and University College Medical School, UK)
Mark Woodward (The George Institute for Global Health, Australia, & Department of Epidemiology, Johns Hopkins University, Baltimore, USA)
Yangfeng Wu (Peking University, China)
Minghui Zhao (Peking University Institute of Nephrology, China)
Appendix 4: Proforma for DSMC Meeting Report

To: Central Executive Committee Chairperson

Meeting Date:

Protocol:

Meeting Attendees:

The DSMC charged with the review of safety and efficacy data for the TESTING study reviewed Data Monitoring Report number <<insert>> dated <<insert>>.

Summary of discussions in open session of the meeting:

As a result, the DSMC recommendation is:

☐ To continue trial unmodified until next scheduled meeting.

☐ To continue trial unmodified, and plan an additional meeting. 
  The following date is proposed for the additional meeting: [insert dd/Mon/yyyy] (to be confirmed with Central Executive Committee Chairperson).

☐ To continue trial unmodified, and request additional expert review/analyses.

  Describe and provide timelines of additional review:

☐ To continue trial and amend protocol(s) as described:

  [Describe sections below and list protocol(s) to be amended]
To set up a meeting with The George Institute and Peking University First Hospital to discuss concerns of safety and/or efficacy within the clinical trial as outlined below.

Additional Comments:

Chairperson, Data Monitoring Committee for TESTING study

Date (Day Month Year)
Appendix 5 – Data Safety Monitoring Committee Charter Signature Sheet

I have read and approve this charter.

Name (print) __________________________________________________________

Signature ____________________________________________________________

Date of Signature (dd/mmm/yyyy)________________________________________