CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761238Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 127265

MEETING MINUTES

TG Therapeutics, Inc.
Attention: Anne Frederick, PhD
Vice President, Global Regulatory Affairs
343 Thornall Street, Suite 740
Edison, NJ 08837

Dear Dr. Frederick:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ublituximab.

We also refer to the teleconference between representatives of your firm and the FDA on April 6, 2021. The purpose of the meeting was to discuss the content and format of a biologics license application.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Sandra Folkendt, Regulatory Health Project Manager, at (240) 402-2804.

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Sincerely,

{See appended electronic signature page}
Paul R. Lee, MD, PhD
Deputy Director
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- TG slide deck

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: April 6, 2021, 11:00 am to 12:00 pm
Meeting Location: Teleconference

Application Number: IND 127265
Product Name: Ublituximab
Indication: Relapsing forms of multiple sclerosis

Sponsor Name: TG Therapeutics
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Paul R. Lee, MD, PhD
Meeting Recorder: Sandra Folkendt

FDA ATTENDEES

Office of Neuroscience
Eric Bastings, MD, Deputy Director, Office of Neuroscience

Division of Neurology 2
Nick Kozauer, MD, Director, Neurology 2
Paul R. Lee, MD, PhD, Deputy Director, Clinical Team Leader
David E. Jones, MD, FAAN, Clinical Reviewer
Laura Baldassari, MD, MSH, Clinical Reviewer
Jessica Stevens, MD, Clinical Reviewer
Tracy Peters, PharmD, Associate Director of Labeling
Alice T.D. Hughes, MD, Deputy Director for Safety, Division of Neurology 2

Office of Clinical Pharmacology
Xiaohan Cai, PhD, Clinical Pharmacology Reviewer

Office of Biostatistics
John Lawrence, Acting Statistics Team Leader
Xiang Ling, PhD, Statistical Reviewer

Office of Biotechnology Products (OBP)
Yan Wang, PhD, Product Quality Team Lead
Xiaoshi Wang, PhD, Product Quality Reviewer
Bruce Huang, PhD, Product Quality Reviewer

Office of Regulatory Operations
Paul David, RPh, RAC, Director, Project Management Staff
Sandra Folkendt, Senior Regulatory Project Manager

Controlled Substances Staff
Chad Reissig, PhD, Supervisory Pharmacologist

Office of Surveillance and Epidemiology
David Croteau, MD, FRCPC, Medical Officer DPV1
Carlisha Gentles, PharmD, Risk Management Analyst
Jacqueline Sheppard, PhD, Team Leader, Risk Management

Office of Scientific Investigations
Cara Alfaro, PharmD, BCPP Clinical Analyst

SPONSOR ATTENDEES
Hari Miskin, MS, Chief Development Officer
Peter Sportelli, Executive VP, Global Operations
Koby Mok, PhD, VP, Clinical and Medical Affairs
Anne Frederick, PhD, VP, Global Regulatory Affairs
Nicole Markus, Associate Director, Global Regulatory Affairs
Mark Glick, PhD, VP, Program Management
Yanzhi Hsu, PhD, VP, Biostatistics
Yihuan Xu, PhD, Senior Director, Biostatistics
Jackie Parker, VP, R&D Quality and Pharmacovigilance
Donald Huang, MD, VP, Pharmacovigilance Medical Oversight
Roshni Shah, PharmD, Director, Safety Scientist
Teja Turpuseema, Associate Director, Nonclinical

1.0 BACKGROUND

On October 22, 2015, TG Therapeutics submitted IND 127265 and proposed to study ublituximab in patients with relapsing forms of multiple sclerosis. Ublituximab is an anti-CD20 monoclonal antibody. In addition to studies in multiple sclerosis, the sponsor has active INDs for ublituximab in (b) (4) chronic lymphocytic leukemia (CLL) patients. TG Therapeutics submitted a biologics license application (BLA) for ublituximab in patients with chronic lymphocytic leukemia on March 25, 2021.

Following its initial submission, IND 127265 was placed on full clinical hold for unreasonable and significant risk of illness or injury to human subjects. On February 16, 2016, the clinical hold issues were resolved, and IND 127265 was allowed to proceed.

On April 27, 2016, the sponsor submitted a Type C meeting request for

general guidance on the design and execution of a Phase 3 program for this product, and the Division issued written response only (WRO) meeting minutes on July 8, 2016. Subsequently, TG Therapeutics and the Division reached agreement on 2 Special Protocol Assessments requests for Phase 3 protocols for IND 127265 on July 29, 2017:

> TG1101-RMS301, "Phase 3: UbLiTuximab In Multiple Sclerosis Treatment Effects (ULTIMATE I Study)".
>
> TG1101-RMS302, "Phase 3: UbLiTuximab In Multiple Sclerosis Treatment Effects (ULTIMATE II Study)".

The sponsor submitted a WRO meeting request for IND 127265 to discuss the pharmacology/toxicology development plan, and FDA issued WRO minutes on December 5, 2019.

A pre-BLA meeting request was submitted to the Division on February 12, 2021, and subsequently granted.

Other communications of note are Advice Letters issued by the Division on December 18, 2019, and August 25, 2020, concerning safety issues identified by the Division.

FDA sent Preliminary Comments to TG Therapeutics on April 2, 2021.

2.0 DISCUSSION

2.1. CMC

Question 1: Does the Agency agree with the proposed plan to evaluate immunogenicity in the BLA?

FDA Response to Question 1:

No, we do not agree. We acknowledge that you are currently developing the neutralizing antibody (Nab) detection assay due to an unexpected facility change. However, you should test samples that are positive for anti-drug antibodies (ADAs) with a validated Nab assay and submit the Nab data obtained in patients with relapsing forms of multiple sclerosis (RMS) at the time of the BLA submission.

From an immunogenicity assay perspective, we recommend that you complete the ongoing development of the Nab assay and submit the Nab assay validation report at the time of the BLA submission.

We noticed that you provided a highly summarized anti-drug antibodies (ADA) method validation data in Appendix 3. Because you did not provide a full method validation report, we are unable to provide comments on the summarized validation results. We

recommend that you validate the multiple-tiered immunogenicity assay in alignment with FDA Guidance for Industry, Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection 2019. The adequacy and acceptability of the ADA assay will be based on the data and information provided in the BLA.

Based on the information provided in Appendix 1. Table of Contents for the ublituximab BLA for RMS, you propose to include an Integrated Summary of Immunogenicity in eCTD subsection 5.3.5.3, "Reports of Analysis of Data from More than One Study". We recommend that you provide the following information in this Integrated Summary of Immunogenicity:

i. An immunogenicity risk assessment specific to your product;

ii. Details on the tiered immunogenicity strategy that you followed in your clinical program, and validation summaries for the various immunogenicity assay methods used in the program;

iii. Links to method development and validation reports for the immunogenicity assays used in your clinical studies, particularly those used to test immunogenicity samples from the pivotal clinical studies;

iv. Immunogenicity sampling plan(s) for all clinical studies that had immunogenicity assessment performed;

v. Summary results of immunogenicity analyses for all clinical studies that collected immunogenicity data, including the results of your correlation analysis between anti-drug antibody status and titers with pharmacokinetic/pharmacodynamic/efficacy/safety (adverse-events) data;

vi. Traceability of drug product lots used in all your clinical studies;

vii. All immunogenicity assays, that were used during clinical development and a description of which assays were used for which studies or patient groups.

Discussion:

No further discussion occurred.

2.2. Clinical

Question 2: Does the Agency agree that the results from Studies TG1101-RMS301 and TG1101-RMS302 adequately describe the efficacy profile of ublituximab for the proposed indication of ublituximab for the treatment of RMS in adults?

FDA Response to Question 2:

On face, the efficacy findings from Studies TG1101-RMS301 and TG1101-RMS302 appear to have the potential to support the filing of a BLA submission for the proposed

indication; however, an indication statement is a matter of review and cannot be determined prospectively without a review of the complete findings within a filed application.

We note that the active comparator in these studies was "bioequivalent teriflunomide." Your submission will need to contain data to support an assertion that the formulation of teriflunomide used in these studies is bioequivalent to the approved formulation of teriflunomide, and a determination of bioequivalence will be a matter of review.

We refer you to the "M4E(R2): The CTD — Efficacy Guidance for Industry" and the Guidance for Industry "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document." See also Attachment 2 for additional requests for the presentation of efficacy data in Module 5.

Discussion:

No further discussion occurred.

Question 3: Does the Agency agree that pooled safety data from Studies TG1101-RMS301 and TG1101-RMS302 comprising a total of 545 subjects treated with ublituximab in addition to the 48 subjects from Study TG1101-RMS201 provides sufficient safety data to characterize the profile of ublituximab so that the Agency may make a benefit-risk assessment in the proposed indication of ublituximab for the treatment of RMS in adults?

FDA Response to Question 3:

We do not agree. A safety database that does not include data from all of your clinical studies in individuals with RMS, including available safety data from the TG1101-RMS303 extension study, would be incomplete and insufficient to support filing of your BLA. We further remind you that a potentially sufficient and adequate safety database needs to include all adverse events that occurred during a clinical trial, regardless of the investigator-determination of relatedness to a study drug or the amount of time since the last administration of a study drug. The adequacy of your safety database to support a BLA ultimately will be a matter of review.

We recommend that the presentation of clinical safety data, including laboratory, vital signs, and narratives in the BLA submission be consistent with the advice enumerated in Attachment 1.

Discussion:

In addition to safety data from the completed TG1101-RMS301 and TG1101-RMS302 studies, the sponsor agreed to include safety data from the ongoing TG1101-RMS303 extension, using November 23, 2020, as a cutoff date, in its

planned BLA submission. The Division agreed to the sponsor's proposal to analyze separately concatenated Phase 3 data (TG1101-RMS301, TG1101-RMS302, and TG1101-RMS303) and concatenated Phase 2 data from TG1101-RMS201 and its extension).

Question 4: The Sponsor proposes to pool safety data from the Phase 3 studies, Studies TG1101-RMS301 and TG1101-RMS302, and present safety data from the Phase 2 single-arm study, Study TG1101-RMS201 concatenated with safety data from its extension study, Study TG1101-RMS201E, separately. The Sponsor does not plan to pool safety data from the Phase 3 studies with safety data from the Phase 2 studies. Does the Agency agree with this approach?

FDA Response to Question 4:

Given the differences in design between the Phase 3 and the Phase 2 RMS studies, it appears reasonable to have separate safety pools for the Phase 3 and the Phase 2 studies of ublituximab. The safety data from the TG1101-RMS303 extension study needs to be concatenated into the Phase 3 safety pool as you propose to do with the safety data from TG1101-RMS201 and its extension. See the response to Question 3.

Discussion:

No further discussion occurred.

Question 5: Does the Agency agree with the proposed list of adverse events of special interest (AESIs) for the safety analysis in Module 2.7.4 and in the ISS?

FDA Response to Question 5:

Your proposed list of adverse events of special interest appears reasonable; we advise the addition of hypogammaglobulinemia to this list as well. See also Attachment 1.

Discussion:

No further discussion occurred.

Question 6: Does the Agency agree with the analyses outlined in the Integrated Statistical Analysis Plan (ISAP)?

FDA Response to Question 6:

We do not agree with your definition of treatment emergent adverse event (TEAE). Given the duration of the pharmacodynamic effects of a monoclonal antibody targeting CD20, we do not agree that adverse events occurring more than 30 days after the last dose of the study medication should not be considered a TEAE. Additionally, the

definition of TEAE should not include considerations about investigator- or sponsor-determined relatedness. See the response to Question 3 and refer to Attachment 1 for further recommendations for the reporting of TEAEs.

Discussion:

No further discussion occurred.

Question 7: Does the Agency agree with the Sponsor's proposal not to include in the BLA any subject-level listings over 1000 pages but to make them available upon request?

FDA Response to Question 7:

We do not agree. Your application should be complete when submitted. See Attachments 1 and 2 regarding expectations of safety and efficacy data reporting, respectively.

Discussion:

No further discussion occurred.

Question 8: Does the Agency agree with the Sponsor's plan to submit summary-level clinical site datasets only for the two Phase 3 pivotal studies, TG1101-RMS301 and TG1101-RMS302? Does the Agency agree with the Sponsor's plan to submit financial disclosure information only for Studies TG1101-RMS301 and TG1101-RMS302?

FDA Response to Question 8:

Your proposal to submit only summary-level clinical site datasets (e.g., clinsite datasets) for the two Phase 3 studies is acceptable if clinical study-level information and subject-level data are included elsewhere in the submission. Financial disclosure information should be included for all of the Phase 2 and the Phase 3 studies of ublituximab in individuals with RMS.

Discussion:

No further discussion occurred.

Question 9: Does the Agency agree that the content of the 120-Day Safety Update Report be based on the ongoing extension Studies TG1101-RMS201E and TG1101-RMS303? Does the Agency agree with the safety data cutoff date of 01 May 2021 for the 120-Day Safety Update Report?

FDA Response to Question 9:

The safety cut-off date appears reasonable but would be expected to change if there is a significant delay in your application's submission. An interim safety analysis of the safety data available for Study TG1101-RMS301 also needs to be submitted in the BLA submission. See the response to Question 3. The 120-Day Safety Update Report therefore should include all safety data accrued since the cut-off date of the interim safety analysis of Study TG1101-RMS301 as well as the updated findings from Study TG1101-RMS201E.

Discussion:

No further discussion occurred.

Discussion of Attachment 1 - General Clinical Safety Requests

General Submission Contents:
5. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following: a) Title of the table or figure in the application, b) A hyperlink to the location of the table or figure with page number, c) A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used).

Sponsor Response:
The Sponsor assumes that all in-text tables and figures refer to those in Summary Documents.

Discussion:

The Division agreed with this assumption.

Other requests:
3. We request that you submit a sample integrated summary of safety datasets (with data definition file) for Division comments prior to submitting the BLA. This process could help to identify and resolve any potential issues of navigability or interpretability that could impact the review of your application.

Sponsor Response:
The Sponsor plans to submit a sample integrated summary of safety datasets prior to the submission of the BLA.

Discussion:

The Division agreed with this plan.

Other requests:
4. Provide an analysis that identifies all opportunistic infections.

Sponsor Response:
The Sponsor plans to provide an analysis of all opportunistic infections in the Summary of Clinical Safety.

Discussion:

The Division agreed that the Summary of Clinical Safety was an appropriate location for this analysis. The Division concurred that the use of standardized MedDRA queries (SMQ) for opportunistic infections seems appropriate.

Other requests:
6. Provide a table of all known cases of malignancy (or pre-malignant conditions) that have occurred in subjects who participated in the clinical development program. The table should include the study, subject number, event Preferred Term, cumulative drug dose received at the time of the event, latency from first dose to malignancy diagnosis, subject's age at the time of diagnosis, subject's country of origin, subject's sex, duration of follow-up for that subject, and a link to the narrative.

Sponsor Response:
The Sponsor plans to provide a table of all known cases of malignancy in the Summary of Clinical Safety.

Discussion:

The Division noted that this plan is acceptable. The Division also concurred that the use of standardized MedDRA queries (SMQ) for malignancies seems appropriate.

Discussion of Attachment 2 - General Clinical Efficacy Requests

Analyses:
5. Provide an analysis and a summary addressing the extent to which the sites with clinical investigators who disclosed financial interests contributed to the trial results. The analysis and summary should include a comparison of the primary outcome for each trial to support efficacy at sites that had investigators who disclosed financial interests with those sites that did not. Also, discuss the significance of the percentage of U.S. sites with investigators who made disclosures compared to non-U.S. sites. Provide comparable analyses of the high level safety results (for example, overall incidence of serious adverse events, discontinuations due to adverse events, and the incidence of any adverse events of special interest).

Sponsor Response:
The Sponsor assumes that this analysis is only needed for Studies TG1101-RMS301 and TG1101-RMS302.

Discussion:

The sponsor reported that none of the investigators in the Phase 2 or 3 studies of ublituximab in their development program for relapsing forms of MS had disclosed any financial conflicts of interest. Given the lack of investigators with disclosures, the Division considered this request to be moot.

Datasets:
1. If you make the request at the time of a pre-BLA meeting, we will review the structure of key efficacy datasets regarding relapse and disability progression outcomes with all variables you plan to include including patient disposition and whether the outcome fulfilled (or not) protocol criteria. Do not submit the full datasets; only empty tables or tables with a few example rows of data.

Sponsor Response:
The Sponsor plans to provide the structure of key efficacy datasets for the Agency's review.

Discussion:

The Division found this proposal to be acceptable, even if the sample datasets contain mock data.

Datasets:
4. Provide a dataset that has one row per subjects and which includes a column for each EDSS determination by visit (including screening, baseline, and unscheduled visits). Place all scheduled EDSS assessments; for example, screening baseline, week 12, etc., in the same column for all subjects. Identify and assign sequential identification numbers for those EDSS assessments that were performed at unscheduled relapse assessments. By reading down the rows, reviewers should be able to see the EDSS score from each scheduled and unscheduled visit ordered by time. Missed visits or missed EDSS scores should be indicated as missing at the scheduled time.

Sponsor Response:
Please see the following slide for the table the Sponsor plans to generate. Can the Agency clarify that this table meets their expectations?

Discussion:

The format of the sample table appears acceptable.

Other requests:
Points 5-9

Sponsor Response:
The Sponsor considers these to be typical inspection documents. **Can the Agency clarify if these points only apply to Studies TG1101-RMS301 and TG1101-RMS302? Can the Agency provide guidance as to the location of these documents in the eCTD?**

Discussion:

The Division agreed that these points (5-9) only apply to Studies TG-1101RMS301 and TG1101-RMS302, and that these documents should be located in Module 5, either as their own folder or as an appendix within the appropriate study's files.

Other requests:
Point 12. Plan to provide a detailed accounting of all instances in which the study database was accessed prior to and at the time of database lock for all blinded trials.

Sponsor Response:
The Sponsor acknowledges that this detailed accounting will be provided at the time of the BLA submission. The Sponsor plans to provide a list of user account information including the time at which data access was granted and the time at which data access was removed. Unblinded treatment assignment information was maintained outside of the study database.

Discussion:

The Division clarified that this accounting should include information about when database access was granted and removed and whether this access was appropriate for the individual given their study role. The sponsor was also encouraged to provide any available information about inappropriate database access if inappropriate access is identified as soon as possible.

3.0 IMPORTANT INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. There was general agreement with you on the submission-related issues discussed at this meeting.

- All applications are expected to include a comprehensive and readily

located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[1] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[2]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[5] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[6]. Submit all related

[5] https://www fda.gov/media/84223/download

[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions,* and the associated conformance guide, *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications,* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[7]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description

[7] https://www.fda.gov/media/85061/download

of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

FDA will provide an example of a table with a column of unscheduled visits.

StudyID	USubjID	TRT01A	TRTSTD	AVISIT	AVISITN	ADT	QSDY	PARAM	AVAL	CHG

Where

- Study ID is the study ID
- USubjID is the unique subject ID,
- TRT01A is the actual treatment being received in the study,
- TRTSTD is the date on which TRT01A was started in the study
- AVISIT is the type of analysis visit, e.g., screening, baseline, Week 4 visit, Week 12 visit, unscheduled visit, end of treatment (EOT) visit, EOT follow-up visit
- AVISITN is a number assigned to the type of AVISIT that represents a chronological sequencing of the AVISIT. For example, the following AVISITNs could be defined: 0 for screening visit, 1 for baseline visit, 4 for week 4 visit, 12 for week 12 visit, 499 for EOT visit, 999 for post-treatment follow-up visit; in this scheme, the AVISITN for an unscheduled visit (to verify a suspected relapse) on day 5 of week 8 might be 8.5.
- ADT is the date of the AVISIT
- QSDY is the Study Day of the AVISIT.
- PARAM is the measurement, e.g., Expanded Disability Status Scale (EDSS), Pyramidal Function System Scale (FSS).
- AVAL is the value of the measurement. A row should be included for missing data.
- CHG is the change in the measurement from baseline.

6.0 ATTACHMENTS AND HANDOUTS

Attachment 1

DN2 Pre-BLA Meetings
General Clinical Safety Requests

Datasets:

1. Each individual subject should be assigned a single unique subject identifier across the entire application (e.g., including open label extensions of the trials). Include the unique subject identifier in the ISS and individual studies' datasets.

For additional guidance refer to the FDA webpage on Study Data Standards Resources.

General Submission Contents:

1. Follow the requirements noted in 21CFR 314.50 (d)(5)(vi), Summary of Safety Information and the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application.

2. Provide an assessment of safety as per the FDA Guidance for Industry: Premarketing Risk Assessment.

3. Include a copy of each clinical study protocol as well as each amended protocol. Provide a list of the inclusion and exclusion criteria for each of the studies, including those introduced as part of protocol amendments. Submit all versions of the protocols (and Statistical Analysis Plan) and the date when changes were implemented. Ensure that a Summary of Changes for each version is included.

4. In addition to the comprehensive analyses performed for the pivotal trials, the ISS should also comprehensively integrate safety analyses for all other study group pools for treatment emergent adverse events (TEAEs), deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups, and vital sign/laboratory/ECG measurements.

5. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:

   a) Title of the table or figure in the application
   b) A hyperlink to the location of the table or figure with page number
   c) A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)

6. Format the tables of the ISS according to examples in FDA's Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review.

7. Include active hyperlinks from the lists of references to the referenced article.

8. Provide DSMB meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, include a place holder for that meeting noting such and signed by a member of the clinical team. Ensure that these packages come with a table of contents and are bookmarked by date.

9. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).

10. Submit an annotated version of the pre-BLA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection: Points to Consider" document accessible at MedDRA.

2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path.

3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.

4. The preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.

5. Ensure that all adverse events are presented, and not only events deemed "drug-related."

6. Provide a table of treatment-emergent adverse events reported in ≥ 2% of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.

7. Provide a table which summarizes the outcomes of all pregnancies. Provide a table which summarizes all known adverse events in subject offspring.

Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, adverse events leading to drug discontinuation, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon

request. Narratives should be integrated. For subjects who had more than one event requiring a narrative (whether in the same trial or in the core study and an extension) present a single narrative (rather than separate narratives for the various events).

2. Include a word file (and excel spreadsheet) that indicates those subjects for whom you submitted a case report form and/or narrative. This file should include an indicator for whether each item was submitted and the reason why it was submitted along with hyperlinks to the narrative and CRF.

3. Provide reports for any autopsies conducted during any of the studies.

4. Provide a line listing, narrative, and case report form for all subjects who fit the Hy's Law laboratory criteria.

5. Note that CRFs should include all clinical documents collected about the patient regardless of whether you label them "CRFs", e.g., Medwatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.

6. Provide a tabular listing of all subjects with all discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for drug or study discontinuation. For reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation. The Division may want to request selected narratives/CRFs from some of these patients, but they do not need to be submitted at the time of the initial NDA/BLA submission.

7. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):

    a) Patient age and gender
    b) Adverse event onset and stop dates (presented as relative Study Day number)
    c) Signs and symptoms related to the adverse event being discussed
    d) An assessment of the relationship of exposure duration to the development of the adverse event
    e) Pertinent medical history
    f) Concomitant medications with start dates relative to the adverse event
    g) Pertinent physical exam findings
    h) Any abnormal vital sign measurements
    i) Pertinent test results (e.g., lab data, ECG data, procedures, biopsy data, autopsy results)
    j) Discussion of the diagnosis as supported by available clinical data

k) For events without a definitive diagnosis, a list of the differential diagnoses
l) Treatment provided
m) Re-challenge results (if performed)
n) Outcomes and follow-up information

Laboratory and Vital Sign Measurements:

1. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests: SI Units.

2. Provide the normal reference ranges for every laboratory value.

3. Clearly list the normal values, as well as the thresholds for analysis of outliers, for outlier analyses of laboratory data, vital signs, and ECG data.

4. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses.

5. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:

   - Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
   - Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
   - Pulse Rate: <60 bpm, >100 bpm
   - Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
   - Temperature: >38.0 °C, <36.0 °C
   - Respiratory rate: <12 breaths/min, > 20 breaths/min

6. Summarize the protocols for collecting ECG data. Summarize the frequency of posttreatment QTc >450 ms, >480 ms, and >500 ms.

Other requests:

1. Submit individual patient profiles containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event, discontinued from the trial due to an adverse event, or had a medically significant event for which a narrative is submitted. Include all the information recorded for that patient, including but not limited to:

   a) Age
   b) Sex
   c) Dates of screening, randomization and starting therapy

d) Whether the patient completed or did not complete the study, with dates and reason for withdrawal
e) Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
f) Prior medications and concomitant medications with dates of start and end
g) Vital signs and laboratories, sorted by date, with reference ranges *
h) Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)
i) Full reports for radiologic studies, ECG, MRI, pathology results, special studies and procedures with dates and reference ranges
j) Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results.
k) For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted.

Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

2. You may submit for comments from the Division an example narrative from a patient who had more than one serious adverse event and participated in the controlled and extension studies prior to submitting your BLA.

3. We request that you submit a sample integrated summary of safety datasets (with data definition file) for Division comments prior to submitting the BLA. This process could help to identify and resolve any potential issues of navigability or interpretability that could impact the review of your application.

4. Provide an analysis that identifies all opportunistic infections.

5. A protocol-defined multiple sclerosis relapse typically should not be classified as a TEAE. If any relapses are reported as adverse events, provide the criteria used to classify a relapse as an adverse event (versus lack of efficacy).

6. Provide a table of all known cases of malignancy (or pre-malignant conditions) that have occurred in subjects who participated in the clinical development program. The table should include the study, subject number, event Preferred Term, cumulative drug dose received at the time of the event, latency from first dose to malignancy diagnosis, subject's age at the time of diagnosis, subject's country of origin, subject's sex, duration of follow-up for that subject, and a link to the narrative.

7. We request tables with the number of reported malignancies, number of subjects, incidence proportions, subject-years of exposure, and incidence rates for cases of malignancy in completed and ongoing trials. We also request presentation of these

analyses stratified by duration of subject follow-up (less than 1 year, 1 to less than 2 years, 2 to less than 3 years, and more than 3 years). For each subject group, we request the median cumulative dose, the cumulative dose range, and the median duration of treatment exposure.

Attachment 2

DN2 Pre-BLA Meetings
General Clinical Efficacy Requests

The purpose of the following recommendations and requests is to facilitate review of Applications for drugs to treat relapsing forms of multiple sclerosis.

Analyses

1. Provide a complete accounting and analysis of all potential relapse events. The dataset should have one row per event and should include the date that the potential relapse events were first reported by the subject and the date that the events were first evaluated by the treating and by the examining investigators. Include a column for the criteria that confirmed that there was a new objective neurologic deficit (i.e., change in EDSS or FSS scores). Include a calculation of the time intervals (in study days) from the onset of symptoms to the various points in the relapse assessment process. Include an analysis for any potential bias in the determination made by the treating investigator in referring events for further evaluation by the Independent EDSS Rater and for the central confirmation process. Provide sensitivity analyses based on relapses as reported by subjects and as determined by the treating and examining investigators in addition to the pre-specified primary analysis based on the central confirmation process. Discuss the impact of any differences in the results of these analyses. Provide a clear indication of any imputed values used for these analyses.

2. Provide an analysis of the effect of any missing baseline EDSS and missing confirmatory EDSS values on confirmed disability progression outcomes. If there are missing baseline EDSS values, explain each missing score. Provide an analysis of the time from baseline EDSS to randomization and baseline EDSS to start of study medication.

3. Provide an analysis of compliance with the study medication for both treatment arms and any relationship of compliance to the primary and key secondary study outcomes in all efficacy trials.

4. Provide an additional analysis of whether the use of systemic corticosteroids varied between treatment conditions in all efficacy trials.

5. Provide an analysis and a summary addressing the extent to which the sites with clinical investigators who disclosed financial interests contributed to the trial results. The analysis and summary should include a comparison of the primary outcome for each trial to support efficacy at sites that had investigators who disclosed financial interests with those sites that did not. Also, discuss the significance of the percentage of U.S. sites with investigators who made disclosures compared to non-

U.S. sites. Provide comparable analyses of the high level safety results (for example, overall incidence of serious adverse events, discontinuations due to adverse events, and the incidence of any adverse events of special interest).

Datasets

1. If you make the request at the time of a pre-BLA meeting, we will review the structure of key efficacy datasets regarding relapse and disability progression outcomes with all variables you plan to include including patient disposition and whether the outcome fulfilled (or not) protocol criteria. Do not submit the full datasets; only empty tables or tables with a few example rows of data.

2. For each study contributing evidence of effectiveness, provide an additional dataset with a row for each site with fields in each row that are needed to evaluate the extent of participation at the different sites. The fields to include in the table are the following: (Unique) SiteID, contact individual, address, city, (state/territory/province), country, mail code, region, telephone number, fax number, email address for contact individual, fields for the number of subjects randomized to each arm of the study, the number enrolled in the corresponding extension trials, fields showing the number of randomized patients in each arm of the study who experienced confirmed relapses, and who experienced 3 and 6 month confirmed progression of disability events, fields with the number of patients who did not complete study treatment or did not complete the trial in each of the treatment arms.

3. Provide an additional dataset of important trial events for each patient with one row per patient per event. Events should include outcome events such as relapses and confirmed progression of disability. Columns should include the patient identifier, trial name, name of event, unscheduled visit, EDSS score, name of new medication, preferred term for adverse event). There should be a column for the date and time of the event, and a column for the time in study days since randomization. The events should include:

    - Sign consent form (date and time)
    - Baseline EDSS (date and time)
    - Randomization (date and time and assigned treatment)
    - Start study medication (medication, date and time)
    - Discontinue study medication (reason, date)
    - Start treatment for acute relapse (medication, date)
    - Scheduled visits that occurred (visit number, scheduled date, missed or not)
    - Every EDSS determination (EDSS Visit Name if visit is scheduled, total score, whether EDSS was scheduled or not, and date, rater)
    - EDSS score changed in audit trail (who, date and time, previous score, new score)
    - Start alternative MS medication (medication name and date).

- Patient reports of relapses to clinic (type of contact: patient calls site, during clinic visit, clinic calls patient, date and time)
- Relapse evaluation visits (date and time, evaluator, confirmed relapse or not)
- Unscheduled visits (reason, date)
- Last subject contact (date)
- Adverse event (preferred term, date)
- Use of steroids (date)
- Relapse event confirmed (date of relapse confirmation)

When sorted by patient and date, this dataset will provide a unified list of safety and clinical outcome events ordered by date and time from across multiple datasets that will allow reviewers to see each event in the context of the entire patient experience.

4. Provide a dataset that has one row per subject and which includes a column for each EDSS determination by visit (including screening, baseline, and unscheduled visits). Place all scheduled EDSS assessments; for example, screening, baseline, week 12, etc., in the same column for all subjects. Identify and assign sequential identification numbers for those EDSS assessments that were performed at unscheduled relapse assessments. By reading down the rows, reviewers should be able to see the EDSS score from each scheduled and unscheduled visit ordered by time. Missed visits or missed EDSS scores should be indicated as missing at the scheduled time.

5. Provide MRI datasets in chronological order. Include in the MRI datasets and tables the following:

    - Date and time the MRI was performed
    - Date the MRI was received and when it was reviewed at the MRI Centralized Reading Center
    - Detail the imputation method(s) employed.

    Describe the MRI scan protocols for sites and central MRI reading center and the extent of deviation from the protocol-defined MRI methods. Describe the process for assessment of the reliability and reproducibility of the central reader(s). Describe the methods for determination of MRI lesion volumes.

    Provide a detailed accounting of all missing primary and key secondary endpoint values. Provide a detailed accounting of all missing MRI scan values. Flag all imputed endpoint values. Identify the extent of missing data in all tables, figures, and graphs.

Other requests:

1. For each study, include a Consolidated Standards of Reporting Trials (CONSORT) diagram of patient disposition with an indication of populations used in analyses of

efficacy and safety. Separate safety and efficacy diagrams may be needed. Indicate the number of subjects who did not receive the randomized treatment and how data from these subjects were handled. Provide complete accounting of all discontinuations and withdrawals from study treatment and withdrawals from the trial including the reason(s) for discontinuation or withdrawal. Identify those discontinuations due to a relapse or worsening MS. Provide an accounting of subjects whose relapse and EDSS outcomes you exclude from the analysis following the use of alternative MS treatment.

2. Provide an overall CONSORT-like diagram that describes the composition of the pools used in the safety analyses; essentially, the number of patients, patient years of observation, and study source for all each pool.

3. Include a table that identifies the date of key milestones in the studies used to support efficacy. Milestones for each study should include:

    a) Protocol Approvals
    b) Protocol Amendments
    c) Statistical Analysis Plan (SAP) approvals
    d) Each SAP Amendment
    e) First subject randomized
    f) Any interim analysis
    g) Last subject randomized
    h) First subject completes follow-up
    i) Last subject completes follow-up
    j) Database lock
    k) Data and Safety Monitoring Committee (DMC) meetings and teleconferences

4. Provide the Charter for the DMC and, for each meeting or teleconference, minutes and copies of interim reports to the DMC.

5. Describe the site monitoring process and document when monitoring visits occurred and the personnel who conducted the visit. Document the extent of source data verification for primary and secondary outcomes.

6. For each study provide a detailed description of each step in the process that determines that a primary outcome event occurred. This summary should include the handling of spontaneous reports of a potential relapse over the telephone including the disposition those reports that were not referred to the treating investigator. This summary should also include the determinations made by the treating investigator, and any other relevant assessments, such as previous relapses. Provide links to the fields in a blank case report form that were used to collect this information.

7. Provide a complete accounting of all EDSS determinations. Include documentation of the process used to arrive at the final EDSS score and how the score was transmitted or transcribed from the rater to the trial database.

8. Describe the process for the certification of EDSS examiners.

9. Describe the process for assessment of the internal consistency of the determination of EDSS scores and any process for assessment of the consistency of the EDSS score with other clinical assessments.

10. For survival curves, the Y-axis should start with zero and end with 1 or 100%. The X axis labels should include the time from 0 and the number of subjects in each treatment arm for each tick mark. The final proportion with outcomes and treatment should be indicated clearly.

11. List any fields that were collected in the CRF but which were not included in the datasets.

12. Plan to provide a detailed accounting of all instances in which the study database was accessed prior to and at the time of database lock for all blinded trials.

23 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

M E M O R A N D U M
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: April 2, 2021

To: Nick Kozauer, MD, Acting Director
Division of Neurology (DN II)

Through: Chad Reissig, PhD, Supervisory Pharmacologist
Controlled Substance Staff (CSS)

From: Joshua Hunt, PharmD, MPH, Senior Regulatory Reviewer
Controlled Substance Staff

Subject: **IND 127265/Ublituximab (TG-1101) / Pre-BLA meeting request**
Indication: Multiple Sclerosis
Dosage form: solution for injection
Sponsor: TG Therapeutics

Materials Reviewed: Sponsor Type B Meeting Request – Pre-BLA Meeting *(2 pgs)*
Sponsor Briefing Document Module 1.6.1 Pre-BLA Meeting Request *(18pgs)*

I. Background

This memorandum is in response to a consult request dated February 26, 2021 from the Division of Neurology (DN II), pertaining to IND 127265 for a Pre-BLA meeting. The consult is a request for CSS to review the IND and provide comments. The Sponsor has several non-clinical and clinical questions for the Agency; however, there were no specific questions from the Sponsor for CSS.

The Sponsor intends to discuss efficacy and safety data from two Phase 3 trials that are meant to serve as pivotal studies to support a BLA using ublituximab for the treatment of relapsing forms of multiple sclerosis (RMS). The two trials are entitled "*Ublituximab In Multiple Sclerosis Treatment Effects (ULTIMATE I STUDY)* (SN0207)" and "*Ublituximab In Multiple Sclerosis Treatment Effects (ULTIMATE II STUDY) (SN0208).*"

The Sponsor pooled safety data from 545 subjects treated with ublituximab across the two Phase 3 studies. According to the Sponsor, treatment emergent adverse events (TEAEs) that were reported by greater than 1 subject in the ublituximab arm within the pooled safety data included acute sinusitis (3), pneumonia (3), appendicitis (2), COVID-19 pneumonia (2), and central nervous system enteroviral infection (2). TEAEs leading to temporary study drug interruption ≥1% within the pooled safety data,

across the two Phase 3 trials, were as follows: pyrexia (14), chills (12), nausea (10), ALT increased (7), and AST increased (6) in the ublituximab arm.

Ublituximab is a recombinant IgG1 chimeric monoclonal antibody which binds to CD20. B lymphocyte antigen CD20 (CD20) is a protein that is expressed on the surface of B lymphocyte immune cells. Ublituximab has two glycosylated heavy and light chains including sixteen paired disulfide bonds, which includes 12 intra-chain and 4 inter-chain disulfide bonds. Ublituximab, also named TG-1101, is not chemically or pharmacologically similar to other drugs with known abuse potential. Ublituximab's mechanism-of-action does not target any known receptor(s) of abuse. The pharmacology and summarized human AE data from the Phase III studies, provided by the Sponsor, demonstrate that ublituximab lacks abuse-related CNS activity. Moreover, currently approved and marketed biologics with anti-CD20 activity (e.g., Rituximab – brand name Remicade) do not elicit abuse-related psychoactivity as a therapeutic class.

II. Conclusions and Recommendations to the Division

- CSS has not identified any abuse or dependence-related concerns with ublituximab
- The proposed drug product, if approved by DN II, will not require section 9 DRUG ABUSE AND DEPENDENCE in its product labeling.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOSHUA S HUNT
04/02/2021 07:24:52 AM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 127265

**MEETING REQUEST-
WRITTEN RESPONSES**

TG Therapeutics, Inc.
Attention: Robert Niecestro, PhD
Executive Vice President, Regulatory Affairs
2 Gansevoort St., 9th Floor
New York, NY 10014

Dear Dr. Niecestro:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ublituximab.

We also refer to your submission dated April 27, 2016, containing a Type C meeting request. The purpose of the requested meeting is general guidance on the design and execution of a Phase 3 program for this product.

Further reference is made to our Meeting Granted letter dated May 4, 2016, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your June 13, 2016, background package.

If you have any questions, contact Laurie Kelley, Regulatory Project Manager, at laurie.kelley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type: C
Meeting Category: Guidance

Application Number: IND 127265
Product Name: Ublituximab
Indication: Treatment of relapsing forms of multiple sclerosis (RMS)
Sponsor/Applicant Name: TG Therapeutics, Inc.
Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

TG Therapeutics, Inc., is currently developing ublituximab, a monoclonal antibody, for the treatment of RMS. On April 27, 2016, the sponsor submitted a Type C meeting request for general guidance on the design and execution of a Phase 3 program for this product.

2.0 QUESTIONS AND RESPONSES

Question 1: TG Therapeutics plans to define relapse as a new or worsening symptom lasting ≥ 24 hours with the absence of fever. The symptoms are attributed to MS and are preceded by 30 days of stability. The change in EDSS is ≥ 0.5 increase assessed by a blinded observer or prior to visit or ≥ 1 point increase in two functional symptoms (FS), except for bladder and cognitive changes. Does the FDA agree with our definition of relapse?

FDA Response to Question 1: We suggest several changes to the definition of a confirmed relapse and the process for confirming that a relapse event has occurred.

a) Exclude possible relapse events caused by infection, injury, or adverse reactions to medications.
b) Include possible relapse event s with an increase of two or more points in any EDSS functional system score except those for bladder function and cognition.
c) Require that only a rater blinded to treatment assignment and all previous EDSS scores perform EDSS ratings.
d) In the protocol, describe a detailed step-by-step process for evaluation of all possible relapse events from the time of first report until the final confirmation that a possible relapse event conforms to the protocol definition. Document all reports of possible relapses and the date and time for each step in the confirmation process.

Question 2: Does the FDA agree with the primary objective/endpoint of annualized relapse rate in patients with RMS after 96 weeks (approximately 2 years)?

FDA Response to Question 2: Yes.

Question 3: Does the FDA agree that teriflunomide is an acceptable active control?

FDA Response to Question 3: Yes. See also our response to Question 4.

Question 4: Does the FDA agree that the proposed Phase 3 study should be a randomized, active control, double-blind, double-dummy study?

FDA Response to Question 4: Yes, this is reasonable.

Question 5 Does the FDA agree with the use of the Poisson regression analysis for testing to analyze the treatment differences between ublituximab and teriflunomide?

FDA Response to Question 5: Before using the Poisson regression model, we suggest that you use available data to determine that it is a good fit. Because it allows for the possibility of overdispersion, the negative binomial model is more common in studies with annual relapse rate endpoints.

Question 5a: In Option A, TG Therapeutics would like to use a single Phase 3 clinical trial (with supportive data) to support a filing of a BLA for approval, does the FDA agree with the use of a two-sided alpha <0.01 and a power of 80% to demonstrate a superior effect of ublituximab in reducing ARR compared with teriflunomide? Does the FDA agree that this study would be sufficient for filing a BLA?

FDA Response to Question 5a: Regardless of whether or not you use evidence from one or more studies to substantiate efficacy, the first opportunity for a meaningful discussion of the possible sufficiency of data for filing a BLA is at a pre-BLA meeting after we review a summary of study results. Prior to knowing the study results, we cannot predict whether a single study is likely to be sufficient. In general, evidence from two persuasive studies is more likely to be sufficient than a single comparably persuasive study. We recommend that you refer to "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products"[1] for a discussion of the characteristics that can contribute to the conclusion that a single study would be adequate to support an effectiveness claim.

Question 5b: In Option B, TG Therapeutics is also willing to conduct two Phase 3 Clinical Trials to support a filing of a BLA for approval, does the FDA agree with the use of a two-sided alpha <0.05 and a power of 80% to demonstrate a superior effect of ublituximab in reducing ARR compared with teriflunomide in these two trials? Does the FDA agree that these two studies would be sufficient for filing a BLA?

FDA Response to Question 5b: Sufficiency for filing an NDA is a matter of review; in general, two adequate and well-controlled persuasive studies would be sufficient for filing an application.

Question 5c: Given the fact that more patients with RMS will be exposed to ublituximab with one “adequate and well-controlled” clinical trial using 2 to 1 randomization instead of two

[1] www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatory/Guidances/ucm071185.pdf

independent clinical trials, does the FDA agree with the TG Therapeutics that one clinical study with supportive data from the ongoing Phase 2a clinical trial will be sufficient to file a BLA?

FDA Response to Question 5c: Please see the answer to question 5a. The randomization ratio is generally not a factor used to determine sufficiency of a single trial; the size the treatment groups would be more relevant.

Question 5d: Does the FDA agree with the proposed indication for ublituximab for the treatment of relapsing forms of MS if the primary efficacy objective is met in either Option A or Option B?

FDA Response to Question 5d: There are no apparent problems with the proposed indication at this time. The final indication will be a matter of BLA review. This answer is not an endorsement of "Option A" or "Option B" and you should refer to our answers 5a and 5b, above.

Question 6: Does the FDA agree that approximately 250 patients with RMS exposed to ublituximab for approximately 96 weeks (approximately 2 years) and the exposure from the oncology studies is sufficient to file the BLA?

FDA Response to Question 6: We refer you to the ICH requirements for safety databases to determine the size of your study populations. Unforeseen or emerging issues could change the number of subjects needed to evaluate safety.

Question 7: TG Therapeutics is planning to develop ublituximab for the treatment of RMS. Attachment 2 is the protocol synopsis for the proposed Phase 3 study. Are the secondary endpoints acceptable (see Attachment 2)?

FDA Response to Question 7: Yes.

Question 8: Does the FDA agree that for any patient experiencing a multiple sclerosis relapse while on study be allowed rescue therapy with intravenous methylprednisolone 1gm/day for up to 5 consecutive days? In addition, does the FDA agree that for patients requiring rescue therapy that they will have an MRI scan 10 days after completion of treatment with steroids?

FDA Response to Question 8: The dose of steroids you have stated is routine and acceptable. With regard to MRI scans, please be mindful of recent FDA concerns about the repeated use of gadolinium contrast agents.[2] It is doubtful that scans done after treatment with methylprednisolone would make a significant contribution to interpretation of study results.

Question 9: Does the FDA agree with the proposed MRI Schedule (Screening, weeks 24 (pre-dose), 48 (pre-dose), and 96?

FDA Response to Question 9: There is no mandatory MRI schedule. Please see our response to Question 8.

[2] http://www.fda.gov/Drugs/DrugSafety/ucm455386.htm

Question 10: Does the FDA agree with the proposed inclusion/exclusion criteria for the Phase 3 study?

FDA Response to Question 10: When you submit your protocol we will perform a detailed review of your safety database and make further recommendations. It would be helpful if the protocol explained the reason for each exclusion criterion.

Question 11: Does the FDA agree that a population pharmacokinetic approach will assist us in preparing a label regarding drug-demographic (e.g., age, weight, gender) and drug-disease (e.g., liver function (ALT and AST), creatinine) interactions?

FDA Response to Question 11:
Your plan to use a population pharmacokinetic approach to support labeling regarding drug-demographic and drug-disease interactions seems reasonable. In addition to the covariates you propose, we suggest that you analyze the effect of baseline B-cell count on ublituximab pharmacokinetics in the population pharmacokinetic analysis. You may also need to consider time-dependent clearance due to target mediated drug disposition.

In addition, the population pharmacokinetic analysis using sparse pharmacokinetic data could help derive exposure metrics for further evaluation of the relationships between ublituximab exposure and pharmacodynamic effects (such as B-cell counts), efficacy, and safety parameters. We recommend that you ensure that pharmacokinetic and pharmacodynamic sampling schedules align with the population pharmacokinetics and pharmacokinetic/pharmacodynamic analyses you plan.

Question 12: Does the FDA agree that a population pharmacokinetic approach will assist us in examining and determining any potential drug-drug interactions?

FDA Response to Question 12: Given the suspected mechanism of cytokine modulation, we recommend that you conduct in-vivo studies with methylprednisolone and fingolimod to assess the potential for drug-drug interactions (DDI). You could use population pharmacokinetic analysis to provide supportive evidence for your evaluation of DDI. Consider the following when you design these studies:

a) Collect accurate dosing records for both the substrate and the perpetrator.
b) Include an adequate number of subjects with the concomitant medication in the study with appropriate pharmacokinetic sampling to characterize pharmacokinetic parameters of interest.

Question 13: TG Therapeutics is not planning to assess for anti-drug antibodies (ADA) in the Phase 3 program since ADA was determined in other clinical studies (e.g., oncology studies and Phase 2a RMS). Is it necessary to perform ADA analyses in the proposed Phase 3 development program for RMS?

FDA Response to Question 13: We note that oncology studies and a Phase 2a RMS study evaluated ADAs. Because the data obtained from the previous RMS study is limited and patient-specific factors influence immunogenicity, we recommend that you evaluate ADAs in the Phase

3 program for RMS. Use an ADA assay that determines whether the antibodies have binding or neutralizing activity and whether they affect pharmacokinetics, pharmacodynamics, safety, or efficacy.

Question 14: Can the Phase 3 protocol be submitted for Special Protocol Assessment (SPA)?

FDA Response to Question 14: Yes.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards

specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017,** the following submission types: **NDA, ANDA, BLA** and **Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to sponsors/applicants when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), sponsors/applicants must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

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/s/

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07/08/2016

WILLIAM H Dunn
07/08/2016