CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210942Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 129187

MEETING PRELIMINARY COMMENTS

Romeg Therapeutics, LLC
c/o B & H Consulting Services, Inc.
400 Trade Center, Suite 5900
Woburn, MA 01801

Attention: Elizabeth N. Dupras, PAC
Regulatory Agent for Romeg Therapeutics, LLC

Dear Ms. Dupras:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Colchicine Oral Solution.

We also refer to your September 15, 2017, correspondence, received September 15, 2017, requesting a meeting to discuss the data to support the planned 505(b)(2) NDA.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me, Regulatory Project Manager, at (301) 796-2402.

Sincerely,

{See appended electronic signature page}

Susan Rhee, PharmD
LCDR, US Public Health Service
Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II

Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: November 15, 2017, 2:00 – 3:00 PM EST
Meeting Location: FDA White Oak, Building 22, Room 1315

Application Number: IND 129187
Product Name: Colchicine Oral Solution
Indication: prophylaxis of gout flares in adults
Sponsor/Applicant Name: Romeg Therapeutics, LLC

FDA ATTENDEES (tentative)

Badrul A. Chowdhury, MD, PhD, Division Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Nikolay Nikolov, MD, Clinical Team Leader, DPARP
Keith Hull, MD, Clinical Reviewer, DPARP
Carol Galvis, PhD, Acting Team Leader Pharmacology/Toxicology, DPARP
Anup Srivastava, PhD, Pharmacology/Toxicology Reviewer, DPARP
Bavna Saluja, PhD, Acting Team Lead, Division of Clinical Pharmacology IV (DCPIV), Office of Clinical Pharmacology (OCP)
Manuela Grimstein, PhD, Clinical Pharmacology Reviewer, DCPIV, OCP,
Craig Bertha, PhD, Application Technical Lead for Product Quality, Division of New Drug Products II
Robert Abugov, PhD., Acting Mathematical Statistician Team Leader, Division of Biometrics II
Susan Rhee, PharmD, Regulatory Project Manager, DPARP

SPONSOR ATTENDEES

Indu Muni, Ph.D., Chairman & CEO, ROMEG Therapeutics, LLC
Naomi Vishnupad, Ph.D., Vice President, Scientific Affairs, ROMEG Therapeutics, LLC
(b) (4) Clinical Consultant for ROMEG Therapeutics, LLC
(b) (4) (Regulatory Consultant)
Elizabeth N. Dupras, RAC; Director, CMC and Global Regulatory Affairs, B&H Consulting Services, Inc. (Regulatory Agent)

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for November 15, 2017 at 2:00 PM, FDA White Oak campus between Romeg and the Division of Pulmonary, Allergy, and

Rheumatology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

In a submission received on Septemeber 15, 2017, Romeg requested a meeting to discuss the data to support the planned 505(b)(2) NDA for Colchicine Oral solution. The meeting was granted on September 25, 2017. Romeg's specific questions from the briefing document received on October 13, 2017, are listed below in *italics* and the FDA responses are provided in normal font.

2.0 DISCUSSION

2.1. Regulatory

Question 1:
The NDA will be submitted in eCTD format through the Agency's Electronic Submission Gateway (ESG) under B&H Consulting Services Inc.'s approved WebTrader account. The electronic submission will be prepared in accordance with the ICH eCTD specifications and all other pertinent and applicable FDA specifications/guidances. The proposed content plan outlining the organization of the eCTD NDA is provided in Attachment 1.

Does the Agency agree with the organization of the eCTD?

FDA Response to Question 1:
Yes, the Agency agrees with the proposed content plan outlining the organization of the eCTD NDA.

Question 2:
Romeg believes that the action on the NDA for Colchicine Oral Solution will not increase the use of the active moiety and therefore meets the criteria for categorical exclusion defined in 21 CFR 25.31(a). In addition, to the best knowledge of Romeg, no extraordinary circumstances exist as defined in 21 CFR 25.21. Therefore, no environmental assessment is required according to 21 CFR 25.20(l).

Does the Agency agree that the action on the NDA for Colchicine Oral Solution will meet the criteria for categorical exclusion defined in 21 CFR 25.31(a) and that no environmental assessment is required?

FDA Response to Question 2:
Yes, we agree, based on your current proposed indication and your claim that no extraordinary circumstances exist.

Question 3:
Romeg will use the FDA-approved labeling for the RLD, Probenecid and Colchicine Tablets USP (ANDA 084279), as well as the available literature and the completed clinical studies described in Section 9.3.1 and Section 11.2 to develop proposed labeling for Colchicine Oral Solution. In order to include the Agency's most recent labeling structure/format for colchicine labeling, the labeling for the listed drugs Colcrys® (colchicine USP) Tablets (NDA 022353) and Mitigare® (colchicine) Capsules (NDA 204820) will be reviewed. The FDA-approved package inserts for Probenecid and Colchicine Tablets USP (ANDA 084279), as well as the listed drugs Colcrys® (colchicine USP) Tablets (NDA 022353) and Mitigare® (colchicine) Capsules (NDA 204820) are provided in Attachment 2, Attachment 3 and Attachment 4, respectively. The draft package insert in Physician's Labeling Rule (PLR) format is provided in Attachment 5. Romeg acknowledges that the current FDA-approved labeling for the RLD and listed drugs does not comply with the Pregnancy and Lactation Labeling Rule (PLLR); sections that will be updated based on PLLR are highlighted in red in the proposed draft labeling provided in Attachment 5.

Does the Agency agree with the proposed approach to draft the PLR-format labeling for Colchicine Oral Solution?

FDA Response to Question 3:
The Agency agrees in principle with your proposed approach to draft the PLR-format labeling for Colchicine Oral Solution; however, ultimately this will be a review issue.

Question 4:
Does the Agency agree that the draft labeling for Colchicine Oral Solution is adequate for submission in the planned 505(b)(2) NDA?

FDA Response to Question 4:
The Agency agrees in principle with your proposed approach to draft the PLR-format labeling for Colchicine Oral Solution; however, ultimately this will be a review issue.

2.2. CMC

Question 5:
Romeg has initiated an extractables study on the proposed high density polyethylene bottle and foil lined cap to be used for Colchicine Oral Solution. Additionally, leachables are being evaluated on accelerated samples of Colchicine Oral Solution stored in the proposed container closure system. The study protocol (PROT902) is provided in Attachment 6.

Does the Agency agree that the extractables/leachables study is adequate and that no additional extractables/leachables studies are needed to support the planned 505(b)(2) NDA?

FDA Response to Question 5:
The planned studies appear to be reasonable, however, final determination of the adequacy of the studies is deferred to review of the NDA when the studies and supporting data may be evaluated in its totality. Further we also refer you to section III. F. of the *Guidance for Industry: Container Closure Systems for Packaging Human Drugs and Biologics, Chemistry, Manufacturing, and Controls Documentation* (1999), and the USP general information chapters <1663> and <1664>.

Question 6:
The NDA will include a minimum of 12-month stability data for four batches manufactured at a minimum of (b)(4)*% commercial scale and packaged in the proposed container closure system. In addition, in-use stability studies are being conducted on the clinical batch and one exhibit batch of Colchicine Oral Solution. An overview of the stability data package to be included in the NDA is provided in Section 10.2.8.*

Does the Agency agree that the proposed NDA stability data package is adequate to support the planned 505(b)(2) NDA?

FDA Response to Question 6:
Yes, we agree it is adequate to support the filing of the NDA.

Question 7:
The clinical supply batch and the NDA registration batches were manufactured using the same process and released against the same specification. Since each batch is considered representative of all batches, Romeg proposes to provide a representative executed production record for one registration batch of Colchicine Oral Solution in the NDA; batch analysis data for all batches will be included in the NDA.

Does the Agency agree that a representative executed production record from one representative registration batch of Colchicine Oral Solution is adequate to support the planned 505(b)(2) NDA?

FDA Response to Question 7:
As the regulation 21 CFR 314.50(d)(1)(ii)(*b)* requires that you provide the executed batch record for each batch used to conduct both bioavailability/bioequivalent and primary stability studies, we find it acceptable for you to provide a representative batch record for one of the primary stability/registration batches if the records for the other batches are made available upon our request if necessary.

2.3. CLINICAL

Question 8:

As agreed during the pre IND meeting, Romeg intends to rely on the Agency's previous findings of clinical safety and efficacy for colchicine in the combination product (Probenecid and Colchicine Tablets USP; ANDA 084279), as well as published literature. In addition, Romeg has conducted a comparative bioavailability study, including a food effect arm, and two drug drug interaction (DDI) studies, [including studies with a P gp inhibitor and three CYP3A4 inhibitors (strong, moderate and weak)]. Romeg has also demonstrated comparable permeability of Colchicine Oral Solution vs. marketed colchicine products (tablets and capsules) in an in vitro Caco 2 study. No further clinical studies are planned to support the planned 505(b)(2) NDA. Summaries of the data from the permeability study, comparative bioavailability study and the DDI studies are provided in Section 11.2.

Does the Agency agree that the comparative bioavailability food-effect study, the DDI studies, the in vitro permeability study and the published literature provide an adequate bridge to the Agency's previous findings of safety and efficacy for Probenecid and Colchicine Tablets USP and are adequate to support the planned 505(b)(2) NDA, and that no further clinical studies are needed?

FDA Response to Question 8:
The Agency agrees that the proposed clinical pharmacology package appears sufficient to support the filing of the NDA. The adequacy of the data submitted will be a review issue.

Question 9:
Romeg plans to summarize the safety and pharmacokinetic (PK) findings from the comparative bioavailability study, supported by safety and PK data from the DDI studies in Module 2.7.3 and Module 2.7.4, respectively, of the NDA. An overview of the safety profile in each study is provided in Section 11.5. Safety data from the comparative bioavailability study showed no statistical difference (for number of events) between the test formulation and RLD under fasted conditions in terms of treatment emergent adverse events (TEAEs) and there were no treatment related discontinuations. When Colchicine Oral Solution was administered in combination with CYP (strong, moderate and weak) or P-gp inhibitors in the DDI studies, the incidence of TEAEs did not increase and there were no treatment related discontinuations. There were no statistically significant or clinically meaningful changes from baseline in hematology, clinical chemistry, vitals, ECG or urine analysis seen in any of studies, no serious adverse events (SAEs) and no deaths were reported. In addition, the studies were conducted in healthy volunteers and not a patient population; therefore, no integrated analyses are planned.

Does the Agency agree that no integrated analyses are needed to support the planned 505(b)(2) NDA?

FDA Response to Question 9:
The Agency agrees in principle that no integrated analyses are needed to support the planned 505(b)(2) NDA.

Question 10:

There were no deaths, no subjects that discontinued due to a study drug related adverse event and no subjects that experienced a serious and unexpected adverse event during the clinical studies for Colchicine Oral Solution; therefore, Romeg proposes not to include any Case Report Forms (CRFs) in the NDA. However, all CRFs are available and can be provided upon request.

Does the Agency agree that submission of CRFs is not needed in the planned 505(b)(2) NDA?

FDA Response to Question 10:
The Agency agrees in principle that CRFs are not needed to support the planned 505(b)(2) NDA.

Question 11:
The safety of colchicine is well established in the reference listed drug (Probenecid and Colchicine Tablets USP) and the approved products containing colchicine only (Colcrys® and Mitigare®). In addition, the clinical development program for Colchicine Oral Solution demonstrated that a favorable risk benefit profile exists for the proposed drug product. Therefore, no specific Risk Evaluation and Mitigation Strategy or other risk minimization activities are planned for Colchicine Oral Solution; a routine pharmacovigilance approach will be applied once Colchicine Oral Solution is marketed.

FDA Response to Question 11:
The Agency agrees in principle that no specific Risk Evaluation and Mitigation Strategy or other risk minimization activities will be needed; however, this will ultimately be a review issue.

3.0 ADDITIONAL 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-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* 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 Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

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 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 and Pregnancy and Lactation Labeling Final Rule 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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** 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 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), you 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).

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's

finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**

1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SUSAN RHEE
11/08/2017