Registry Protocol 10PLK13

PROCLAIM℠

Proleukin® Observational Registry to Evaluate the Treatment Patterns and Clinical Response in Malignancy

Registry Protocol Date: 18 September 2012
Version 2.0

Registry Sponsor

Prometheus Laboratories Inc.,
Prometheus Laboratories Inc.
9410 Carroll Park Drive
San Diego, Ca 92121

Confidentiality Statement

The information contained in this document is strictly confidential. It is disclosed to you as a (potential) Investigator. Acceptance of this document constitutes your agreement that the information contained herein will not be disclosed or in any way communicated to any third party without prior written approval of Prometheus (or it's representative(s)) of the registry described therein except – to the extent necessary – to your staff, to members of appropriate review committee(s) and/or to persons to whom the investigational product may be administered or to their legal representative(s) to obtain their informed consent.

Registry Protocol 10PLK13

PROCLAIM[SM]

Proleukin® Observational Registry to Evaluate the Treatment Patterns and Clinical Response in Malignancy

Registry Protocol Date: 18 September 2012
Version 2.0

This protocol is prepared by: Theresa Luna (Theresa Luna)

Any concerns regarding the Registry protocol should be discussed directly with the preparer and documented on the review copy of the protocol.

Registry Protocol approved by:

24 SEPT 2012
Date

James Lowder, MD (Prometheus)
Senior Director of Clinical Development and Medical Affairs, Oncology

18 Sep 2012
Date

Randall Fong, RPh, MS (Prometheus)
Director, Drug Safety and Pharmacovigilance

19 Sep 2012
Date

Bruce Wagman (Prometheus)
Vice President, Regulatory and Quality Systems

Digitally signed by Michael Wong
DN: cn=Michael Wong, o=University of Southern California, ou, email=mike.wong@med.usc.edu, c=US
Date: 2012.09.27 19:06:29 -07'00'

Date

Michael Wong, MD, PhD (University of South California)
Chair, PROCLAIM Registry Steering Committee

INVESTIGATOR AGREEMENT

PROCLAIM[SM] Registry
Protocol 10PLK13

Proleukin Observational Registry to Evaluate the Treatment Patterns and Clinical Response in Malignancy

Registry Protocol Date: 18 September 2012
Version: 2.0

By my signature below, I acknowledge that I have read the protocol and agree that it contains all necessary details for complying with the terms of inclusion into the Registry as described herein. Furthermore, I agree to conduct this clinical Registry in compliance with said Protocol, the ICH Good Clinical Practice guideline, as well as with any and all applicable federal, state and/or local laws and regulations and with my contractual obligations towards Prometheus Laboratories Inc. or its representatives(s).

THIS REGISTRY WILL BE CONDUCTED IN ACCORDANCE WITH GOOD CLINICAL PRACTICE REQUIREMENTS.

APPROVED _____
(Print Principal Investigator Name and Title)

APPROVED _____
(Principal Investigator's Signature) Date

REGISTRY CONTACTS

PROMETHEUS REGISTRY COORDINATING CENTER:	Tel: 877-216-3678 Email: study-proclaim@prometheuslabs.com
STEERING COMMITTEE:	Michael Wong, MD, PhD (Committee Chair) USC University Hospital 1500 San Pablo St Los Angeles, CA 90033-9281 Tel: 323 442 8672
REGISTRY SPONSOR:	Prometheus Laboratories Inc. 9410 Carroll Park Drive San Diego, CA 92121 Tel: 888 423 5227

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

AE	Adverse event
BOR	Best overall response
CFR	Code of Federal Regulations
CR	Complete response
CRF	Case report form
CRO	Contract Research Organization
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic Data Capture
FDA	Food and Drug Administration-USA
GCP	Good Clinical Practice
HD	High dose
HIPAA	Health Information Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IL-2	Interleukin-2
IRB	Institutional Review Board
LDH	Lactate dehydrogenase
mM	Metastatic melanoma
mRCC	Metastatic renal cell carcinoma
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressing disease
PI	Principal Investigator (at each site)
PET	Positron Emission Tomography
PFS	Progression free survival
PR	Partial response
RECIST	Response Evaluation Criteria in Solid Tumors
rIL-2	Recombinant interleukin-2
RSC	Registry Steering Committee
SAE	Serious adverse event
SD	Stable disease
TEM	Treatment emergent mortality
TTF	Time to treatment failure
TTP	Time to tumor progression
US	United States
WHO	World Health Organization

1. INTRODUCTION AND REGISTRY RATIONALE

1.1 Proleukin for Cancer Therapy

Proleukin® (the brand name of aldesleukin for injection), also commonly known as interleukin-2 (IL-2) or recombinant IL-2 (rIL-2), was approved by US FDA in the1990s for treating adult patients with metastatic Renal Cell Carcinoma (mRCC) or metastatic melanoma (mM). High dose IL-2 (hereafter "HD IL-2") is the first immunotherapy approved for use as a single agent in the treatment of cancer. It appears necessary to create a profound systemic cytokine reaction to maximize tumor response[1, 2]. Careful patient selection, hospitalization, and careful monitoring and management are mandatory for the administration of HD IL-2[3, 4].

As an immunotherapy, the IL-2 therapy aims to activate/stimulate a patient's immune system by producing more cytotoxic T-cells to fight tumor or metastasized cancer cells[5-7]. However the exact mechanism by which the therapy mediates its antitumor activity in humans remains unclear and proper criteria allowing pre-therapy patient stratification for likelihood of response have not yet been established in clinical practice[4].

To date, HD IL-2 is the only therapy for metastatic kidney cancer and melanoma that can produce a long lasting remission of disease. In the non-randomized small phase 2 trials from the approval of Proleukin to the modern era, the complete and overall response rates (CR and ORR) in treating melanoma and RCC were 5-6% and 15-28% respectively[8-10]. The most significant feature of these responses is the fact that the majority of CRs and a smaller proportion of Partial Responses (PRs) persist for years as measured by disease and treatment free survival, suggesting durable immunologic control or eradication of the malignancy. In these studies used for Proleukin approval, median Overall Survival (OS) of HD IL-2 was reported as 16-19 months for RCC but only 4.5-8.8 months for melanoma (data from a variety of trials reported prior to 2003)[11]. Treatment-related death rates of HD IL-2 therapy were reported as 2% and 4% for melanoma and RCC respectively in the registration studies[8, 9]. The follow-up for these studies is variable and is largely limited to the responder population[12]. Subsequent reports of using HD IL-2 in these indications have been confounded by the following circumstances: a) selection bias; b) publication bias; c) small sample size; d) follow-up difficulty; e) frequent use of historical controls; f) combination drugs; and g) environment changes in medical practice. Therefore further data collection in the post-approval setting, e.g. a patient registry, is necessary to explore the use of the drug in the current environment.

Prognostic factors for HD IL-2 therapy are also controversial[13, 14]. Predictive features including age, site and bulk of metastases, lactate dehydrogenase (LDH), hemoglobin etc., have been variable in their influence and subgroups are usually too small for reliable multivariate analysis. The clear cell carcinoma variant of renal cell and good performance status in both malignancies are reliable predictions of response in all studies.

1.2 Registry Rationale

Therapies requiring hospitalization and substantial expertise to administer, are difficult to evaluate utilizing the usual instrument, the randomized clinical trial, with endpoints of safety and effectiveness[15]. Blinding is impossible as comparative therapy does not require hospitalization or is so distinctly different that blinding is impossible.

The diseases treated in this manner are usually serious and often life threatening. Patient management, treatment outcomes, and safety are very dependent upon the experience of the hospital personnel. Evolving technologies and management strategies based on experience may greatly influence both safety and effectiveness but are likely to be individualized from site to site.

Registries have evolved as a method of investigating such therapies[15], most notably, marrow and stem cell transplantation. By collecting observational data on all patients in a standardized way, the aforementioned challenges can be evaluated through both larger sample sizes and the ability to evaluate adequately sized cohorts of patients over various time periods with significantly different initial prognoses, management techniques or therapy combinations[16]. Prognostic factors hypothesized in small trials can be verified and refined using such a registry. Furthermore, the therapy's administration will become more standardized as it is studied and evolution will proceed more effectively.

The PROCLAIM^{SM} Registry, is designed to create an observational database that will allow evaluations of the real world treatment patterns and trends involving HD IL-2 effectiveness, tolerability, and other patient management outcomes in treating patients with mRCC, mM or other malignancies in the United States (US).

2. REGISTRY OVERVIEW

2.1 Registry Design

The PROCLAIM^{SM} Registry is a US-based, multicenter Registry designed to establish a high quality observational database of real-world clinical data on HD IL-2 when used to treat patients with mRCC, mM or other malignancies. The Registry will not, in any way, suggest changes in the treatment or management of the patients enrolled in the Registry. Therefore, physicians will continue to manage and treat patients according to standard of care and their own judgment.

The PROCLAIM^{SM} Registry will start with a retrospective pilot data collection from a de-identified finite number of patient cases abstracted from their existing medical charts. The features collected will be identical to those planned for the prospective registry. The resulting database will be used to formulate hypotheses to be tested using the prospective registry database. Patients utilized in the retrospective analysis will be excluded from the prospective portion of the PROCLAIM^{SM} Registry.

In the prospective portion of the Registry, sites will enroll patients who are expected to start a course of HD IL-2 therapy or have not yet completed their 1st course of HD IL-2

treatment. Once enrolled, the patient must receive at least one dose of HD IL-2 to remain in the Registry. Patients will be treated and followed according to the site's standard of care. This Registry will in no way induce changes in the management of individual patients. Clinical data features will be entered into an Electronic Data Capture (EDC) system, and organized into a registry database. The registry database will be interrogated according to database query protocols approved by the Steering Committee. (See **Appendix A** for an example data query proposal to the Registry Database). A subset of patients will participate in one of the Prometheus Proclivity studies (12PLK01, 12PLK02, 12PLK03). The Proclivity studies involve HD IL-2 in sequence with another therapy. Patients enrolled into any of the Proclivity studies and received a least one dose of HD IL-2 will be enrolled and followed in the Proclaim registry.

The data contained in the registry database will be observational data. The PROCLAIM^{SM} Registry does not stipulate patient care, specific visits or interventions but merely surveys standardized parameters regarding HD IL-2 and associated therapies as they are applied by treatment centers. The collection of standard data over time permits the evaluation of trends in patient survival and subsequent therapy exposure. The database will be used to answer future queries formulated by researchers.

The PROCLAIM^{SM} Registry will be sponsored by Prometheus Laboratories, Inc.

2.2 Registry Database Structure

The registry database will, contain individual patient demographic and clinical data as well as, data on the HD IL-2 treatment centers. This will include:

- Site specific practices in HD IL-2 administration
- Patient specific features
- Treatment emergent features
- HD IL-2 related outcomes
- Subsequent treatment

The Sponsor will be the sole custodian of the registry database. The Registry Steering Committee (RSC), a governance body of the PROCLAIM^{SM} Registry, will be responsible for determining who has access to the data, what, and how the analyses are performed (see Section 7 "Queries of the Registry Database"). Section 7 also describes the process for releasing data from the registry database to querying investigators. The RSC is also responsible for determining if and when data will be extracted from the database or shared with others.

3. REGISTRY OBJECTIVES

3.1 Primary Objectives

- To establish a standardized source of observational data that can be used to report and query patient care patterns, clinical outcomes and trends from HD IL-2 therapy in treating mM, mRCC or other malignancies.

3.2 Secondary Objectives

- To create a retrospective database which can be used for hypothesis generation
- To report pre-specified summary data (see Section 6) on an annual basis

4. REGISTRY PLAN

4.1 Investigator Site Selection Criteria

Investigator sites will be included based on feasibility analysis of established medical centers where patients are treated with HD IL-2 by qualified physicians. Additional data on site characteristics, standard treatment approach, and volume of patients treated will be assessed. An adequate blend of high volume sites (sites that treat a minimum of 25 HD IL-2 patients per year) and low volume sites (sites that treat 5-15 HD IL-2 patients per year) as well as a representative distribution of patients with mM and mRCC, will be needed to participate in the Registry. Once sites are selected to participate in the Registry, the site physicians will enroll patients into the Registry. Treatment and follow up will occur per the site's standard of care.

The Registry is planned to include 25 sites in the US for prospective patient entry. Once the Registry procedures are established, additional sites may be added. Of the initial 25 planned sites, approximately 10 will apply the registry data collection instruments retrospectively to their HD IL-2 patients from several previous years, as a test of the system, and to create a separate database.

For retrospective participation, a site must have treated approximately 25 HD IL-2 patients in the previous year prior to participation in the Registry and have a medical record database that allows efficient retrospective data extraction (e.g., a qualified EMR system or research database). The PROCLAIM^{SM} Registry will adjust the starting date for retrospective data collection to accrue an average of 25 consecutive patients at each site.

4.2 Selection of Patient Population

All eligible patients will be offered the opportunity to participate in the PROCLAIM^{SM} Registry. Patients approached for participation who do not enter the registry will be recorded on the screening log with the reason for non-participation.

The PROCLAIM^{SM} Registry will include approximately 250 patients in the retrospective cohort and a prospective cohort accrued over 5 years or longer.

4.3 Informed Consent

Prior to completing their 1st course of HD IL- 2, patients will be provided information about participation in the Registry and must sign an Institutional Review Board (IRB) approved

informed consent document indicating their consent to participate. For patients that are participating in one of the Proclivity studies, 12PLK01, 12PLK02 or 12PLK03, it is acceptable for patients to sign consent for the Proclaim study at any time. The consent form must be signed by the patient or legal representative, and the investigator-designated site staff must obtain the consent. Documentation of consent must be maintained at the treating center. A copy will be provided to the patient and placed in the patient's medical record. Formal consent must be obtained before any prospective data collection occurs. No study data should be entered in the eCRFs until the patient has had at least one dose of HD IL-2.

Written consent is not required for the retrospective data collection as only de-identified patient data will be extracted from medical records of the patients who have conformed to site specific guidelines permitting research on their medical records without personal identification. Sites involved in the retrospective data collection are responsible for extracting and de-identifying patient data prior to data entry into the registry database. Prospective follow-up on surviving patients in the retrospective patient cohort will not be performed as this subset will not have been consented to participate.

4.4 IRB Approval of the PROCLAIM^{SM} Registry

The PROCLAIM^{SM} Registry protocol and its associated consent forms will be provided to registry sites. Sites are responsible for submitting the protocol and consent forms to their designated IRBs for review and approval. IRB approval must be documented prior to treatment facilities presenting the registry protocol to patients. Patient informed consent must be obtained prior to submission of data to the registry database.

4.5 Patient Inclusion/Exclusion Criteria

4.5.1 Inclusion Criteria

Patients who meet all of the following criteria will be eligible for inclusion into the Registry:

Prospective Cohort:

- 18 years of age and older
- Given informed consent for participating in the Registry
  Is receiving or has received an initial course (2 cycles) of HD IL-2 and has not had post treatment imaging studies performed prior to enrollment. Data will only be collected and analyzed for patients who received at least one dose of HD IL-2. Exception: Patients enrolled in a Proclivity study (12PLK01, 12PLK02 or 12PLK03) can be enrolled into the registry at anytime.

Retrospective Cohort:

- 18 years of age and older
- Received HD IL-2 at the site prior to site initiation
- Have conformed to site specific guidelines permitting research on medical records without personal identification

4.5.2 Exclusion criteria

Patients who meet the following criteria will be excluded from participation in the Registry:

Prospective Cohort:

- Received more than 1 course of HD IL-2 as defined in 4.5.1

Retrospective Cohort:

- Treatment with HD IL-2 occurring more than 5 years ago

4.6 Participant Withdrawal

At any time a patient may request that his or her data no longer be available for research purposes. Instructions on how to withdraw consent will be provided in site specific informed consent documents.

4.7 Data Collection Strategies

Data will be collected for this registry database using an electronic data capture (EDC) platform. Site staff will use an electronic case report form (eCRF) to enter specific clinical data of interest into the registry database. All data submitted into the registry database must have corresponding source documentation (medical records or management charts, physician notes, etc). Preliminary retrospective data or any other data needed for the study may be collected on paper CRFs and entered into the EDC database by the sponsor or the sponsor's delegate.

4.7.1 Collection of Site Specific Data

Data pertinent to site specific practices on HD IL-2 administration will be collected from each participating site using a set of standard CRFs. Site staff are responsible for submitting these data to the registry database at the time of site initiation.

4.7.2 Collection of Patient Data

Pre-specified standard patient data will be collected at the time a patient joins the Registry, at each cycle of HD IL-2 therapy, at the standard initial tumor assessment (usually it's approximately 3-months after the beginning of HD IL-2 therapy), and at the standard interval follow-up visits (approximately every 6-months). All these data should be abstracted from the patient's medical records maintained at the treatment site. The registry database will be

available for future data queries approved by the PROCLAIM[SM] Registry Steering Committee.

Standard of Care Visits	Data to Collect[a]
Baseline Assessment	Informed Consent Inclusion/exclusion criteria Demographics and relevant history
HD IL-2 Treatment – For Each Cycle	Relevant laboratory results Dosing information, including reasons for discontinuation Concomitantly administered anti-tumor therapy
Initial Treatment Assessment	Best overall response determined by clinician Continuation of HD IL-2 therapy
Post-Treatment Follow-ups – For Each Interval Visit	Autoimmune disease (+/-) Disease response since last assessment, determined by clinician Interval therapy history Survival status Note: If the patient is not able to have an in office follow- up visit, the information can be collected via phone.

[a] Only de-identified data will be collected on retrospective patients.

4.8 Data Management

The CRO is responsible for all data management functions and documents related to this Registry (See Section 11.2 for detailed CRO responsibilities). The CRO's EDC database system will be designed to provide data entry, editing, and quality control, integrated with data management functions.

5. CLINICAL METRICS

The following clinical metrics will be used to measure the standard clinical outcomes and treatment emergent events that will be assessed through this Registry:

5.1 Tumor Assessments and Response

The tumor responses to HD IL-2 treatment will be determined by the site PI. Tumor responses will be assessed and categorized as CR, PR, SD, or PD using either RECIST or WHO criteria per site's standard procedure*. The sites will be required to indicate which criteria were employed in each patient's tumor assessments.

* PET scan may be used to confirm a CR or a conversion of a PR to a CR. There may also be surgical conversion of a PR to a CR. The site staff will adequately document these conversion cases on the case report forms for inclusion in the database.

Best Overall Response (BOR):

BOR is defined in this Registry as the investigator determined best response, occurring at or prior to Month 3; if the BOR is CR, PR, or SD, response since the last evaluation and TTP (first progression after Proleukin will be evaluated at standard of care interval visits (approximately every 6 months) until disease progression.

5.2 Patient Survival

Overall Survival (OS):

The OS is defined as the time from initiation of HD IL-2 treatment until patient death for any reason

Progression Free Survival (PFS):

PFS in this Registry is defined as the time from initiation of HD IL-2 treatment until disease progression or death.

5.3 Treatment Emergent Events

Treatment emergent events are defined as changes in specific features occurring during and shortly after HD IL-2 administration.

Treatment Emergent Mortality (TEM):

TEM is defined as patient death occurring from Day 1 of HD IL-2 administration until 2 weeks after the last dose of HD IL-2.

Other treatment emergent events of interest will include, at a minimum, the following:

- Number of doses administered per cycle
- Cause(s) for concluding dosing each cycle
- Number of cycles administered
- Cause(s) for discontinuing HD IL-2 therapy

6. ANNUAL DATA OUTPUT SUMMARY

It is anticipated that a report will be generated on an annual basis in order to track the status of the registry database and have an executive summary on current use of IL-2 and outcomes. The following data will be included in the annual summary.

- Number of sites in the PROCLAIM^{SM} Registry
- Number of patients enrolled (total, mM, and mRCC)
- Number of patients treated with HD IL-2 alone
- OS and PFS

- Investigator-determined ORR at 3-month assessment
- Number of dose per HD IL-2 treatment cycle
- Number of HD IL-2 cycles received per patient
- Causes of discontinuation of HD IL-2 treatment

7. QUERIES OF THE REGISTRY DATABASE

7.1 Request for Data Access

The PROCLAIM^{SM} Registry database may be made available to research investigators both within and outside the registry network. The RSC is responsible for defining the policies and procedures for data query and analysis, data sharing with others, and registry data publications.

7.2 Query Review and Approval

A data request to use the registry database will be reviewed and approved by the RSC to ensure that the query is scientifically sound, strategically feasible, and fits within the limits defined in this Registry, and is covered by the participant's informed consent.
A data extract plan will be prepared and the necessary data will be extracted from the database into a query-specific dataset for analyses. The data query is then added to the overall research portfolio of the registry database.

Data from these analyses will be shared with investigators upon request, but always as summarized, aggregate data. No identifying information will be released beyond a Registry ID number randomly assigned to each patient at the enrollment visit. At no time is an individual investigator given the names of participants, or the identity of the site where the patients were treated.

8. TYPES OF ANTICIPATED DATABASE QUERIES

Observational data queries may use the registry database for examining HD IL-2 therapy patterns including trends in care, comparative effectiveness and complications of treatment found in the patient population. Proposals for data provision must be submitted to the RSC for review and approval prior to data extraction or any additional data collection from the Registry. The following are the general types of anticipated data queries using the observational registry database:

- Changes in treatment patterns of HD IL-2
- Prognostic factors and patterns for HD IL-2 therapy
- Clinical responses to HD IL-2 therapy
- Late and rare effects of HD IL-2 therapy
- Long-term outcomes after HD IL-2 therapy
- Death incidence/relapse in patients received HD IL-2 therapy
- Persistence/resolution of complications after HD IL-2 administration
- Doses and cycle numbers of HD IL-2 in treated patients
- Reasons for HD IL-2 discontinuation
- Impact of site/patient specific features on treatment outcomes

- Success of different treatment models for the registry population
- Potential improvement of patient management in use of HD IL-2 therapy

9. SAFETY REPORT

9.1 Reporting

Sites enrolled in the PROCLAIM^{SM} Registry are encouraged to report serious adverse events (SAEs) related to HD IL-2 treatment in compliance with the US Code of Federal Regulations. If Proleukin (Aldesleukin, HD IL-2) is a suspect or co-suspect drug reported on the FDA form 3500A Medwatch report, Prometheus laboratories requests a courtesy copy of the report. Within this reporting, Prometheus requests a courtesy copy Medwatch form of any deaths related to Proleukin treatment. Please e-mail or fax the courtesy copy to Prometheus Laboratories' drug safety department at drugsafety@prometheuslabs.com or faxed to (858)754-3046. Please also include your contact information.

10. DISCLOSURE OF DATA AND PUBLICATIONS

10.1 Data Ownership and Confidentiality

All information provided by the registry will be held in strict confidence. Access to all information in the registry database will be tightly controlled with passwords and logins. Access to the registry database is limited to personnel based on their specific roles and responsibilities.

Patients will be assigned a unique identification number when the treatment center enrolls the patient into the PROCLAIM^{SM} Registry. The identifying patient information, such as first and last name, social security number, contact phone number, and city, state and country may be verified at enrollment by the site staff to ensure that the patient has not been enrolled previously in the registry. A unique identification number is then assigned. The information will be maintained within the site's secure medical database which is separate from the registry database. These identifying data will not be included in data sets for analysis. The unique identification number contains no identifying information within it and will be used to track all information about the patient in the registry database.

The patient identity in the registry will be kept confidential at all times. Identifying information that will be included in the registry includes diagnosis date, birth date, treatment date and site. Data released to investigators outside the registry shall not include identifying data such as birth date and location of treatment, Sites will be assigned a unique identification number when initiated into the registry which will be used for reporting purposes. Public reporting of data will maintain the anonymity of both patients and sites.

All deliverables that come out of the registry database are considered confidential and may not be distributed without documented permission by the Sponsor (See "Data Sharing Policies" for more detailed instructions).

All research personal participating in the PROCLAIM^{SM} Registry will maintain up-to-date training in protection of human subjects.

10.2 Data Sharing and Publications

The registry data, either summary data and/or individual patient data, may be shared and published with agreement between the investigators and the Registry Steering Committee (RSC). An investigator who wishes to use data from the registry database must make a formal query request. The request is reviewed on the basis of scientific merit and feasibility.

Study results will not be published without the prior review and approval of the RSC. Authorship of manuscripts shall be in accordance with normal academic standards as described in the Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Each party shall acknowledge the role of the other parties in all manuscripts. Potential coauthors will include members of the RSC, site investigators, and personnel from the Sponsor.

11. REGISTRY MANAGEMENT

11.1 Registry Oversight

A Registry Steering Committee (RSC) will be formed as a governance body to provide scientific oversight for the Registry, CRO and Sponsor). The RSC will act on behalf of the Sponsor and key stakeholder groups to oversee the feasibility, operations and the achievement of outcomes of the Registry.

A charter will be generated to define the responsibilities and scope of activities of the RSC, the composition and membership of the RSC, the purpose, timing and schedule of RSC meetings, and the relationship between RSC, Sponsor, and investigators. The RSC will be made up of between 4-6 members, with at least 1 member being a sponsor representative. Key opinion leaders will be invited to participate as RSC members and a chair person will be selected from amongst the members.

In practice, the RSC is responsible to carry out the following functions:

- Provide scientific and medical guidance on the design and conduct of the PROCLAIM^{SM} Registry
- Hold periodical webinar and face to face committee meetings. Convene ad hoc meetings to monitor and review the registry progress and aggregate outcome data
- Control the scope of the PROCLAIM^{SM} Registry by providing strategically and scientifically sound advice as emergent issues force justifications to be considered
- Review and approve research proposals using the database of the PROCLAIM^{SM} Registry
- Define and oversee plan for use of data
- Make recommendations regarding data interpretation
- Approval and communication of the registry's deliverables

- Oversee completion and quality of the PROCLAIM^{SM} Registry
- Nominate individuals to serve on the committee

11.2 Contract Research Organization Responsibilities

The CRO is responsible for site monitoring, data management, data extraction, and other relevant project management responsibilities. Safety reporting that is routed to the CRO, must be forwarded to the Sponsors DSPV group per section 9.0 of the protocol.

11.3 Sponsor Responsibilities

Prometheus Laboratories, Inc. is the Sponsor of the PROCLAIM^{SM} Registry. The Sponsor is responsible for funding and managing the overall conduct of the registry program.

11.4 Principal Investigator Responsibilities

The Principal Investigator (PI) has the overall responsibility for patient treatment and management per site standard of care.

11.5 Access to Source Data/Documents

Site investigators in the Registry will allow clinical monitors from the Sponsor or the CRO direct access to all source data and documents including a patients complete medical record if necessary. Access must also be granted to authorized auditors, IRB reviewers, and all applicable regulatory bodies as necessary.

12. ETHICAL CONSIDERATIONS

The registry is to be conducted according to US and international standards of Good Clinical Practice, applicable government regulations and IRB policies and procedures.

12.1 Institutional Review Board

The registry protocol and any amendments will be submitted to an Institutional Review Board (IRB), in agreement with local legal requirements, for formal approval of the Registry. The IRB decision concerning the Registry will be made in writing to the investigator and a copy of this decision will be provided to the Sponsor before commencement of the registry. Copies of the IRB approved documents, as well as the IRB approval letters, will be retained in the Registry Trial Master File.

The site investigators will allow the IRB direct access to all relevant documents throughout the life cycle of the Registry. The IRB review will be conducted in accordance with all applicable regulatory requirements.

12.2 Informed Consent and Patient Protection

All patients in the prospective data collection will be provided written informed consent for participation in the Registry and release of their HIPAA compliant data to Prometheus and

the CRO for analysis.

The Informed Consent Forms (ICF) must be written in language readily understood by the patient. The ICF and any other related documents will be submitted with the protocol for review and approval by the IRB before the registry initiation. The formal consent must be obtained before any patient data can be entered into the registry database. The consent form must be signed by the patient or legal representative, and the investigator-designated site staff obtaining the consent. After informed consent is obtained, the original signed ICF copy will be retained in the investigator site records, and a copy will be provided to the patient.

In addition, the investigators and registry personnel will be responsible for complying with the Health and Information Portability and Accountability Act (HIPAA) requirements. The registry site is responsible for the accuracy and completeness of the data submitted and for ensuring all medical records are available to the clinical monitor, IRB auditors, and regulatory agents, as needed.

12.3 Record Retention

Per FDA and ICH GCP requirements, the RSC requires that all the registry-related documentation be retained for two years after the registry is closed or as mandated by the institution, whichever is longer. The investigator should contact Prometheus before any documentation is discarded.

13. SOURCE OF FUNDING

The PROCLAIM^{SM} Registry will be supported by Prometheus Laboratories, Inc. as the Sponsor.

14. APPENDIX A: AN EXAMPLE REGISTRY DATABASE QUERY

Query Proposal #: 10PLK13-01

Proposal Title:

Treatment Related Mortality in Today's Clinical Practice in Patients with Metastatic Melanoma or Renal Cell Carcinoma Treated with High-Dose Interleukin-2: An Embedded, Controlled Analysis Using PROCLAIM^{SM} Registry Database

1. BACKGROUND

Proleukin® (the brand name of aldesleukin for injection), also commonly known as interleukin-2 (IL-2) or recombinant IL-2 (rIL-2), was approved by US FDA in early 1990s for treating adult patients with metastatic melanoma (mM) or metastatic Renal Cell Carcinoma (mRCC). Today high-dose IL-2 remains as an effective immunotherapy for fighting cancers and have been used alone as well as in conjunction with chemotherapy and other treatment options. It is an efficacious yet toxic therapy as it works through patient's profound immune system to trigger tumor response. Over the years, despite the high mortality and severe morbidity rates initially produced, HD IL-2 can now be safely and effectively administered by experienced clinicians. It is crucial to have and adhere to a standard dosing and patient assessment criteria during IL-2 administration in order to manage symptoms and minimize toxicities[7].

In the studies leading to the approval of Proleukin, the complete and clinical overall response rates (CR and ORR) in treating mM and RCC were reported to be 5-6% and 15-28% respectively, median Overall Survival (OS) of HD IL-2 were reported at 16-19 months for mRCC but only 4.5-8.8 months for mM, and treatment-related death rates were reported as 2% and 4% for mM and RCC respectively[8, 9, 10]. All those data all collected from patients studied prior to 1998.

2. HYPOTHESIS:

We hypothesize that patient mortality in contemporary clinical practice is significantly lower than the historical data reported in initial clinical trials in 1990s on patients with mM or mRCC treated with HD IL-2 therapy.

3. SPECIFIC AIMS:

- To estimate the cumulative treatment emergent mortality (TEM) observed in patients treated with HD IL-2 for mM or mRCC using prospective data from the PROCLAIM^{SM} Registry database.
- To compare the TEM derived from the PROCLAIM^{SM} Registry in mM patients treated with HD IL-2 with historical mortality data.
- To compare the TEM derived from the PROCLAIM^{SM} Registry in mRCC patients treated with HD IL-2 with historical mortality data.
- To compare the TEM derived from the PROCLAIM^{SM} Registry between mRCC and mM in patients treated with HD IL-2.

4. DESIGN AND PROCEDURE:

The PROCLAIM[SM] Registry database will be the source of information to support all the data for fulfilling the query. One purpose of the registry database is to provide a research platform for researchers to study the real world treatment patterns and trends, as well as clinical outcomes, related to HD IL-2 therapy in patients with mRCC, mM or other malignancies in the United States. Treatment emergent mortality (TEM), which is defined as the incidence of patient death occurring from Day 1 of HD IL-2 administration until 2 weeks after the last dose of HD IL-2 with causality determined by the treatment physician, is standard data fields collected in the PROCLAIM[SM] Registry and will be the primary endpoint of this database query.

The primary endpoint will be analyzed for all patients and by stratifications for disease type (mM vs. mRCC). If a statistical difference is found in mortality rate comparison between this analysis dataset vs. historical data in Proleukin Prescription Information, analysis will be further stratified for metastatic sites, toxicity experience, line of treatment, and other ad hoc strata. The study outcomes will be compared to historical data as reported in the Prescription Information and literature, where such information exists.

The study will also examine incidence of treatment emergent death and overall survivals as time-dependent and patient-dependent variables and the cause of death between the two disease indications (mM vs. mRCC).

5. PATIENT POPULATION:

All prospective patients in the PROCLAIM[SM] Registry

6. ENDPOINTS:

The primary outcome is treatment emergent mortality (TEM). TEM is defined as the incidence of patient death occurring from Day 1 of HD IL-2 administration until 2 weeks after the last dose of HD IL-2 with causality determined by the treatment physician. The death event will be summarized by the cumulative incidence rate with disease types as stratification factors.

7. STRATIFYING FEATURES TO BE ANALYZED:

The TEM comparisons between data derived from the PROCLAIM[SM] Registry vs. historical data may be stratified for multiple tiers of analyses by the following features:

7.1 Patient related:

- Gender
- Age
- Weight and height
- Ethnicity
- Race
- ECOG score
- First Dose of HD IL-2 date

7.2 Disease related:

- Initial diagnosis date
- Disease type
- Metastasis
- Stage/remission status at enrollment
- Prior cancer therapies
- Surgery history
- Line of treatment with HD IL-2 (1e versus 2nd, 3rd ...)

7.3 HD IL-2 treatment related (for each cycle):

- Dosing start date
- Dose received
- Dose frequency
- Number of doses received
- Other interval cancer therapy received
- Toxicity experienced
- Reason for dose discontinuation

7.4 Treatment assessment and survival follow-up:

- Investigator determined response
- Method of response assessment
- Patient interval survival status
- Patient death date, as applicable
- Reported as SAE? If yes, try to get case narrative via Proleukin safety monitoring report

8. STATISTICAL CONSIDERATIONS

8.1 Determination of Sample Size

The sample size for this analysis is determined based on anticipated differences between data from the PROCLAIM^{SM} Registry and historical data on the death rate observed in patients with mM or mRCC treated with HD IL-2. The death rates of 2% and 4% were reported in the historical data for mM and mRCC respectively but are expected to be no more than 1% for either disease. The methods of Fleiss are used to determine the sample size necessary to detect differences in death rate between data from the PROCLAIM^{SM} Registry and historical data. The number of patients necessary to detect 2% and 3% difference in death rate between PROCLAIM and historical data with 80% power at α=0.05 significance level is 1381 and 276 for patients with mM and mRCC respectively. To allow for a 20% dropout rate, a target sample size of N=1727 patients with mM and N=345 patients with mRCC is chosen for a total of N=2027 patients.

8.2 Statistical Analyses

Statistical analysis will be generated on a specific case by case basis.

8.3 Interim Analyses

Data will be requested and analyzed periodically and descriptively throughout the life cycle of the PROCLAIM^{SM} Registry. Statistical significance of the difference in death rate between data from the PROCLAIM^{SM} Registry and historical data will be summarized once and after the dataset reach the sample size requirements as specified in Section 8.1. After this analysis protocol is approved by the Registry Steering Committee, a data extract plan will be prepared and the data to conduct the necessary analyses will be extracted from the registry database into a query-specific research dataset with controlled assessment.

--- End of the Example Registry Database Query ---

15. REFERENCE LIST

(1) Panelli MC, White R, Foster M et al. Forecasting the cytokine storm following systemic interleukin (IL)-2 administration. *J Transl Med* 2004;2(1):17.

(2) Panelli MC, Wang E, Phan G et al. Gene-expression profiling of the response of peripheral blood mononuclear cells and melanoma metastases to systemic IL-2 administration. *Genome Biol* 2002;3(7):RESEARCH0035.

(3) Schwartz RN, Stover L, Dutcher J. Managing toxicities of high-dose interleukin-2. *Oncology (Williston Park)* 2002;16(11 Suppl 13):11-20.

(4) Schwartzentruber DJ. Guidelines for the safe administration of high-dose interleukin-2. *J Immunother* 2001;24(4):287-293.

(5) Conlon PJ, Henney CS, Gillis S. Cytokine-dependent thymocyte responses: characterization of IL 1 and IL 2 target subpopulations and mechanism of action. *J Immunol* 1982;128(2):797-801.

(6) van der Vliet HJ, Koon HB, Yue SC et al. Effects of the administration of high-dose interleukin-2 on immunoregulatory cell subsets in patients with advanced melanoma and renal cell cancer. *Clin Cancer Res* 2007;13(7):2100-2108.

(7) Jarkowski A, Wong M. A re-assessment of the safety and efficacy of interleukin-2 for the treatment of renal cell carcinoma. *Clinical Medicine:Therapeutics* 2009;1:527-540.

(8) Fyfe G, Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Louie AC. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *J Clin Oncol* 1995;13(3):688-696.

(9) Atkins MB, Lotze MT, Dutcher JP et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. *J Clin Oncol* 1999;17(7):2105-2116.

(10) McDermott D, Ghebremichael MS, Sognoretti S et al. The high-dose aldesleukin (HD IL-2) "SELECT" trial in patients with metastatic renal cell carcinoma (mRCC). *J Clin Oncol* 2010;28(15 suppl):Abstract 4515.

(11) Fisher RI, Rosenberg SA, Fyfe G. Long-term survival update for high-dose recombinant interleukin-2 in patients with renal cell carcinoma. *Cancer J Sci Am* 2000;6(Suppl 1):S55-S57.

(12) Klapper JA, Downey SG, Smith FO et al. High-dose interleukin-2 for the treatment of metastatic renal cell carcinoma : a retrospective analysis of response and survival in patients treated in the surgery branch at the National Cancer Institute between 1986 and 2006. *Cancer* 2008;113(2):293-301.

(13) Fumagalli LA, Brivio F. Immunotherapy and prognostic factors. *J Clin Oncol* 2006;24(25):4218-4219.

(14) Mannam P, Dutcher J, Eapen J et al. Role of prognostic factors in patients with metastatic renal cell carcinoma (MRCC) eligible for treatment with Interleukin2 (IL-2). *J Clin Oncol* 2003;22:Abstract 1770.

(15) Port FK. Role of observational studies versus clinical trials in ESRD research. *Kidney Int* 2000;57(S74):S3-S6.

(16) Registries for evaluating patient outcomes: a user's guide. Rockville, MD: Agency for Healthcare Research and Quality; 2007. Report No.: AHRQ Publication No. 07-EHC001-1 .