GALLIUM-IP-13
Final Report

PROTOCOL NUMBER:	GALLIUM-IP-13
PROTOCOL TITLE:	A Phase 2, Multi-Center, Randomized, Placebo-Controlled Study of IV Gallium Nitrate in Patients with Cystic Fibrosis
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OVERVIEW

Study Rationale and Design

Much attention has been focused on the need for new antibiotics. One reason for this is that heavy antibiotic use has greatly increased resistance due to genetic mutations. But new agents are also needed because conventional antibiotics work poorly in chronic infections, even when the organisms are sensitive when tested *ex vivo*. These chronic infections resist treatment in large part because the organisms live in biofilms. Biofilms are communities of bacteria associated with surfaces and encased in a polymeric matrix making the bacteria far more resistant to killing than they are in the free-living (planktonic) state. Examples of biofilm infections include cystic fibrosis (CF) lung infections, endocarditis, osteomyelitis, wound, sinus, and device infections.

We are pursuing a novel approach that uses the metal gallium (Ga) to disrupt intracellular bacterial iron metabolism. Gallium has a nearly identical ionic radius as iron, and many biologic systems are unable to distinguish gallium from iron. Gallium disrupts iron dependent processes because Ga^{3+} cannot be reduced and redox cycling is critical for iron's biological functions. Importantly, gallium is already approved by the Food and Drug Administration (FDA) for intravenous (IV) use. Our data shows that gallium kills *Pseudomonas aeruginosa* (*P. aeruginosa;* including antibiotic resistant strains), is active against biofilms, and treats three different animal models *P. aeruginosa* infections. In our phase 1b study, we demonstrated that IV gallium was both safe and had favorable pharmacokinetics in CF patients. We also found suggestions of preliminary efficacy. We will study the preliminary efficacy as assessed by both lung function and sputum microbiology of IV gallium in CF adults. We will also continue to assess pharmacokinetics (PK) and safety of IV gallium in CF patients.

This is a phase 2, multi-center, randomized, placebo-controlled trial in adults with CF chronically infected with *P. aeruginosa*. The study will evaluate the safety and clinical efficacy of a five-day infusion of IV gallium nitrate (IV gallium).

The primary objective of this study is to assess the efficacy of IV gallium to improve pulmonary function as measured by a 5% or greater relative improvement in forced expiratory volume in one second (FEV_1) from baseline to Day 28. The secondary objectives are:

- To assess the efficacy of IV gallium in improving measures of lung function including relative change in FEV_1, absolute change in FEV_1, and forced vital capacity (FVC)
- To assess the efficacy of IV gallium in reducing *P. aeruginosa* in the lungs of CF patients based on quantitative cultures of sputum
- To assess the efficacy of IV gallium in improving respiratory symptoms as measured by the CF Respiratory Symptoms Diary – Chronic Respiratory Infection Symptom Severity Score (CFRSD-CRISS)
- To assess the sputum PK profile of IV gallium
- To assess the rate of acquired resistance of *P. aeruginosa* to gallium
- To explore the anti-inflammatory properties of IV gallium
- To explore the efficacy of IV gallium in reducing the use of antibiotics for an acute indication

Interim DSMB Reviews

Oversight for this trial is provided by the Cystic Fibrosis Foundation (CFF) Data Safety Monitoring Board (DSMB; Chair, Wayne Morgan, MD). The monitoring committee has been selected by the DSMB Chair to monitor this trial. Dr. Susan Banks-Schlegel, PhD, Senior Scientific Advisor of Airways Biology and Disease Branch NHLBI, serves as the point of contact for NHLBI.

Summary reports tabulating SAEs by treatment group are provided on a quarterly basis to the DSMB. Comprehensive safety interim reports is provided twice yearly to the DSMB and includes an overview of enrollment by site, detailed summaries of all SAEs, AEs, withdrawals, drug discontinuations, hospitalizations, protocol violations, laboratory parameters and other clinical safety endpoints.

All the summaries are presented by treatment group in a semi-unblinded fashion (A or B corresponding to Treatment or Placebo groups). The unblinded treatment code is available to the DSMB at any time upon request.

Report Generation

The final report will be generated using the data from the final locked database comprised of all study visits from XX randomized and treated subjects. All analyses will be performed using SAS 9.4 and R 3.3.X software.

Definition of the Analysis Populations

Intent-to-Treat Population (ITT): all randomized participants who were started on the study drug. The ITT population is analyzed for the primary and secondary endpoint analyses and comprises the safety population used for all safety analyses.

Per Protocol Population (PP): all participants in the ITT population who have no protocol violations, received no bisphosphonates or inhaled chronic antibiotics from 7 days prior to Day 1 through Day 28, and received gallium infusion for at least five sequential days. The PP population is used in the sensitivity analyses of the primary and secondary endpoints.

PLANNED ANALYSES

Enrollment and Study Visit Completion

Figure 1.1 shows participant disposition and Figure 1.2 the actual and projected enrollment over time. Table 1.1 displays an overview of enrollment and study completion by site. Table 1.2 summarizes the screen failures. Table 1.3 details the number of enrolled participants completing each study visit.

Withdrawals and Drug Discontinuation

Table 2.1 displays a summary of the reasons for withdrawal, and Table 2.2 summarizes participants who discontinued study drug early, and reasons for study drug discontinuation. Table 2.3 summarizes drug compliance based on participant diary information and unused study drug bags returned.

Demographics

Table 3.1 summarizes demographic and baseline characteristics at randomization.

Adverse Events

Table 4.1 presents the total number of serious adverse events (SAEs), Figure 4.1 displays a histogram of SAEs by treatment group, and Figure 4.2 and Table 4.2 show SAEs by system organ class. Table 4.3 displays the incidence of SAEs by relation to the study drug and Table 4.4 summarizes the incidence of SAEs by severity. Table 4.5 presents the total number of adverse events (AEs), Figure 4.3 displays a histogram of AEs by treatment group, and Figure 4.4 and Table 4.6 show AEs by system organ class. Table 4.7 displays the incidence of all adverse events by relatedness to the study drug and Table 4.8 displays the incidence of all AEs by severity.

Laboratory Parameters

Tables 5.1 and 5.2 summarize clinical hematology and chemistry results by visit and as a change from screening value. Table 5.3 shows urinalysis results by visit. Tables 5.4 and 5.5 summarize normal, abnormally high, abnormally low, and clinically significant hematology and chemistry results at each visit. Table 5.6 summarizes clinically significant abnormal urinalysis results.

Figures 5.1-5.4 summarize the values of serum creatinine, calcium, ionized calcium, and BUN as boxplots at each study visit. Also displayed are changes in from screening for each analyte.

Figures 5.5-5.8 show emergent high and emergent low hematology and chemistry results.

Hospitalizations

Table 6.1 provides a summary of hospitalization events and hospitalization days.

Primary Endpoint and Stopping Boundaries

The primary endpoint results will be summarized in relationship to the stopping boundaries in the second and third interim reports (at approximately 50% and 75% of accrual). The final primary endpoint analyses will be adjusted for the interim reviews.

Table 7.1 summarizes the primary endpoint, the difference between treatment groups in proportion of participants in ITT population experiencing a 5% or greater relative improvement in FEV_1 (L) from baseline to Day 28. The final primary endpoint analysis adjusted for the interim reviews is summarized. Table 7.2 repeats the primary endpoint analysis using the PP population.

Figure 7.2 show the relative change in FEV_1 (L) by visit and Table 7.3 shows the results of the MMRM model for relative change from baseline in FEV_1 (L) using the ITT population. Table 7.4 shows the results of MMRM model using the PP population.

Spirometry

Figures 8.1-8.5 show changes from baseline over time in FEV_1 (L), FEV_1 (% predicted), and FVC (L). Table 8.1 summarizes spirometry results from baseline and through the end of study, along with changes from baseline.

Tables 8.2-8.6 summarize the results of the MMRM models for changes from baseline in FEV_1 (L), FEV_1 (% predicted), and FVC (L).

CFRSD-CRISS

Table 9.1 summarizes CFRSD-CRISS at each study visit, along with changes from baseline. Figure 9.1 shows changes from baseline in CFRSD-CRISS at each point of diary completion. Table 9.2 summarizes the results of MMRM model for changes from baseline in CFRSD-CRISS.

Inflammatory Markers

Table 10.1 summarizes the names, abbreviations, units and source of inflammatory and oxidative markers analyzed in this report, while Table 10.2 provides the lower and upper limits of detection. Table 10.3 shows the inflammatory marker results by visit, along with changes from baseline to Day 28 and Day 56 when blood was collected for cytokines and chemokines. Table 10.4 summarizes the results of MMRM models for changes from baseline in inflammatory markers.

Bacterial Density and Emergence

Table 11.1 shows the availability of culture results and incidence of *P. aeruginosa* and other CF pathogens at Day 1, 28 and 56 when sputum was collected for microbiology.
Table 11.2 shows quantitative cultures results for *P. aeruginosa* density and changes from baseline to Day 28 and Day 56 when sputum was collected for microbiology. Table 11.3 summarizes the results of MMRM model for changes from baseline in *P. aeruginosa*.
Figure 11.1 shows quantitative *P. aeruginosa* density by visit, whereas Figure 11.2 displays changes from Baseline to Day 28 and Day 56 when sputum was collected for microbiology.
Table 11.3 summarizes emergence of *P. aeruginosa* and other CF pathogens from baseline and through the end of study.

Additional tables and figures showing quantitative changes in sputum density of other CF pathogens, such as *B. cepacia, A. xylosoxidan, S. maltophilia, S. aureus,* and *H. influenza* will be shown if sufficient data is present for these isolates.

Antibiotics

Table 12.1 provides a summary of the usage of acute oral, inhaled, and IV antibiotics initiated during study.

Appendix A

Listing A.1 shows protocol violations and exceptions and Listing A.2 provides SAE narratives from the clinical tracking spreadsheet.