Childhood Liver Disease Research and Education Network (ChiLDREN)

A RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED TRIAL OF CORTICOSTEROID THERAPY FOLLOWING PORTOENTEROSTOMY IN INFANTS WITH BILIARY ATRESIA

Manual of Operations (MOO)

1 April 2007 (Version 1)

LAST EDITED on 01 September 2010

CHAPTER 0. TABLE OF CONTENTS

CHAPTER 1. OVERVIEW

1.1 Summary of Study

CHAPTER 2. SCREENING AND RECRUITMENT

- 2.1 Population
- 2.2 Screening/Recruitment Plan
- 2.3 Eligibility/Exclusion Criteria
 - 2.3.1 Inclusion Criteria
 - 2.3.2 Exclusion Criteria
- 2.4 Exceptions to the Inclusion/Exclusion Criteria
 - 2.4.1 Details about Certain Eligibility Criteria
- 2.5 Screening/Enrollment Logs

CHAPTER 3. INFORMED CONSENT

3.1 Informed Consent Document

Chapter 0 1 of 5

3.2 Obtaining Informed Consent

3.3 Re-Consent

3.4 Health Insurance Portability & Accountability Act (HIPAA) Compliance

3.5 Non-English-Speaking Subjects

3.5.1 Other issues related to translators

CHAPTER 4. STUDY VISIT DETAILS

4.1 Visit Descriptions

4.1.1 Types of Visits

4.2 Case Report Form (CRF) Description and Instructions

- 4.2.1 Baseline
 - 4.2.1.1 Form S11 Eligibility (web-entry)
 - 4.2.1.2 Randomization Process at Baseline
 - 4.2.1.3 Drug Kit Assignment at Baseline
 - 4.2.1.4 Administration of Study Drug or Placebo at Baseline
 - 4.2.1.5 Adjunct Medications and Treatment at Baseline (ursodiol, vitamin K, AquADEK™, TMP-SMZ (Bactrim), Ranitidine (Zantac®))
 - 4.2.1.6 Discharge to Home Information
- 4.2.2 2-Week Follow-Up Visit
- 4.2.3 1-Month Follow-Up Visit
- 4.2.4 2-Month Follow-Up Visit
- 4.2.5 3-Month Follow-Up Visit
- 4.2.6 6-Month Follow-Up Visit
- 4.2.7 12-Month Follow-Up Visit
- 4.2.8 18-Month Follow-Up Visit
- 4.2.9 24-Month Follow-Up Visit
- 4.2.10 Study-Specific Procedures for Subjects Undergoing Liver Transplantation Prior to 2 Years of Age
- 4.2.11 Important CRFs Used Throughout the START Study

4.3 Pharmacy Dispensing of Study Medications

- 4.3.1 Dispensing Steroid/Placebo
- 4.3.2 Dispensing Other Study Medications
- 4.3.3 Patient Drug Accountability

4.4 Dose Reductions

4.5 Tapering

- 4.5.1 Blinded Taper
- 4.5.2 Unblinded Taper
- 4.5.3 Restarting Study Drug Related to Complication

Chapter 0 2 of 5

4.6 Steroid Pulses

4.7 Tracking Study Medication Use

4.8 Administration Instructions for Study Medications

- 4.8.1 Administration Instructions for Steroid/Placebo
 - 4.8.1.1 Schedule of Dosing
 - 4.8.1.2 Guidelines for Giving a Second Dose if Child Spits Ups/Vomits First Dose
 - 4.8.1.3 Two-Week Drug Adjustment
 - 4.8.1.4 Instructions for the Family Administering Steroid/Placebo
- 4.8.2 Administration Instructions for AquADEK™ and Vitamin K (Mephyton®)
 - 4.8.2.1 Schedule of Dosing
 - 4.8.2.2 Guidelines for Giving a Second Dose if Child Spits Ups/Vomits First Dose
 - 4.8.2.3 Accountability for Vitamins
 - 4.8.2.4 Instructions for the Family Administering AquADEK™ and Vitamin K
- 4.8.3 Administration Instructions for Ursodeoxycholic Acid (Urso 250® or Actigall®)
 - 4.8.3.1 Schedule of Dosing
 - 4.8.3.2 Instructions for the Family Administering Ursodeoxycholic Acid (Urso 250® or Actigall®)
- 4.8.4 Administration Instructions for Trimethoprim-Sulfamethoxazole (TMP-SMZ) (Bactrim)
 - 4.8.4.1 Schedule of Dosing
 - 4.8.4.2 Dose Adjustment
 - 4.8.4.3 Instructions for the Family Administering TMP-SMZ (Bactrim)
- 4.8.5 Administration Instructions for Ranitidine (Zantac®)
 - 4.8.5.1 Schedule of Dosing
 - 4.8.5.2 Instructions for the Family Administering Ranitidine (Zantac®)
- 4.8.6 Administration Instructions for Ranitidine (Zantac®)
 - 4.8.6.1 Schedule of Dosing

4.9 Transferring START Subjects from One Clinical Site to Another

- 4.9.1 Subjects Taking Steroid/Placebo
 - 4.9.1.1 Tasks: <u>'From'</u>-Site (study site from which subject is transferring from)
 - 4.9.1.2 Tasks: 'To'-Site (study site to where subject is transferring to)
 - 4.9.1.3 Tasks: Central Pharmacy
- 4.9.2 Subjects Done Taking Steroid/Placebo
 - 4.9.2.1 Tasks: 'From'-Site (study site from which subject is transferring from)
 - 4.9.2.2 Tasks: 'To'-Site (study site to where subject is transferring to)

CHAPTER 5. SPECIMEN COLLECTION

5.1 Vitamin Levels Assessment

- 5.1.1 Schedule
- 5.1.2 Testing
- 5.1.3 Sample Size Requirements

Chapter 0 3 of 5

- 5.1.4 Specimen Labeling
- 5.1.5 Specimen Collection and Processing
- 5.1.6 Shipping Procedures
- 5.1.7 Results

5.2 Whole Blood for Genetics

5.3 Antibody Titers

CHAPTER 6 ADVERSE EVENT (AE) / SERIOUS ADVERSE EVENT (SAE) / REGULATORY BODIES REPORTING

6.1 Definitions

6.2 Procedures for Reporting Serious Adverse Events (SAEs)

- 6.2.1 Personnel Involved with SAEs
- 6.2.2 Contacts for Reporting of SAEs
- 6.2.3 Automated SAE Notification System
- 6.2.4 Reporting to the Food and Drug Administration (FDA)
- 6.2.5 Reporting to the Local Institutional Review Board (IRB)
- 6.2.6 Forms Completion for SAEs
 - 6.2.6.1 Form 45 Adverse Event (web-entry)
 - 6.2.6.2 Form 45A SAE Supplemental Data

6.3 Other Reporting Scenarios

- 6.3.1 Unexpected SAEs
- 6.3.2 Unexpected, Non-Serious AEs
- 6.3.3 Expected AEs During Follow-Up Visits
- 6.3.4 SAEs After Transplant for START
- 6.3.5 Reporting Summary

6.4 Monitoring and Management of Specific Expected AEs

- 6.4.1 Hypertension
 - 6.4.1.1 Measuring Blood Pressure (BP)
 - 6.4.1.2 Hypertension Prior to the First Dose of Steroid/Placebo
 - 6.4.1.3 Hypertension at Follow-Up Visits
 - 6.4.1.4 Summary of Hypertension Action Plan
 - 6.4.1.5 Treatment Choices
- 6.4.2 Hyperglycemia
 - 6.4.2.1 Measuring Hyperglycemia
 - 6.4.2.2 Hyperglycemia Decision Tree
 - 6.4.2.3 Summary of Hyperglycemia Action Plan
- 6.4.3 Hypokalemia
 - 6.4.3.1 Hypokalemia Decision Tree
 - 6.4.3.2 Summary of Hypokalemia Action Plan
- 6.4.4 Impaired Wound Healing
 - 6.4.4.1 Impaired Wound Healing Decision Tree

Chapter 0 4 of 5

- 6.4.4.2 Summary of Impaired Wound Healing Action Plan
- 6.4.5 Gastrointestinal (GI) Bleeding
 - 6.4.5.1 GI Bleeding Decision Tree
 - 6.4.5.2 Summary of GI Bleeding Action Plan
- 6.4.6 Pancreatitis
 - 6.4.6.1 Pancreatitis Decision Tree
 - 6.4.6.2 Summary of Pancreatitis Action Plan
- 6.4.7 Irritability
 - 6.4.7.1 Irritability Decision Tree
- 6.4.8 Hypersensitivity Reaction to Trimethoprim-Sulfamethoxazole (TMP-SMZ) (Bactrim)
- 6.4.9 Cataracts
- 6.4.10 Vitamin Toxicity
- 6.4.11 Any Infectious Acute Illness
- 6.4.12 Development of Septicemia and Opportunistic Infections
- 6.4.13 Adrenal Insufficiency
 - 6.4.13.1 Adrenal Insufficiency While the Subject is Receiving Study Drug/Placebo Prior to the First Dose of Steroid/Placebo
 - 6.4.13.2 Adrenal Insufficiency Following Taper
- 6.4.14 Failure to Thrive or Poor Weight Gain
- 6.4.15 Life Threatening Events
 - 6.4.15.1 Breaking the Study Blind

CHAPTER 7 PREGESTIMIL

- 7.1 Schedule of Supplementation
- 7.2 Receiving/Shipment Schedule
- 7.3 Dispensing
- 7.4 Sterility
- 7.5 Returning Formula to Mead Johnson
- 7.6 Damaged or Expired Formula
- 7.7 Contacts

Appendix A Pregestimil Log

Chapter 0 5 of 5