PROTOCOL

THE SAVELLA® PREGNANCY REGISTRY

Sponsor:	Allergan Inc. Harborside Financial Center, Plaza V Jersey City, New Jersey 07311
Contract Research Organization:	INC Research InVentiv Health Research Park, 1011 Ashes Drive Wilmington, NC 28405
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CONFIDENTIALITY STATEMENT

The information contained in this protocol should not be disclosed, other than to those directly involved in the execution or ethical review of the Registry, without written authorization from Allergan.

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PROTOCOL SIGNATURE PAGE

Protocol Title: **SAVELLA PREGNANCY REGISTRY**

CRO: INC Research InVentiv Health

[redacted]

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Date

Co-Author: Susan Sinclair, PhD
Title: Epidemiologist, Registries & Health Outcomes

[redacted]

12-Sep-2017
Date

Biostatistician

Original Author: [redacted]

Sponsor: Allergan Plc

[redacted]

Date

Title: Head of Epidemiology

REGISTRY CONTACT INFORMATION

Principal Investigator:
Jessica Albano, PhD, MPH
Epidemiologist, Registries & Health Outcomes
INC Research inVentiv Health
1011 Ashes Drive
Wilmington, NC 28405

SYNOPSIS

Protocol No.	**MLN-MD-30 / CMO-EPI-NEU-0539**
Protocol Title	Savella Pregnancy Registry
Product	Savella (milnacipran HCl)
Clinical Phase	4, Observational Pregnancy Exposure Registry
Coordinating Center	INC Research inVentiv Health 1011 Ashes Drive, Wilmington, NC 28405
Objectives	The primary objective is to estimate the prevalence of major congenital anomalies among offspring of women exposed to Savella during pregnancy. The secondary objectives are 1) To estimate the prevalence of full-term live births (≥37 weeks), pre-term live births (<37 weeks), recognized spontaneous abortions, stillbirths, induced abortions (elective and therapeutic), chromosomal abnormalities, and minor congenital anomalies, 2) To summarize • Serious pregnancy complications and maternal adverse events • Adverse pregnancy outcomes • Serious adverse outcomes observed during the first year of life in infants born from exposed pregnancies, including alterations in fetal/infant growth, presence of functional deficits, biochemical abnormalities, transient or infectious conditions, symptoms of poor neonatal adaptation (i.e., neonatal withdrawal), and persistent pulmonary hypertension of the newborn.
Design	This is a prospective, observational, exposure-registration and follow-up registry of women and their offspring exposed to Savella during pregnancy and among infants during the first year of life.
Patient Population	Women exposed to Savella at any time during pregnancy, beginning on or after the first day of the last menstrual period (LMP).
Procedures	Registry enrollment is voluntary and initiated by pregnant patients or their healthcare providers (HCP). Patient-initiated reports must be verified by the HCP. Enrollment should occur as early in pregnancy as possible, preferably before any prenatal testing has occurred; however, enrollment at any time during pregnancy is allowed. Near the estimated date of delivery, the Registry prompts the HCP to provide pregnancy outcome data. If a live birth is reported, the Registry conducts follow-up with the infant's HCP at outcome, 4 months, and 12 months of age. If a birth defect is indicated, the Registry requests additional targeted follow-up information from the HCP. Data are collected on exposure to Savella,

	potential confounding factors, pregnancy outcome, and pediatric outcome for all live born babies. Cases are reviewed and classified according to type of birth defects. Adverse event cases are forwarded to Allergan.
Comparison Groups	Given the inherent difficulties in identifying a comparison group, several different methods may be used. First, the prevalence of birth defects are compared to the prevalence observed in the Centers for Disease Control's (CDC) population based birth defects surveillance system, the Metropolitan Atlanta Congenital Defects Program (MACDP). The most recent five-year prevalence rate of 2.78% (6945 cases with birth defects / 249,999 live births) from 1999 to 2003 is used (Correa et al., 2007). The methods and patient population in this Registry differ from those used in the CDC MACDP and therefore it may not be the most appropriate comparator. Second, the prevalence of birth defects may be compared to published data from other studies, if available at the time of analysis. The Registry is committed to identifying other appropriate comparison groups and continues to research the literature and explore other sources to obtain appropriate comparators.
Number of Patients	The Registry seeks to enroll approximately 350 prospective pregnancies. According to data from the general population, approximately 62% of clinically recognized pregnancies result in a live birth (FDA, 2002). Based on data from similar pregnancy registries, 10% are lost to follow-up. Thus, 196 live births are expected. Compared to a baseline frequency of total birth defects of 2.78% from the MACDP (Correa et al., 2007), a sample size of 196 exposed live births provides 80% power to detect an overall prevalence rate of birth defects of at least 6.95%, which corresponds to a 2.5-fold increase over baseline. This estimate is based on the one-sample exact binomial method using a 2-sided type I error rate of 5%. Sample size considerations are based on the one-sample exact binomial test, although 95% confidence intervals (CI) will be used, rather than hypothesis testing, as the primary method to guide comparative assessments to the MACDP rate.
Statistical Methods	For the primary objective, the prevalence of major birth defects is calculated by dividing the number of major birth defects (i.e., the number of pregnancy outcomes occurring at or after 20 weeks gestation with a noted birth defect) by the total number of live births. Defects detected in pregnancy outcomes prior to 20 weeks gestation will be described in the report but will not be part of the prevalence estimate. All prospective reports with appropriate outcome information that meet the criteria for enrollment are included in the analysis. The outcome data (i.e., birth defects) are stratified by pregnancy outcome (i.e., induced abortions occurring at or after 20 weeks gestation, stillbirth, and live birth (overall, full-term, and pre-term) as well as by the earliest trimester of exposure to Savella. Calculations of 95% confidence intervals (two-sided) for birth defect rates are based on the exact method using binomial probability distribution. The prevalence in exposed cases is compared with the observed prevalence in the CDC MACDP (Correa et al., 2007). In

	addition, one-sample exact binomial tests are used to compare the observed proportion of birth defects in the Registry with rates from the MACDP assuming a two-sided significance level of 5%. If feasible, comparisons between the Registry and other appropriate external comparison groups will be examined. For the secondary objective, overall and by-stratum point estimates and 95% confidence intervals are calculated for rates of spontaneous abortions, stillbirths, induced abortions (overall, elective, and therapeutic), minor congenital anomalies, serious adverse pregnancy outcomes, abnormalities detected on prenatal or postnatal ultrasounds, and other adverse outcomes (including functional deficits, alterations in fetal growth, biochemical abnormalities, transient or infectious conditions, or persistent findings in pre-term live infants that require surgical intervention) observed during the first year of life in offspring born from exposed pregnancies. Strata are comprised by earliest trimester of exposure and potentially other variables as appropriate given the sample size.

LIST OF ABBREVIATIONS

AE	Adverse Event
AEMP	Adverse Event Management Plan
CDC	Centers for Disease Control and Prevention
CEDD	Corrected Estimated Date of Delivery
CFR	Code of Federal Regulations
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case Report Form
DRF	Data Resolution Form
EDD	Estimated Date of Delivery
EDOC	Estimated Date of Conception
FDA	Food and Drug Administration
FM	Fibromyalgia
GPP	Good Pharmacoepidemiology Practices
HCP	Healthcare Provider
ICH	International Conference on Harmonization
ID	Identifier
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LMP	Last Menstrual Period
MACDP	Metropolitan Atlanta Congenital Defects Program
NCHS	National Center for Health Statistics
NICU	Neonatal intensive care unit
NIH	National Institutes of Health
OTC	Over-the-Counter
OTIS	Organization of Teratogen Information Services
PDA	Patent Ductus Arteriosus
PFO	Patent Foramen Ovale
RS	Research Specialist
RM	Records Management
SAC	Scientific Advisory Committee
WIRB	Western Institutional Review Board

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1. INTRODUCTION

The Savella Pregnancy Registry is a US based registry designed to monitor pregnancies exposed to Savella (milnacipran HCl). This is an observational, exposure-registration and follow-up registry designed primarily to estimate the prevalence of major congenital anomalies. The secondary objectives are to estimate the prevalence of live births (full-term and pre-term), recognized spontaneous abortions, stillbirths, induced abortions (elective and therapeutic), and minor congenital anomalies, and to summarize serious pregnancy complications and maternal adverse events; adverse pregnancy outcomes; and serious adverse outcomes observed during the first year of life in infants born from exposed pregnancies, including alterations in fetal/infant growth, presence of functional deficits, biochemical abnormalities, transient or infectious conditions, symptoms of poor neonatal adaptation (i.e., neonatal withdrawal), and persistent pulmonary hypertension of the newborn. Liveborn infants are followed from birth until age one. The Savella Pregnancy Registry is sponsored by Allergan Inc. (Allergan) and managed by INC Research, LLC (INC Research InVentiv Health). The Registry will be initiated upon approval of this protocol by an institutional review board (IRB).

The Registry is overseen by a Scientific Advisory Committee (SAC) whose members are experts in maternal and fetal medicine, teratology, fibromyalgia, epidemiology, and/or biostatistics from private practice, academia, government or other agency, and the Sponsor company.

Background

Savella (milnacipran HCl) was approved for the indication of management of fibromyalgia in adults, in the US on January 14, 2009 from the Food and Drug Administration (FDA). Milnacipran HCl has been marketed since 1997 for depression by Pierre Fabre Medicament in Europe, and their business partner Asahi-Kasai in Japan.

Milnacipran HCl is a selective norepinephrine (NE) and serotonin (5-ydroxytryptamine [5-HT]) reuptake inhibitor (SNRI), with preferential inhibition of NE reuptake over 5-HT reuptake. Milnacipran HCl is a small molecule that is structurally unrelated to other antidepressants, such as tricyclic antidepressants (TCAs) and more recently developed compounds. Milnacipran HCl has no significant direct actions on α_1-, α_2-, β-adrenergic, muscarinic, or histaminergic receptors—actions that impart many of the adverse events (AEs) associated with TCAs.

According to preclinical data, after oral dose administration, milnacipran HCl is rapidly absorbed and extensively distributed in different animal species. There is no accumulation of milnacipran or its metabolites in various tissues. Milnacipran HCl is distributed in equal amounts in plasma and red blood cells, and protein binding is mainly due to albumin. Milnacipran HCl is eliminated predominantly unchanged in urine following oral administration. Milnacipran HCl crosses the blood-brain barrier. Relative to the administered dose, animal studies indicate that a small fraction of milnacipran HCl and/or its metabolites can cross the placental barrier, and milnacipran HCl is rapidly eliminated from the fetus. No major CNS (central nervous system), respiratory, or gastrointestinal effects were observed in animals at therapeutically relevant doses. Cardiovascular and urogenital effects observed in some studies were attributed to the

inhibition of reuptake of NE and/or 5-HT, i.e., the proposed mechanisms of action of milnacipran (Allergan).

Fibromyalgia (FM), also known as fibromyalgia syndrome (FMS), is the most common cause of chronic widespread pain; FM affects an estimated 2% to 4% of the population (Jacobsen and Bredkjaer, 1992; Wolfe et al., Arthritis Rheum 1995; Wolfe et al., J Rheumatol 1995). FM is second only to osteoarthritis as the most common diagnosis among patients seen in rheumatology offices. It is diagnosed four times more often in women than men (Wolfe et al., 1990) and most commonly diagnosed in individuals between the ages of 20 and 50, though onset can occur in childhood. Since the vast majority of FM patient's are within the child bearing age group, importance for this pregnancy registry was noted. The FDA requested Allergan in the NDA approval letter, as a post-marketing requirement, "*to develop and maintain a prospective, observational pregnancy exposure registry in the United States that compares the pregnancy and fetal outcomes of women exposed to milnacipran during pregnancy to an unexposed control population*". The Registry is designed to detect and record major and minor congenital anomalies, spontaneous abortions, stillbirths, induced abortions, and any serious adverse pregnancy outcomes. These events are assessed among the enrolled women throughout the pregnancy, and among infants through the first year of life. Annual interim reports are submitted to the FDA until they acknowledge that sufficient data has been collected.

Preclinical studies indicated a lack of teratogenicity or embryotoxicity while receiving milnacipran, but limited maternal and offspring toxicities were observed among rodents. No clinical studies with milnacipran have been performed in pregnant women or neonates.

Reports of human pregnancy exposures from clinical trials (total no. of patients exposed n=6806) and post-marketing use since 1996 (ex-US) (total exposure: more than 20 million patient-months) with milnacipran HCl have been limited in number (Table 1). Five reports related to congenital anomalies fail to demonstrate a particular defect pattern. Three spontaneous abortions, one elective abortion, and one normal pregnancy outcome (not medically confirmed) were reported in addition to a number of other obstetrical and neonatal events. The total number of reports is low and no specific signal for events or birth defects was observed from review of these data. The current approved US package insert (USPI) for Savella states that there are no adequate and well controlled studies in pregnant women and that Savella should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (please visit www.savella.com for the most recent FDA approved Package Insert).

SNRI drugs are classified as FDA pregnancy category C due to adverse effects observed in animal studies. Category C drugs should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. The American College of Obstetrics and Gynecology (ACOG) recommends that therapy with SSRIs or SNRIs during pregnancy be individualized (ACOG, 2008).

Table 1. Reports of Milnacipran Pregnancy Exposures from Clinical Trials and Ex-US Post-marketing Use

Congenital Anomalies	Pre-mature rupture of membrane at approximately 4 months in which a female fetus had bilateral malformation of the ureters and anal imperforation
	Birth of a baby born with limb reduction defect from a patient who had discontinued milnacipran 3 months prior to becoming pregnant
	Birth of a premature male baby with Down's syndrome
	Pregnant mother on multiple drugs who gave birth to a baby with microcephaly, clinodactyly and dysmorphism
	Birth of a baby with family history of epidermolysis bullosa who was born with congenital epidermolysis bullosa
Other Pregnancy Outcomes	Spontaneous miscarriage at 10 weeks of pregnancy
	Spontaneous abortion
	Spontaneous abortion
	Induced abortion to terminate pregnancy as per patient's wish
	Drug exposure during pregnancy and birth of healthy baby (not medically confirmed)
Obstetric Complications	Pregnancy induced hypertension in a patient with multiple drug exposures during pregnancy
	Caesarean section to avoid breech presentation vaginal delivery
	Placenta previa and threatened labor
Neonatal Complications	Hypotonia, clonic spasms and poor feeding in a premature infant
	Neonatal feeding disorder, infantile apneic attack and Cheyne-Stokes respiration in an infant delivered by elective cesarean section at 37 weeks gestation

No additional information is available regarding the above cases

2. PURPOSE AND RATIONALE

The purpose of Allergan's Savella Pregnancy Registry (Registry) is to monitor pregnancies exposed to Savella (milnacipran HCl) to determine the risk of birth defects. Because Savella is commonly used among reproductive age women, this pregnancy registry has been established to prospectively assess the birth outcomes of babies born to women that are exposed to Savella during pregnancy. The lack of human fetal safety data concerning this product makes such a monitoring system an important component of epidemiologic research on the safety of Savella. Due to the lack of human data regarding fetal safety, the Registry is primarily exploratory.

The primary objective of the Savella Pregnancy Registry is:

- To estimate the prevalence of major congenital anomalies among offspring of women exposed to Savella during pregnancy.

The secondary objectives are

1) To estimate the prevalence of full-term live births (≥37 weeks), pre-term live births (<37 weeks), recognized spontaneous abortions, stillbirths, induced abortions (elective and therapeutic), chromosomal abnormalities, and minor congenital anomalies

2) To summarize

- Serious pregnancy complications and maternal adverse events
- Adverse pregnancy outcomes
- Serious adverse outcomes observed during the first year of life in infants born from exposed pregnancies, including alterations in fetal/infant growth, presence of functional deficits, biochemical abnormalities, transient or infectious conditions, symptoms of poor neonatal adaptation (i.e., neonatal withdrawal), and persistent pulmonary hypertension of the newborn

3. REGISTRY DESIGN

This is a prospective, observational, exposure-registration and follow-up registry of women exposed to Savella during pregnancy. The Registry is strictly observational; the schedule of patient visits and treatment regimens are at the discretion of the treating physician. HCPs submit patient data that are routinely collected and documented in the patient's medical record.

4. REGISTRY POPULATION

The Registry population includes women with any Savella exposure during pregnancy, defined as exposure on or after the first day of the LMP. Women must be ≥ 18 years of age and reside in the US.

4.1 Eligibility Criteria

The following criteria must be met in order to be eligible to participate in the Registry:

- At least 18 years of age
- A US resident
- Sufficient evidence (e.g., date or gestational age) to confirm that Savella exposure occurred during pregnancy

  Reported cases that do not meet the eligibility criteria are deemed ineligible.

4.2 Minimum Criteria for Registry Enrollment

In addition to meeting the eligibility criteria, the following information must be provided in order to qualify for Registry enrollment:

- Sufficient data to establish in which trimester of pregnancy the exposure to Savella first occurred (i.e., first, second or third trimester)
- Sufficient information to determine whether the pregnancy is prospectively or retrospectively registered (i.e., whether the outcome of pregnancy was known at the

time of first contact with the Registry)

- Date the pregnancy exposure is reported to the Registry
- Source of the report (HCP or pregnant patient)
- Full contact information (name, address, phone number, etc.) for the patient and HCP willing and able to provide accurate pregnancy-related information \

Reported cases that do not meet the minimum criteria for Registry enrollment are deemed invalid. Section 6.3 details follow-up procedures for obtaining necessary data.

5. GENERAL REGISTRY PROCEDURES

Enrollment may be initiated by pregnant patients or their HCPs. Patients are followed through their HCPs who are willing to provide information on maternal risk factors, pregnancy outcome, and infant health. Patient reports must be verified with an HCP. Section 5.3 describes this process in detail.

Enrollment should occur as early in pregnancy as possible, preferably before any prenatal testing has occurred; however, enrollment at any time during pregnancy is allowed. Near the estimated date of delivery, the Registry prompts the HCP to provide pregnancy outcome data. If a birth defect is reported, the Registry requests additional targeted follow-up information from the HCP. Follow-up of live-born infants continues through the first year of life.

Summary of Evaluations

Information Requested	Maternal Contact		Maternal HCP Contact			Infant HCP Contact		Evaluator
	Enrollment	Outcome	Registration	Interim Follow-Up (2nd trimester)	Outcome Follow-Up	Follow-Up (at birth)	Follow-Up (4 and 12 months)	Targeted Follow-Up
Reporter Information and Permissions								
Report source, permission to contact HCP (for pregnant patient), pediatrician, and alternate patient contact information as applicable (see section 5.3.1)	✓	✓[a]	✓					
Maternal Information								
Maternal characteristics (age, ethnicity, disease status)	✓		✓					
Maternal prenatal information (LMP, EDD, CEDD, prenatal test results & timing)	✓		✓	✓[a]	✓[a]			
Obstetrical history, family history (maternal and paternal)	✓		✓					✓[d]
Savella therapy (dosage, routes, start/stop dates)	✓		✓	✓[a]	✓[a]			
Concomitant medications (Rx, OTC, dietary supplements, herbals), during pregnancy (dosage, routes, start/stop date of administration), and alcohol, tobacco, and recreational drug use during pregnancy	✓		✓	✓[a]	✓[a]			✓[d]
Maternal concurrent medical conditions, pregnancy complications, maternal adverse events	✓		✓	✓[a]	✓[a]			
Outcome of Pregnancy Information								
Pregnancy Status	✓	✓	✓	✓	✓[a]			
Outcome data (fetal loss, live birth, gestational age, weight)		✓		✓[b]	✓	✓		
Birth defect noted, description, attribution, if applicable				✓[b]	✓			
Other factors that may have contributed to outcome (etiology)				✓[b]	✓			✓[d]
Infant Follow-up Information								
Infant assessments: anthropometric, developmental, functional, growth, postnatal conditions, medications,						✓[b]	✓	
Birth defect noted, description, attribution, if applicable						✓[b]	✓	
Other factors that may have contributed to outcome (etiology)						✓[ac]	✓[c]	✓

[a] Obtain updated information since the previous contact.
[b] Obtain this information if outcome has occurred.
[c] Collect only for live birth outcomes.
[d] Collect information not previously obtained, to facilitate the characterization of the fetal loss and/or birth defect(s).

5.2 Sources of Reports

Reports to the Registry come from HCP, pregnant patients, or Allergan's Drug Safety Surveillance department. Reports from the published literature are also included if they contain sufficient information to meet the minimum criteria for enrollment.

5.3 Registration Process

Patients initiate the enrollment process by accessing the Registry. A pregnant patient who contacts the Registry is asked to provide verbal consent and authorization for release of medical information along with sufficient contact information for the Registry to contact her HCP for verification and/or completion of pregnancy registration, exposure, and follow-up information.

Once the pregnant patient's consent is obtained, the Registry contacts the obstetric HCP and asks them to complete the ***Registration Form***. Healthcare professionals can also obtain forms to register their patients via the Registry website or by calling the Registry Coordinating Center. All of the Registry forms are in English. This form can be mailed or faxed to the Registry Coordinating Center or the data may be provided over the telephone.

The Registry maintains a toll-free telephone number, a toll-free fax, and a web page with Internet address to facilitate patient recruitment, data collection, and data queries.

5.3.1 Information Collected at Registration

Reporter Information

- Reporter contact information
- Permission to contact the HCP (if pregnant patient reporter)
- Contact information for two additional personal contacts living outside the patient's home will also be requested. Patients unwilling to provide contact information for family members or friends may use HCPs (e.g., obstetric HCP, prescriber, etc).

Maternal Information

- LMP
- Estimated date of delivery (EDD by LMP)
- Corrected estimated date of delivery (CEDD) (e.g., by ultrasound), if available
- Age (at conception) and ethnic origin
- Whether or not the patient has enrolled in this Registry for a previous pregnancy

Maternal Obstetrical History

- Number of previous pregnancies
- Number of live births
- Number of spontaneous fetal losses, includes number of spontaneous abortions and number of stillbirths

- Number of ectopic pregnancies
- Number of induced abortions
- Number of molar pregnancies
- Number and type of previous congenital anomalies among offspring
- Maternal and paternal family history of birth defects
- Contributing factors to previous adverse pregnancy outcomes or significant previous pregnancy complications

Prenatal Tests

- Type of test, date of test, and gestational age at the time of testing for all prenatal tests including obstetrical dating ultrasounds, if applicable.
- Type of prenatal test (diagnostic or screening) for aneuploidy or fetal anomalies
- Description of birth defect or abnormality found

Savella Exposure Information

- Clinical indication for Savella exposure (at start of pregnancy)
- Date treatment course began
- Total daily dose with units
- Gestational age in weeks of first exposure
- Gestational age in weeks or date treatment stopped, if applicable

Other Exposures During Pregnancy

- Prescription drugs, over-the-counter medications, and other herbal and/or dietary supplements
- Indication, if applicable
- Total daily dose with units
- Route of administration
- Date treatment course began
- Gestation week the treatment course began
- Gestation week or date treatment stopped, if applicable
- Tobacco use during pregnancy
- Alcohol use during pregnancy
- Recreational drug use during pregnancy

Concurrent Medical Conditions

- Other concurrent medical conditions during pregnancy (including complications of pregnancy such as gestational hypertension, pre-eclampsia, eclampsia, gestational diabetes, etc)
- Date condition began
- Gestation week the condition began

- Gestation week or date the condition stopped, if applicable

5.4 Prenatal Follow-up Evaluation

5.4.1 Timing of Interim Prenatal Follow-Up

At the end of the second trimester, the Registry again contacts the obstetric HCP to obtain interim follow-up information on maternal medications including dose, duration, and dates of use, medical conditions, and pregnancy status.

5.4.2 Information Collected at Interim Prenatal Follow-up

Savella, Other Medication Exposure Information, and Concurrent Medical Conditions

- Medication (Savella, or other medications, including herbals and dietary supplements)
  - Total daily dose with units
  - Route of administration
  - Gestation week the treatment course began and how the gestation week was calculated (from LMP or CEDD)
  - Start date of treatment course
  - Gestation week or stop date of the treatment
- Concurrent medical conditions (including complications of pregnancy such as gestational hypertension, pre-eclampsia, eclampsia, gestational diabetes, etc)
- Tobacco use during pregnancy
- Alcohol use during pregnancy
- Recreational drug use during pregnancy

Pregnancy Status

- CEDD
- If a subsequent prenatal test (diagnostic or screening) has indicated a birth defect or other abnormality
- Pregnancy outcome (live birth (full-term or pre-term), spontaneous abortion, stillbirth, ectopic pregnancy, induced abortion (elective or therapeutic), molar pregnancy) and as applicable:
  - Date of outcome of pregnancy
  - Gestational age at outcome
  - Gender
  - Birth weight
  - Birth defect noted
    - Type of birth defect(s) if applicable, attribution to Savella therapy, and other factors that might have contributed to the outcome
  - Chromosomal abnormalities and details, if noted

- Evidence of alterations in fetal growth
- For a fetal loss (spontaneous abortion, stillbirth): Birth defects or other factors that may have had an impact on the fetal loss and attribution to Savella therapy

5.5 Follow-up Evaluation at Pregnancy Outcome

5.5.1 Timing of Pregnancy Outcome Follow-Up

In the month of the expected date of delivery, the Registry prompts the pregnant patient's obstetric HCP to complete the ***Obstetric Follow-Up Form***. The patient is also contacted to obtain contact information for the baby's pediatrician and a medical release.

Obstetric Follow-up Form

5.5.2 Information Collected at Pregnancy Outcome Follow-up

Fetal outcome (for each outcome if multiple gestation)

- Pregnancy outcome: live birth (full-term or pre-term), spontaneous abortion, stillbirth, ectopic pregnancy, induced abortion (elective or therapeutic), molar pregnancy
- Date of outcome of pregnancy
- Gestational age at outcome
- Gender
- Birth weight
- Birth defect noted
- Type of birth defect(s) if applicable, attribution to Savella therapy, and other factors that might have contributed to the outcome
- For a fetal loss (spontaneous abortion, stillbirth): Birth defects or factors other than birth defects that may have had an impact on the fetal loss and attribution to Savella therapy

Maternal Complications

- Gestational hypertension, pre-eclampsia, eclampsia

5.6 Follow-up Evaluation by Pediatrician for Live Births

5.6.1 Timing of Pediatric Follow-Up

If a live birth occurs, the mother is asked to give consent for the infant's pediatrician to provide follow-up information. If consent is obtained, the pediatrician completes the ***Pediatric Follow-Up Form*** immediately after birth, at 4 months, and 12 months of age.

Pediatric Follow-up Form

5.6.2 Information Collected at Pediatric Follow-up

Infant at outcome

- Date of follow-up evaluation
- Current age of infant (at the time of assessment)
- Gender
- Gestational age at birth
- APGAR scores at birth
- Birth weight, length, head circumference and corresponding population-based percentiles
- Birth defect(s) and details, if noted
    - Type of birth defect(s)
    - Attribution to Savella drug therapy
    - Other factors that might have contributed to the outcome
    - Defect absent/present on pre- or post-natal test
- Chromosomal abnormalities and details, if noted
- Immediate post-natal health problems requiring resuscitation, admission to the neonatal intensive care unit (NICU)
- Medications
- Surgical interventions required of pre-term infants
- Other serious infant adverse outcomes noted on physical examination
    - Evidence of alterations in fetal/infant growth (e.g., intrauterine growth restricted, small for gestational age, etc.)
    - Presence of functional deficit (e.g., poor muscle tone, abnormal reflexes)
    - Presence of biochemical abnormality
    - Presence of transient or infectious conditions
    - Symptoms of poor neonatal adaptation (i.e., neonatal withdrawal)
    - Persistent pulmonary hypertension of the newborn

Infant at 4 and 12 months

- Date of follow-up evaluation
- Current age of infant (at the time of assessment)
- Birth weight, length, head circumference and corresponding population-based percentiles
- Birth defect(s) detected since last assessment and details, if noted
    - Type of birth defect(s)
    - Attribution to Savella drug therapy
    - Other factors that might have contributed to the outcome
    - Defect absent/present on pre- or post-natal test
- Chromosomal abnormalities and details, if noted
- Medications
    - Other serious infant adverse outcomes noted on physical examination

- Evidence of alterations in infant growth
- Presence of functional deficits
- Developmental delays

5.7 Targeted Follow-Up

5.7.1 When is Targeted Follow-Up Conducted?

If a birth defect is noted at pregnancy outcome, or at any time during the infant follow-up period, additional details regarding the birth defect are requested from the maternal and/or pediatric provider, as appropriate, using the **Targeted Follow-up Form**, to facilitate classification and to assess the presence of potential confounders.

Targeted Follow-up Form

5.7.2 Information Collected at Targeted Follow-up

- Details of the birth defect, chromosomal abnormality, or other condition warranting teratology follow-up.
  - The Targeted Follow up form is individualized to the unique history and presentation of each potential defect case.
    - The specific term used to describe the condition under review (i.e, birth defect, chromosomal abnormality, or other condition) is entered on the Targeted Follow up form,
    - Specific questions requested by the sponsor and/or the birth defect evaluator reviewing the case are also entered on to this form.
  - Etiology
  - Outcome attribution

6. METHODS AND PROCESSES

6.1 Registry Awareness / Recruitment

The Registry can be accessed by text, phone or internet (www.savellapregnancyregistry.com)

The Registry phone number of 877-643-3010 is available in the following locations:

1) Savella prescribing information

3) Allergan website (www.Allergan.com) and/or Savella website (www.Savella.com)

4) FDA website listing pregnancy registries: http://www.fda.gov/womens/registries/default.htm

5) INC Research InVentiv Health website: https://www.incresearch.com/what-we-do/standalone-services/cro-pregnancy-registries

6) ClinicalTrials.gov

7) Others as deemed appropriate

At initiation, the Registry may conduct a direct mailing of Registry information to healthcare professionals who might provide patients to the Registry. These healthcare professionals are identified through professional organizations (e.g., appropriate professional societies for fibromyalgia), and large academic medical centers specializing in the relevant fibromyalgia and high-risk obstetrics. Additional venues for increasing awareness of the Registry include: 1) providing Registry methods presentations at scientific or clinical meetings (e.g., ACOG) and 2) dissemination of Dear Doctor Letters to a variety of specialties. For example, 136,242 Dear Doctor Letters were sent to HCPs in 15 specialty areas in 2011; of which, 84,379 were family practice HCPs and 1,479 were obstetrics/gynecology HCPs. Therefore, included in these awareness efforts is contact with HCPs caring for women during their pregnancies, particularly, early in pregnancy. In addition, the Registry enlists the aid of the FDA, Centers for Disease Control and Prevention (CDC), the Organization of Teratogen Information Services (OTIS), and other relevant organizations in facilitating patient recruitment.

6.2 Registry Case Report Management

Reports that come to the Registry are first classified as either prospective or retrospective. They are further classified as complete, valid, not verified by the HCP, lost to follow-up, invalid, or duplicate. All reports that come to the Registry are summarized for Allergan safety reporting purposes in the annual line-listings. Evaluable reports are evaluated and accounted for in the Registry Interim/Final Report. However, only the prospective reports are included in the primary analysis and statistical calculation of risk.

6.2.1 Prospective Registry Reports

Prospective reports are reports provided during pregnancy, following an exposure to Savella, but before prenatal tests have been conducted that provide information on the outcome of the pregnancy. In order to achieve adequate numbers, only those pregnancies with anomalies or other abnormalities identified on a prenatal test are considered as retrospective reports. Those with no abnormalities noted on prenatal tests are considered prospective and included in the primary analysis. Section 8.6 addresses the potential bias introduced by this practice in more detail.

6.2.2 Retrospective Registry Reports

A report is considered retrospective when an abnormality has been identified on a diagnostic or screening prenatal test at the time of initial reporting. Additionally, retrospective reports for which the pregnancy outcome has already occurred will only be accepted if the following two criteria are met, 1) a birth defect was noted, and 2) the outcome occurred within two years of the time of the initial report.

Retrospective reports can be biased toward the reporting of more unusual and severe outcomes and are less likely to be representative of the general population experience. Therefore, the inclusion of such reports in the calculation of risk is inappropriate. Retrospective reports with birth defects and/or spontaneous fetal losses are reviewed to aid in detecting early signals, but they are not included in the statistical analysis.

Occasionally, the Registry may receive retrospective reports of exposed pregnancies resulting in normal outcomes. Although the Registry does not actively solicit this type of

information, the data will be recorded on a contact form and then entered into a log which is separate from the analysis database.

6.2.3 Evaluable Registry Reports

An evaluable report is a case, submitted or verified by a HCP, containing at least the minimum criteria for Registry enrollment, and is not lost to follow-up. Prospectively reported evaluable cases with known outcomes are included in the primary analyses for the Interim Report produced annually and the Final Report. Retrospective reports are summarized separately in the Interim Reports and the Final Report.

6.2.4 Patient Reports Not Confirmed by the Provider

Reports received directly from pregnant women that are not verified by the HCP are included in the Registry, but identified as a non-HCP-verified report. If the obstetric HCP does not provide the requested data after all follow-up attempts have been made by the Registry, the patient will be contacted to obtain interim and outcome information. Section 6.3 provides a complete description of the follow-up process. If she reports a live birth, the Registry requests her consent to contact the infant's HCP. These reports are analyzed separately and may be included in the analysis if appropriate.

6.2.5 Ineligible Registry Reports

A report that does not meet the eligibility criteria outlined in Section 4.1 is ineligible. Ineligible reports are not captured in the Registry database.

6.2.6 Invalid Registry Reports

An invalid case is a report for which the minimum criteria for Registry enrollment are never obtained despite requests for the missing data. If the minimum data are not provided on receipt of a prospective report, the case is considered pending until all attempts to resolve queries for missing data and requests for follow-up information are complete. If after all follow-up attempts, the minimum criteria are still not met, the case receives a status of "invalid" with a reason of "insufficient information". Section 6.3 provides a complete description of the follow-up process. Invalid reports are summarized for Allergan's safety reporting purposes, but are not included in the Registry analyses.

6.2.7 Losses to Follow-Up (LTFU)

A prospective report meeting the minimum criteria for enrollment but for which follow-up information on the pregnancy outcome (live birth, fetal loss, etc.) is never obtained, is unavailable, and/or where the indication of a birth defect is designated as "unknown" is considered "pregnancy lost to follow-up". For the infant portion of the Registry, live born infants where pediatric follow-up information is never obtained, is unavailable, and/or where infant status is designated as "unknown" is considered "infant lost to follow-up". Section 6.3 provides a complete description of the follow-up process. Losses to follow-up are tallied in the Registry Interim Reports and the Final Report, but are not included in the statistical analyses.

6.2.8 Identification of Duplicate Registry Reports

Reports received by the Registry are reviewed for possible duplicate reporting. On receipt of a registration form from an HCP, the report is compared to other reports to determine if the same report was received previously. If a duplicate is not identified, the report is entered into the database. If a duplicate is later identified, the case reported earliest or the one with the most complete data is maintained as the valid case and updated with any data from the other report not already captured. The duplicate report is flagged and designated as "invalid", with reason of "duplicate report".

6.3 Follow-up Process

6.3.1 Attempts to Obtain the Follow-up Information

The standard process for obtaining follow-up at interim reporting periods is to notify the reporter by telephone that a letter with the appropriate follow-up data forms are being sent. The reporter is asked to complete and return it to the Registry or provide the data by phone. If the data forms are not returned in one month the reporter is contacted 3 times (every 2 weeks) by telephone. If no response is received, a final letter is sent encouraging return of data forms. All follow-up attempts are documented, and all appropriate reporters (healthcare professionals, patients, alternate contacts) are contacted according to the follow-up plan outlined above.

6.3.2 Follow-up Process for Resolution of Information

If there are outstanding questions, discrepancies between the registration and follow-up forms, or there are missing data, the query resolution process is as follows: either a hard copy of the data resolution form (DRF) is sent to the provider or the provider is contacted by phone. Three subsequent attempts, as necessary, are made every 2 weeks via mail, e-mail, fax or phone call. If no further information is obtained on an otherwise evaluable case, the discrepant information in the data fields may be left blank, identified as "unspecified", or on a case-by-case basis a determination of discrepant information made by the principal investigator (e.g., determination of partially illegible word or illogical year).

6.4 Calls to the Registry

All incoming and outgoing calls are tracked by the Research Specialist (RS) to monitor the source, type, purpose of the call, and whether or not further activity is needed to resolve the reason for the call.

7. OUTCOME CLASSIFICATION, EVALUATION AND MONITORING

7.1 Definitions

7.1.1 Pregnancy Outcome

Pregnancy outcomes are classified into one of the following mutually exclusive categories:

- Live birth - full-term (≥ 37 weeks)
- Live birth – pre-term (<37 weeks)
- Stillbirth
- Spontaneous abortion
- Induced abortion
    - Therapeutic
    - Elective
- Ectopic pregnancy
- Molar pregnancy
- Maternal/fetal death

Definitions of the individual outcome categories are located in the Glossary beginning on page 35.

7.1.2 Birth Defect

The Registry adopts the term “birth defect” for an abnormality usually referred to as a “congenital anomaly” and defines birth defect as follows:

- Any major structural or chromosomal defect diagnosed with signs/symptoms, using the CDC MACDP classification of birth defects (CDC, 1998).

On a case-by-case basis, subject to independent review, clusters of two or more minor abnormalities may in combination constitute a birth defect, even if the outcome of each event alone would not constitute a birth defect according to the MACDP classification. Defining two or more minor defects as a birth defect case is used to increase the sensitivity of pregnancy databases (Scheuerle and Covington, 2004). The presence of multiple minor defects has been shown to increase the likelihood that a major defect or syndrome exists (Leppig et al, 1987, Holmes et al, 1987). To maintain as much consistency with the CDC birth defect surveillance system as possible without missing a potential signal, only cases meeting the MACDP criteria and those with at least two minor defects are included for analysis. Cases with two minor anomalies will trigger further investigation by the registry’s birth defect evaluator; the determination of the birth defect evaluator would then decide whether the specifics of any particular case merit its inclusion as a birth defect case. All infants with three or more minor anomalies will be counted as a birth defect case.

The inclusion of cases with minor defects is a conservative approach with the potential to inflate point estimates and enhance signal detection. Individual minor abnormalities are listed in the report but are not included in the analysis of defects.

Under certain circumstances, structural or chromosomal defects detected in the prenatal evaluation of a pregnancy or in the gross or pathologic examination of an abortus, fetus, or deceased infant, that would not otherwise be included in the primary analysis following normal protocol procedures, may be included in a subsequent analysis to increase the sensitivity of Registry monitoring. Such determinations are made on a case-by-case basis and are subject to independent review.

The CDC guidelines disqualify as birth defects:

- Conditions that are attributed to prematurity alone, such as patent ductus arteriosus (PDA), patent foramen ovale (PFO), and inguinal hernias. If these conditions are present in infants born < 37 weeks gestational age or if gestational age is unavailable, weighing < 2500 grams, they are not considered birth defects. If these conditions are present in infants born ≥ 37 weeks gestational age, they are considered birth defects.

- Infants with only transient or infectious conditions, or biochemical abnormalities, are classified as being without birth defects unless there is a possibility that the condition reflects an unrecognized birth defect.

The Registry focuses on birth defect data detected and reported during pregnancy and up to one year of age for live born infants. Most major structural defects and clusters of minor abnormalities are readily apparent during this time frame. However, under ascertainment of birth defects is possible. The Registry does update case reports if information is received on any birth defect diagnosed with signs/symptoms occurring up to six years of age. However, this information is not systematically collected. The Registry collects information on minor abnormalities, transient or infectious conditions, and biochemical abnormalities that reporting clinicians deem important.

7.2 Birth Defect Evaluation

The Registry retains the services of a consultant birth defect evaluator, a physician with expertise in genetics and the evaluation and classification of birth defects. Upon Registry receipt of a case report of a birth defect the report (without provider information) is transmitted to the evaluator within 5 working days for individual case evaluation. This review includes identification of specific aspects of the case for further inquiry from the reporter(s), and clarification and classification of the defect(s) reported in accordance with the classification conventions of the MACDP (CDC, 1998) and a classification system, developed by Scheuerle (Scheuerle and Tilson, 2002) to increase the ability to generate potential signals. In addition, the review includes a temporality assessment with is a determination of the potential relevance of timing of exposure to the event(s) reported.

The birth defect evaluator assessment includes the following:

- Cases that are prospectively reported and deemed evaluable – The evaluator may assess a report as “pending further information” if more information is needed to determine the etiology of the defect and/or the temporality. However, if no further information is received despite repeated attempts, the evaluator makes an assessment based upon available information.

- Cases reported retrospectively (i.e., after an abnormal condition has been noted on a prenatal test and/or for which a defect was noted at outcome) – The evaluator makes an assessment on the defect and temporality with the information available at initial review. However, if follow-up questions are requested and responses received later, the evaluator re-evaluates the case.

The assessments of temporality with the Registry drug exposure are classified as one of the following:

- Pending
- The development of this defect and the timing of the exposure to drug cannot rule out a possible association
- No temporal association
- Unable to assess temporality
- Defect with known cause, temporality may be irrelevant
- Pathogenesis of this defect has yet to be defined specifically enough to assess temporality
- Not a defect

7.3 Monitoring of Outcomes and Signal Detection

The data are reviewed regularly by the staff of health professionals at the Registry Coordinating Center for the appearance of any unusual events or unexpected numbers of specific events. All reports of defects are transmitted promptly to the Sponsor for their independent and immediate review and further regulatory reporting. Additionally, any other fetal, neonatal, or maternal adverse events received by the Registry, are also transmitted to the Sponsor for safety surveillance management and processing.

A Scientific Advisory Committee (SAC) oversees the scientific affairs of the Registry, including its on-going monitoring of transactions. The SAC is composed of recognized experts in the fields of teratology, epidemiology, maternal and fetal medicine, and fibromyalgia, from academia, private practice, government or other agency, and the Sponsor company. The SAC convenes annually to review all individual case reports received in the interim and the overall accumulation of Registry experience, as well as to review Registry processes, awareness activities, and the analysis plan. The SAC is also available for *ad hoc* consultation, data review, and advice.

The intent of the Registry is to determine whether there is a signal that might indicate a potential risk for major birth defects in the offspring of women following exposure to Savella during pregnancy. Therefore, it is necessary to monitor the cumulative data to

detect potential signals or patterns, to evaluate them, and to determine the necessary course of action when a signal is noted. The Registry may never have sufficient power to detect a risk for a particular rare outcome to Savella. However, the Registry SAC has adopted a plan developed by the Antiretroviral Pregnancy Registry for determining what constitutes a signal for a birth defect, how it is reviewed, and what action might be taken should such a signal be seen (Covington et al., 2004). For example, the “Rule of Three” convention specifies that once 3 similar birth defects have accumulated with any specific exposure or exposure combination, these cases are flagged for immediate review. The likelihood of finding three of any specific defects in a cohort of <600 by chance alone is less than 5% for all but the most common defect classes (i.e., those occurring with a rate of <1/700). To enhance the assurance of prompt, responsible, and appropriate action in the event of a potential signal, the Registry employs the strategy of “threshold” based on the Council of International Organizations for the Medical Sciences (CIOMS, 1999). The threshold for action is determined by the extent of certainty about the cases, driven by statistical considerations, and tempered by the specifics of the cases.

In addition, the evaluator reviews all birth defects in aggregate to identify any possible patterns reported. Should a potential pattern occur, it is discussed at the annual SAC meeting. However, if at any time discussion prior to the annual meeting is deemed necessary, a teleconference or meeting would be scheduled. Once a potential signal is identified the component cases can be evaluated individually to determine if there is cause for concern.

Thus, the Registry Staff, along with consultants, review, on an ongoing basis, between periodic meetings of the SAC, all individual reports and the cumulative collection of reports for signals of potential problems. The SAC meets annually and more frequently, if an issue arises, to review individual and aggregate data.

8. STATISTICAL CONSIDERATIONS

8.1 Analysis Population

The primary population for analysis includes prospective evaluable cases that are not “lost to follow-up” (i.e., cases with appropriate outcome information and meeting the minimum criteria for evaluation). Retrospective cases are reviewed and reported separately.

8.2 Analysis Parameters for Birth Defects

Pregnancy outcomes are categorized as live birth (full-term or pre-term), stillbirth, spontaneous abortion, induced abortion (elective or therapeutic), ectopic pregnancy, and molar pregnancy. Most structural defects have their origins in the first trimester of pregnancy; the period of organogenesis. Therefore, the outcome data (i.e., birth defects and other pregnancy outcomes) may be stratified by the earliest trimester of exposure to Savella (first trimester, second trimester, and third trimester).

Gestational weeks are calculated beginning from the first day of the LMP when it is considered to be a reliable predictor of the EDD. However, if a CEDD is available (e. g., by ultrasound), the CEDD is preferred for calculating gestational weeks. The second

trimester begins at 14 weeks and 0 days, and the third trimester begins at 28 weeks and 0 days.

Descriptive statistics are the primary approach for summarizing data from this pregnancy registry. Confidence intervals are provided for purposes of estimation and are not used for statistical inference.

8.3 Comparison Groups

Given the inherent difficulties in identifying an appropriate comparison group, several different methods may be used to review the data for any signals of teratogenicity. First, assuming a sufficient sample size is attained, the prevalence of birth defects in this Registry is compared to the prevalence observed in the MACDP, a population-based birth defects surveillance system that is administered by CDC (1998). The total prevalence of birth defects identified among births from 1968 through 2003 was 2.67% (Correa et al., 2007). However, the MACDP recognizes that prior to 1973 the annual prevalence was lower because of incomplete case ascertainment and that since 1973 the total defect prevalence has remained stable with only minimal year-to-year variation. The most recent five-year prevalence rate of 2.78% (6945 birth defect cases in 249,999 live births) from 1999 to 2003 is deemed the most appropriate comparator rate for this Registry (Correa et al., 2007). The baseline prevalence rate for specific birth defects varies.

The methods and patient population in this Registry differ from those used in the MACDP and therefore it may not be the most appropriate comparator. The primary objectives of MACDP are to monitor, regularly and systematically, births of malformed infants for changes in incidence or other unusual patterns suggesting environmental influences and develop a case registry for use in epidemiological studies. MACDP actively searches for birth defects among the 50,000 annual births to residents of metropolitan Atlanta's five counties and abstracts medical records at all Atlanta obstetric hospitals, Atlanta pediatric referral hospitals, genetics labs, and vital records (Correa-Villasenor et al., 2003). MACDP data has been used as a comparator group when examining birth defects for several existing pregnancy registries (acyclovir; sumatriptan; lamotrigine; and zidovudine) (Honein et al., 1999).

As a second method of analysis, the prevalence of birth defects among women in the Registry may be compared to the prevalence observed in published studies of pregnant women exposed to other drugs for similar indications if available at that time.

The Registry is committed to identifying other appropriate comparison groups and continues to research the literature and explore other sources to obtain appropriate background rates. It is important to note that other studies may vary in methodology, ascertainment and classification of birth defects, geographic location, and sample size, among other factors that could impact results. Therefore quantitative comparisons between the Registry and the studies reported in the literature may be difficult to interpret.

8.4 Sample Size

The Registry seeks to enroll approximately 350 prospective pregnancies. According to data from the general population, approximately 62% of clinically recognized pregnancies results in a live birth (FDA, 2002). Based on data from similar pregnancy registries, 10% are lost to follow-up. Therefore, the resulting number of live births is expected to be 196.

Compared to a baseline frequency of total birth defects of 2.78% from the MACDP (Correa et al., 2007), a sample size of 196 exposed live births provides 80% power to detect an overall prevalence rate of birth defects of at least 6.95%, which corresponds to a 2.5-fold increase over baseline. This estimate is based on the one-sample exact binomial method using a 2-sided type I error rate of 5%. Sample size considerations are based on the one-sample exact binomial test, although 95% confidence intervals (CI) will be used, rather than hypothesis testing, as the primary method to guide comparative assessments to the MACDP rate. For specific defects, the power to detect an increased risk varies depending on the frequency of the defect in the population and the evolving size of the exposed group.

8.5 Data Analysis

8.5.1 Birth Defects

For the primary analysis, the prevalence of birth defects reported to the Registry in the evaluable population is calculated by dividing the number of birth defects (i.e., the number of pregnancy outcomes occurring at or after 20 weeks gestation with a noted birth defect) by the total number of live births in the evaluable population. Pregnancy losses with reported birth defects occurring at or after 20 weeks gestation are included in the numerator of the estimate of risk for birth defects to increase sensitivity and to allow for comparison with the MACDP which calculates rates using this convention. A secondary analysis is conducted including pregnancy losses with reported birth defects occurring at any gestational age in the calculation of risk. An additional secondary analysis will be performed that only includes birth defects that are noted from ultrasound examinations (pre-natal or post-natal). Birth defects will be reported by outcome (live birth (overall and full-term or pre-term)), stillbirth, induced abortion (elective or therapeutic) and trimester of exposure. All defects detected <20 weeks of gestation will be described in the report. Additionally, birth defects noted by non-HCP reports will be reported descriptively.

Calculations of 95% confidence intervals (two-sided) for individual birth defect rates are based on the exact method using binomial probability distribution. The prevalence in exposed cases is compared with the observed prevalence in the MACDP (Correa et al., 2007). In addition, one-sample binomial tests at the two-sided 0.05 level are used to test the association of elevated levels of major birth defects in pregnancy exposures to Savella by comparing the observed proportion of birth defects in the Registry with rates from the MACDP.

Enrolled pregnancies that are LTFU without pregnancy outcome, as defined in section 6.2.6, will be enumerated in the interim/final report, but will not be included in the

calculation of risk. Prospectively enrolled pregnancies with an outcome will be included in the calculation of risk regardless of whether they are subsequently designated as infant LTFU.

If feasible, comparisons between the Registry and an appropriate external comparison group will be examined.

8.5.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics are summarized for the evaluable population for birth defects. Demographics and baseline characteristics are also summarized for the LTFU population and compared to the evaluable population to assess potential differences. These data are reviewed for potential confounding factors that could affect interpretations of comparisons with the MACDP. Additional data including concomitant medications, maternal concurrent medical conditions, previous births with congenital anomalies, and Savella dosing information are summarized using simple descriptive statistics and data listings. Birth defect rates are also summarized by maternal age, gestational age at enrollment, earliest trimester of exposure, Savella dosing information, and concomitant medications. Further details are provided in the statistical analysis plan.

8.5.3 Adverse Pregnancy Outcomes

Overall and by-stratum point estimates of rates and 95% confidence intervals will be calculated for the following outcomes:

- Spontaneous abortions
- Stillbirths
- Induced abortions (overall and elective or therapeutic)
- Minor congenital anomalies,

Other adverse pregnancy outcomes among pregnancies exposed to Savella and their live births during the first year of life will be summarized as counts and percentages of the total number of prospective evaluable outcomes. Summaries will also be presented by subgroups including maternal age at conception (<25, 25-35, >35), family history of birth defects, smoking status, and alcohol use during pregnancy. Additional subgroups may be analyzed if deemed appropriate and necessary given the sample size. These other adverse pregnancy outcomes include:

- Functional deficits
- Alterations in fetal growth
- Transient or infectious conditions
- Biochemical abnormalities
- Pre-term infants with findings that persist and require surgical intervention

Strata are comprised by earliest trimester of exposure and potentially other variables as appropriate given the sample size, such as maternal age, history of birth defects, lifestyle variables, comorbidities, and concomitant drug exposures.

All chromosomal abnormalities, whether classified as a birth defect or other adverse outcome, will be displayed in a separate listing.

8.5.4 Infant Follow-Up

Descriptive statistics will be presented for infant outcomes including mean gestational age at outcome, mean birth weight, medications, head circumference, APGAR scores, immediate post-natal health problems requiring resuscitation or admission to the NICU, and developmental milestones

8.6 Potential Biases

Because early prenatal testing is so prevalent in the US, it may be difficult to achieve adequate numbers of prospectively identified patients if all pregnancies with prior prenatal testing are excluded from the analysis. Therefore, the primary analyses includes pregnancies enrolled prior to outcome but after a prenatal test as long as the test does not indicate an abnormality. However, this practice could potentially bias the results by lowering the overall risk of birth defects (Honein et al., 1999). The analysis attempts to address whether this practice biases the results.

As reporting of pregnancies is totally voluntary, it is possible that even in prospectively reported cases, potential bias could exist. For example, high-risk pregnancies or low-risk pregnancies may be more likely to be reported.

Enrolled pregnancies that have reached their estimated date of delivery and for which outcome information is unobtainable are considered “lost to follow-up”. It is possible that outcomes among pregnancies lost to follow-up could differ from those with documented outcomes. Because of differences in follow-up and reporting patterns, it is currently not possible to assess with any certainty what impact the potential biases the losses to follow-up may have on the analysis. However, efforts at comparing some of the characteristics of each group are conducted in an attempt to address this potential source of bias.

Following the MACDP convention, calculation of birth defect risk excludes fetal losses (spontaneous abortions, induced abortions, stillbirths, etc.) for which no birth defects have been detected as they may introduce a classification bias. It is unknown what percentage of these pregnancies consists of potentially normal outcomes or birth defects. The Registry attempts to obtain information on birth defects detected at the time of the outcome. However, the reporting physician may not know the condition of the aborted fetus.

While the Registry analysis is limited to prospective reports, some pregnancy exposures are reported following pregnancy outcome (retrospective cases). Each retrospective report is carefully reviewed. In general, retrospective reports of exposures to therapy following notification of outcome are biased toward reporting the severe and unusual

cases and are not reflective of the general experience with the medication. Moreover, information about the total number of exposed persons is not known. Therefore, rates of outcomes cannot be calculated from these data. However, a series of reported birth defects can be evaluated to detect patterns of specific birth defects and can help to identify early signals of therapy risks.

9. REGISTRY ADMINISTRATION

9.1 Regulatory Agency Reporting Considerations

The Registry follows the FDA Guidance for Industry, *Establishing Pregnancy Exposure Registries* (FDA, 2002) for regulatory reporting of adverse events to FDA. "The Agency considers pregnancy exposure registry reports (both prospective and retrospective) as derived from active solicitation of patient information." Therefore Allergan is responsible for, "reporting any serious and unexpected events by regulatory definition and where a reasonable possibility exists that the drug or biological product caused the adverse event within 15 calendar-days" (FDA, 2002).

For FDA status reporting, the Registry Interim Report can be appended to the annual report submission as described in the FDA Guidance (FDA, 2002). The Interim Report, published annually, contains the background, Registry design, and analysis plan. It summarizes the status and the cumulative data on the Registry to date. In addition, the Registry can generate individual case line listings to assist Allergan in preparation of its submission. The Interim Report, generated annually, is cumulative and current to the most recent data cutoff period.

9.2 Reporting of Adverse Events

Reports of pregnancy exposures to Savella are carefully reviewed for reports of any adverse events.

The Registry systematically collects information on major structural and chromosomal defects that are apparent at birth and noted through infant age one (1) year, as well as other specified fetal and maternal outcomes. Information on events not routinely collected is sometimes reported to the Registry. These data are of limited utility since the Registry does not systematically collect them. HCPs are encouraged to report such events to the manufacturer.

The Registry reports all adverse pregnancy outcomes including birth defects, spontaneous fetal losses, and induced abortions (elective or therapeutic), maternal and non-defect fetal events regardless of attribution, temporal association, or seriousness, for Registry participants, to Allergan Global Drug Safety department, which forwards the reports to the regulatory authorities in accordance with federal regulations. Specifically, Allergan will:

- Report any unexpected fatal or life-threatening adverse experiences associated with use of the drug by telephone or fax no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)];

- Report any serious, unexpected adverse experiences, as well as results from animal studies that suggest significant clinical risk, in writing to this Division and to all investigators within 15 calendar days after initial receipt of this information [21 CFR 312.32(c)(1)]; and
- Submit annual progress reports within 60 days of the anniversary of the date that the IND went into effect (the date clinical studies were permitted to begin) [21 CFR 312.33].

10. ETHICAL CONSIDERATIONS

10.1 Institutional Review Board/Ethics Committee

According to the FDA Guidance document (FDA, 2002), registries such as this must comply with ethical principles and regulatory requirements involving human subject's research. Therefore, institutional review board (IRB) approval is necessary. Notification of the Board's approval of the Registry must be provided to Allergan or its designee.

The Registry protocol is submitted for initial review, annual review, and amendments as necessary to Western Institutional Review Board (WIRB), 3535-7th Avenue SW, Olympia WA 98502, 360-943-1410.

10.2 Ethical Conduct of the Registry

This Registry is conducted in compliance with the Registry protocol, International Society for Pharmacoepidemiology's (ISPE) Guidelines for Good Pharmacoepidemiology (2004), US FDA regulatory requirements, ISPE's Data Privacy, Medical Records Confidentiality and Research in the Interest of Public Health (1998), and in accordance with the ethical principles of the Declaration of Helsinki (1995).

10.3 Waiver of Documentation of Consent

Based on the following regulations a waiver of documentation of consent is appropriate for this Registry.

As stated in the US Code of Federal Regulations (CFR) 21 CFR 56.109 (and additionally in 45 CFR 46.117(c)(2)):

> "(c) An IRB shall require documentation of informed consent in accordance with 50.27 of this chapter, except as follows:
>
> (1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subjects legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context.
>
> (d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research."

The research involves no more than minimal risk to the subjects. This is an observational Registry that involves no experimental intervention and poses no possibility of physical harm. The only potential risk is a breach of confidentiality, and the Registry has well-established procedures in place to prevent any such breach of confidentiality. As described above, extensive safeguards are in place to assure that patients' privacy is protected:

a) An adequate plan is provided to protect the identifiers from improper use and disclosure (See section 12.5).

b) An adequate plan is provided to remove the identifiers at the earliest opportunity.

c) Adequate assurances are provided that the protected health information will not be reused or disclosed to any other person or entity.

The research involves no procedures for which written consent is normally required outside the research context. Enrollment in this observational Registry is strictly voluntary. The schedule of patient visits and treatment regimens are at the complete discretion of the treating physician. Data submitted to the Registry is limited to data routinely collected and documented in the patient's medical record.

10.4 Patient Consent Process

10.4.1 Patient Initiated Enrollment

When a patient calls the Registry requesting to participate, a Research Specialist (RS) gathers information regarding the woman's exposure and explains the Registry goals and procedures. If the subject is eligible and wishes to participate, the RS reviews the Patient Information Sheet with the patient over the phone and answers her questions. Once the essential information has been provided and the RS is assured that the patient understands the implications of participating in the Registry, the patient is asked to give her verbal consent to participate. If the patient agrees to provide verbal consent, the RS consents the patient over the telephone, marks the verbal consent box on the Patient Information Sheet, enters the date that verbal consent was obtained, and then signs the consent form. The RS then mails a copy of the Patient Information Sheet to the patient and maintains a copy in the patient's file at the Registry Coordinating Center. This verbal patient consent is in compliance with the waiver of documentation of consent according to 21 CFR 56.109(c)(1) and 45 CFR 46.117(c)(2) as outlined in section 10.3. The consent document complies with 21 CFR 56.109(d) and 45 CFR 46.117(c).

10.4.2 Healthcare Provider Initiated Enrollment

Before enrollment into the Registry, the patient is read, by the reporting HCP, the Patient Information Sheet which explains the Registry goals and procedures. Once the essential information has been provided and the HCP is assured that

the patient understands the implications of participating in the Registry, the patient is asked to give her verbal consent to participate, which includes consent for the Registry to contact her. The HCP marks the verbal consent box on the Patient Information Sheet, enters the date that verbal consent was obtained, and provides his/her signature in the appropriate space. The HCP gives a copy of the Patient Information Sheet to the patient, maintains a copy in the HCP's file, and forwards a copy to the Registry Coordinating Center to be filed in the patient's file. This verbal patient consent is in compliance with the waiver of documentation of consent according to 21 CFR 56.109(c)(1) and 45 CFR 46.117(c)(2) as outlined in section 10.3. The consent document complies with 21 CFR 56.109(d) and 45 CFR 46.117(c).

Healthcare providers, particularly those with limited time to adequately administer the informed consent process, may refer the patient to the Registry for the consent process as described in section 10.4.1 above.

10.5 Exemption of HIPAA Authorization

As a post marketing safety reporting activity, this Registry meets the criteria outlined below and is therefore exempt from the Health Insurance Portability and Accountability Act (HIPAA) Authorization.

45 CFR 164.512 states:

> "(iii) A person subject to the jurisdiction of the Food and Drug Administration (FDA) with respect to an FDA-regulated product or activity for which that person has responsibility, for the purpose of activities related to the quality, safety or effectiveness of such FDA-regulated product or activity. Such purposes include:
>
> (A) To collect or report adverse events (or similar activities with respect to food or dietary supplements), product defects or problems (including problems with the use or labeling of a product), or biological product deviations;
>
> (B) To track FDA-regulated products;
>
> (C) To enable product recalls, repairs, or replacement, or lookback (including locating and notifying individuals who have received products that have been recalled, withdrawn, or are the subject of lookback); or
>
> (D) To conduct post marketing surveillance;"

To further clarify this issue, an article published by the Pregnancy Labeling Task Force, US FDA, states:

> "…the HIPAA Privacy Rule specifically permits the disclosure of protected health information by covered entities such as physicians or hospitals for public health purposes related to the quality, effectiveness and safety of

FDA-regulated products to both the manufacturers and directly to the FDA. This includes collecting or reporting adverse events, tracking FDA-regulated products and conducting post-marketing surveillance to comply with requirements or at the direction of the FDA" (Kennedy et al., 2004).

11. BENEFITS, RISKS, COMPENSATION AND COST

11.1 Benefits

There are no direct benefits to participation for either the patient or her HCP for providing data to the Registry.

The overall benefit of participation in the Registry is contribution of information obtained from systematically monitoring prospective reports of pregnancy exposures to Savella. The Registry may make it possible to identify a signal or early warning of major structural birth defects associated with a pregnancy exposure to Savella more quickly and efficiently than other means. A Registry is one of the only projects expressly established to evaluate outcomes following prenatal exposure to certain prescription medications. The success of registries relies on the continued participation of Providers.

11.2 Risks to Subjects

As stated in Section 10.3, there are no physical risks associated with participation in the Registry. The potential risks to subjects associated with participation include those related to breach of confidentiality. Every effort is made to minimize this risk.

11.3 Compensation and Costs

Reporters – No compensation is provided to participants or HCPs for participation in the Registry.

Birth Defect Evaluator – Compensation for the time to review and evaluate the reports of birth defects is provided to a consultant. Compensation is made through the Registry Coordinating Center.

Scientific Advisory Committee – The SAC members are reimbursed for travel and expenses to attend the annual Advisory Committee meeting. They will also receive a stipend to attend meetings.

Coordinating Center – Allergan provides full financial support of the Registry for the Registry Coordinating Center and its activities.

IRB – Payments to the institutional review board are made through the Registry Coordinating Center.

12. ADMINISTRATIVE CONSIDERATIONS

12.1 Scientific Advisory Committee

The SAC meets annually with the Sponsor representative to review the data. The SAC makes a full assessment of the individual cases reporting birth defects and reviews the accumulated body of data from the prospective and retrospective reports. Between the annual meetings, should a signal of a major drug-associated risk emerge from the Registry or another source (e.g., toxicology data), such information would be shared with the SAC. Additional discussions via conference calls or an *ad hoc* meeting may be scheduled if deemed necessary. In addition to the above activities, the SAC designs and implements strategies to heighten awareness of the Registry and may form sub-committees to address particular issues or activities.

12.2 Sponsor

Allergan has oversight responsibilities for this Registry including monitoring and safety reporting.

12.3 Principal Investigator

The principal investigator (PI), Jessica Albano, PhD, MPH is responsible for providing oversight of the Registry and all submissions (protocol, amendments) to the IRB. The PI works with Allergan and the SAC to set Registry policy and be available for ongoing consultations regarding the review, analysis, and conduct of the Registry.

12.4 Registry Coordinating Center

The Registry Coordinating Center is responsible for the collection, management, and follow-up of the reports of pregnancy exposures to the Savella Pregnancy Registry, conducting the analysis of the data, and updating of the Registry Interim Reports. In addition, the Coordinating Center schedules, plans, and facilitates Advisory Committee meetings, and forwards case reports of adverse events to the Sponsor. Also, as appropriate or required, the Registry Coordinating Center assists in identifying and/or contacting groups, organizations, and journals to increase awareness of the Registry.

Each full-time and temporary employee of INC Research InVentiv Health, i.e., the Registry Coordinating Center, signs a confidentiality agreement (Statement of Confidentiality, Use and Non-Disclosure) as a condition of employment. This agreement describes the confidential nature of the industry and the work performed at INC Research InVentiv Health. In addition, during training, all new employees within the Registries & Epidemiology Department are informed of the confidential nature of the Registry participant and HCP data and any other Registry documents that employees may be exposed to during their employment within the Department.

12.5 Disclosure of Data

12.5.1 Confidentiality

The Registry makes every effort to assure patient confidentiality within the Registry. When information on reports is distributed to Advisory Committee members, no reporter contact information is included. Contact information is not shared outside the Registry except with Allergan for regulatory safety surveillance purposes.

12.6 Physical Files

Registry documents are maintained at the Registry Coordinating Center within the Registries and Health Outcomes Department at INC Research InVentiv Health in a secure storage area which remains locked at all times. Badge access to the locked secure storage areas is granted only to authorized INC Research InVentiv Health associates. Document case files are maintained in the locked secure storage areas when they are not actively being reviewed in the TMF Review Room or at the desk of a Registry associate. Faxed data are received electronically via a secure server with access by Registry and IT staff only. Patient files will be minimal as an electronic data capture system is utilized which allows RSs to enter data directly while speaking to participants and HCPs on the telephone.

12.7 Electronic Back-Up

The database is backed up as part of the **INC Research InVentiv Health** backup process. The server is backed up to tape daily as an incremental backup, (i.e., only files with changes since the last backup are backed-up). A full backup of the database is performed weekly and stored securely off-site for two weeks. One full backup per month is stored off-site for two years.

13. PUBLIC RELEASE OF THE DATA

The Registry publishes the Registry data, encourages and initiates presentations, and uses several strategies to raise awareness of the Registry. However, the Registry never identifies individual subjects or shares its list of providers.

13.1 Interim/Final Reports

The Interim Report is produced annually. Since it contains historical information as well as the new data, it completely replaces all previous reports. The Interim Report primarily summarizes the prospective, evaluable Registry case reports. Though it is not possible to calculate the risk of birth defects from the retrospective reports, a list of the outcomes with birth defects retrospectively reported to the Registry is presented. A copy of the data collection form is included in the Interim Report. Furthermore, a copy of this report will be provided to Allergan in order to comply with regulatory requirements.

At the conclusion of the Registry, the Registry Coordinating Center will issue a final, cumulative report to Allergan to meet regulatory requirements.

14. DISCONTINUATION OF REGISTRY

This Registry could consider discontinuation after one of more of the following occurs:

- Sufficient information has accumulated to meet the scientific objectives of the Registry;
- Other methods of gathering appropriate information become achievable or are deemed preferable; or
- The feasibility of collecting sufficient information diminishes to unacceptable levels because of low exposure rates, poor enrollment, or losses to follow-up.

The Registry's Scientific Advisory Committee will review the above criteria on a yearly basis and assess the need to discontinue the Registry as currently designed. ***Allergan will not discontinue the registry until they have consulted with the FDA to ensure that the FDA has reviewed the final study report and determined that the study data has met the study objectives and the obligations of the Post Marketing Requirements.***

At the time of discontinuation, the PI will notify the IRB of the Pregnancy Registry discontinuation and/or termination. These considerations are documented in the FDA Guidance document, *Establishing Pregnancy Exposure Registries* (FDA, 2002).

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GLOSSARY

Birth Defect – A ”birth defect” in this Registry follows the CDC guidelines and is defined as (1) any major structural malformation or chromosomal defect diagnosed or with signs/symptoms before one year of age, (2) on a case-by-case basis, subject to independent review, any cluster of at least two minor abnormalities (cases with two minor defects will trigger further investigation by the registry’s birth defect evaluator; the determination of the birth defect evaluator would then decide whether the specifics of any particular case merit its inclusion as a birth defect case. Cases with three or more minor defects will be counted as a birth defect cases., or (3) on a case-by-case basis, subject to independent review, any structural or chromosomal defect detected in the prenatal evaluation of a pregnancy or in the gross or pathologic examination of an abortus, fetus, or deceased infant. The Registry excludes birth defects attributed to prematurity itself (e.g., patent ductus arteriosus, patent foramen ovale, and inguinal hernias).

Corrected EDD – Estimated date of delivery obtained by prenatal test (e.g., ultrasound)

Ectopic pregnancy – Implantation of a conception outside of the uterus.

Induced abortion – Voluntary interruption of pregnancy. Includes pregnancy termination which occurs electively or therapeutically, to preserve maternal health, or due to fetal abnormalities.

MACDP (The Metropolitan Atlanta Congenital Defects Program) – A program that monitors all major birth defects in five counties of the metropolitan Atlanta area (Clayton, Cobb, DeKalb, Fulton, and Gwinnett) with approximately 50,000 annual births from a population of about 2.9 million. MACDP acts as the model for many state-based programs and as a resource for the development of uniform methods and approaches to birth defect surveillance.

Maternal/fetal death – A pregnant woman expires with the fetus in utero.

Molar pregnancy – A conception that results in a gestational trophoblastic tumor.

Neonatal death – An infant expired after a live birth.

Pregnancy Category A – Controlled studies show no risk: Adequate, well-controlled studies in pregnant women have failed to demonstrate risk to the fetus.

Pregnancy Category B – No evidence of risk in humans: Adequate, well-controlled studies in pregnant women have not shown increased risk of fetal abnormalities despite adverse findings in animals, or, in the absence of adequate human studies, animal studies show no fetal risk. The chance of fetal harm is remote, but remains a possibility.

Pregnancy Category C – Risk cannot be ruled out: Adequate, well-controlled human studies are lacking, and animal studies have shown a risk to the fetus or are lacking as well. There is a chance of fetal harm if the drug is administered during pregnancy, but the potential benefits may outweigh the potential risk.

Pregnancy Category D – Positive evidence of risk: Investigational or post-marketing data show risk to the fetus. Nevertheless, potential benefits may outweigh the potential risk.

Pregnancy Category X – Contraindicated in pregnancy: Studies in animals or humans, or investigational or post-marketing reports, have shown fetal risk which clearly outweighs any possible benefit to the patient.

Premature Birth – An infant at outcome < 37 weeks gestational age or if gestational age not available, weighing < 2,500 grams as defined by CDC's criteria in the MACDP manual.

Prospective report – Any report of a pregnancy exposure to the Registry drug reported before the outcome of pregnancy is known.

Retrospective report – Any report of a pregnancy exposure to the Registry drug reported after the outcome has occurred or for which an abnormal condition was identified on a prenatal test.

Spontaneous Abortion – Fetal death or expulsion of products of conception prior to 20 weeks gestation or if the gestational age is unknown, a fetus weighing less than 350 grams. Terminology may include: missed abortion, blighted ovum, incomplete abortion, and inevitable abortion

Stillbirth – A fetal death occurring at 20 weeks gestation or greater, or if the gestational age is unknown, a fetus weighing greater than or equal to 350 grams.

Temporality Assessment – The determination of the probable association or non-association of the timing of the maternal exposure in pregnancy relative to the probable timing of organogenesis of a defect.

Term Birth – An infant at outcome ≥ 37 weeks gestational age or if gestational age is not available, weighing ≥ 2,500 grams as defined by CDC's criteria in the MACDP manual.