1.0 EXECUTIVE SUMMARY

Savella (milnacipran HCI) was approved by the Food and Drug Administration (FDA) on January 14, 2009 for the management of fibromyalgia in adults. Milnacipran is a selective norepinephrine and serotonin (5-hydroxytryptamine [5-HT]) reuptake inhibitor (SNRI). The Savella Pregnancy Registry (Registry) was established on October 01, 2009 as a post-marketing requirement. The Registry is a US-based, prospective, observational, exposure-registration and follow-up study designed to monitor and investigate the outcomes of pregnancies, focusing on congenital anomalies, among women exposed to Savella during pregnancy. This report is the fifteenth and final study report and describes the monitoring of pregnancy exposures and outcomes in the Registry from inception date, October 01, 2009 through October 08, 2024 (end of study).

Summary of Enrollment

There are 6 enrolled patients. No additional patients were enrolled since the prior interim report (issued January 24, 2024).

Five enrolled pregnant women delivered live born infants: Patient 1 at 32 weeks of gestation, Patient 2 at 35 weeks of gestation, Patient 3 at 38 weeks of gestation, Patient 4 delivered twins at 35 weeks of gestation, and Patient 5 delivered at 39 weeks of gestation. Three of the infants were lost to follow-up: the infant of Patient 1 after Month 4, the infant of Patient 2 immediately after birth, and the infant of Patient 5 after outcome was reported. All data was collected for the infants of Patients 3 and 4.

One pregnant woman, Patient 6, enrolled September 27, 2023. Outcome for this pregnancy was unknown. This patient was lost to follow-up.

Scientific Advisory Committee Consensus

The Scientific Advisory Committee last met in 2020 to review data that was subsequently reported in the interim report of February 14, 2020. The Consensus statement below was developed by members of the Scientific Advisory Committee, Sponsor representatives, and the Registry Coordinator Center staff during review of this final study report.

> *Since the study inception in October 2009, 6 pregnancies, resulting in 6 live births and one pregnancy lost to follow-up, have been captured. Of those, no birth defects have been observed and no new safety data related to the use of Savella during pregnancy have been identified. Following 15 years of recruitment efforts, the Committee no longer recommends that enrollment efforts continue. The Committee believes that it is not feasible to enroll the targeted number of pregnant women (350 exposed pregnancies and 196 live births) for this registry to provide sufficient data to adequately address the primary objective of the study.*

Given the Registry's low enrollment, lack of new data and the lack of reported birth defects, the Scientific Advisory Committee's 2021, 2022, and 2023 meetings were deferred.

Conclusion

Six pregnant patients have been enrolled into the Registry from October 01, 2009 to October 8, 2024. Five pregnancies resulted in 6 live born infants (Patient 1 in 2011, Patient 2 in 2012, Patients 3 and 4 in 2017, and Patient 5 in 2020. Patient 4 was a twin pregnancy). Four of the six infants were born prematurely (infants born to Patients 1, 2 and 4. See case summaries, Section 7.2). Three infants were lost to follow-up (infants of Patients 1, 2, and 5). Pregnancy outcome for Patient 6 was lost to follow-up.

No birth defects have been reported of the infants enrolled in the Registry. Three of the infants have incomplete follow-up information (see case summaries, Section 7.2). The infant of Patient 1 was lost to follow-up after the 4-month infant follow-up visit at which time no birth defects had been reported. The infant of Patient 2 was lost to follow-up at delivery, and the Registry was unable to obtain information on the presence or absence of birth defects. The infant of Patient 5 was lost to follow-up after outcome was reported, and the Registry was unable to obtain 4-month and 12-month follow-up assessments to confirm the presence or absence of birth defects. Follow-up assessments were completed for the full 12-month period for the infants of Patient 3 and 4; of those, no birth defects were reported. The pregnancy outcome of Patient 6 was lost to follow-up.

Current data from the 6 enrolled infants were insufficient to determine an association between maternal use of Savella and premature births or birth defects.

On 13 November 2024 the US FDA released AbbVie from the postmarketing requirement for this study, as it was determined to no longer be feasible due to the decrease in drug utilization of Savella and the subsequent inability to recruit a sufficient number of patients to enroll in the Savella Pregnancy Registry. As a result, Study MLN-MD-30 has been terminated.