Market Authorisation Holder/Sponsor:

Otsuka Pharmaceutical Development & Commercialization, Inc.

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EU RISK MANAGEMENT PLAN (RMP) for

Aripiprazole

Version: 12.1

Data Lock Point for this RMP: 30 Nov 2021

Date of Final Sign Off: 07 Jun 2023

[redacted].

Signature	Electronically signed
	PPD [redacted] PPD
Signature	Electronically signed
	[redacted]

EU Risk Management Plan for Abilify and Abilify Maintena (aripiprazole):

RMP version to be assessed as part of this application:

RMP Version number: 12.1

Data Lock Point for this RMP: 30 Nov 2021

Date of Final Sign Off: 07 Jun 2023

Rationale for submitting an updated RMP: Submission of line extension application for Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe i.e. aripiprazole 2-month ready-to-use long-acting injectable (Aripiprazole 2M RTU LAI).

RMP version 12 was submitted within Asimtufii marketing authorisation application (EMEA/H/C/005929/0000) in May 2022, however, this application was withdrawn on 04 May 2023. Therefore, the current approved RMP is version 11.1.

Summary of significant changes in this RMP: Inclusion of data for aripiprazole 2M RTU LAI as per version 12.0, and update nomenclature of Asimtufii to Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe.

Table 0-1 Summary of Changes to this RMP by Module

RMP Part / Module / Annex	Version No.	Date of Approval (Opinion date)	Significant Changes
Part I - Product Overview	12.1		Updated to include Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe (Aripiprazole 2M RTU LAI)
Part II /Module SI: Epidemiology of the Indication(s) and target population (s)	12.1		Updated epidemiology data for existing indications
Part II /Module SII - Non-clinical part of the safety specification	12.1		Not Applicable
Part II /Module SIII - Clinical trial exposure	12.1		Updated clinical trial exposure to include aripiprazole 2M RTU LAI
Part II /Module SIV - Populations not studied in clinical trials	12.1		Updated populations not studied in clinical trials, including aripiprazole 2M RTU LAI clinical trials
Part II /Module SV - Postauthorisation experience	12.1		Updated postauthorisation exposure

Table 0-1 Summary of Changes to this RMP by Module			
RMP Part / Module / Annex	**Version No.**	**Date of Approval (Opinion date)**	**Significant Changes**
Part II /Module SVI - Additional EU requirements for the safety specification	12.1		Updated analysis for potential for misuse for illegal purposes
Part II /Module SVII - Identified and potential risks	12.1		Updated to include aripiprazole 2M RTU LAI
Part II /Module SVIII - Summary of the safety concerns	12.1		Updated to include aripiprazole 2M RTU LAI
Part III: Pharmacovigilance Plan (including postauthorisation safety studies)	12.1		Removed PASS 15893N and 31-10-270 studies from additional PV activities since they have been completed
Part IV: Plans for postauthorisation efficacy studies	12.1		Not Applicable
Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)	12.1		Updated to include aripiprazole 2M RTU LAI
Part VI: Summary of the risk management plan	12.1		Updated to include Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe
Part VII: Annexes	12.1		Updated content for completed studies (PASS 15893N and 31-10-270)

Details of the currently approved RMP:

- Version number: 11.1
- Approved with procedure: EMEAH/C/002755/R/0025
- Date of approval (opinion date): 27 Aug 2018

There are no previously submitted versions of this EU RMP that are still under evaluations by the Agency.

QPPV name: Emiel van Heumen, MD, MSc.

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder Otsuka's QPPV. The electronic signature is available on file and provided on the title page.

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List of In-text Tables

List of Abbreviations, Acronyms, and Definitions of Terms

Abbreviation/Acronym	Definition
5-HT	5-Hydroxytryptamine
ADHD	Attention Deficit Hyperactivity Disorder
ADR	Adverse Drug Reaction
AE	Adverse Event
AESOP	Aetiology and Ethnicity in Schizophrenia and Other Psychoses
ASD	Autism Spectrum Disorder
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area Under the Curve
BMI	Body Mass Index
BMS	Bristol-Myers Squibb
CCDS	Company Core Data Sheet
CD	Conduct Disorder
CDC	United States Centers for Disease Control and Prevention
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CNS	Central Nervous System
CSR	Clinical Study Report
DLP	Data Lock Point
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
EEA	European Economic Area
EM	Extensive Metaboliser
EMA	European Medicines Agency
EOS	Early-Onset Schizophrenia
EPAR	European Public Assessment Report
EPS	Extrapyramidal Symptoms
EU	European Union
HIV	Human Immunodeficiency Virus
HLGT	High Level Group Term
HLT	High Level Term
HR	Hazard Ratio
ICD	International Classification of Diseases
ICPE	International Consortium of Psychiatric Epidemiology
IM	Intramuscular
INN	International Nonproprietary Name
IRR	Incidence Rate Ratio
LAI	Long-Acting Injectable
MAH	Marketing Authorisation Holder
MDD	Major Depressive Disorder
MDE	Major Depressive Episodes

Abbreviation/Acronym	Definition
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	Maximum Recommended Human Dose
NMS	Neuroleptic Malignant Syndrome
NOS	Not Otherwise Specified
OCD	Obsessive-Compulsive Disorder
ODD	Oppositional Defiant Disorder
OPC	Otsuka Pharmaceutical Company, Ltd.
OR	Odds Ratio
PASS	Post-Authorisation Safety Study
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PM	Poor Metabolizer
PRS	Polygenic Risk Score
PT	Preferred Term
PTSD	Post-Traumatic Stress Disorder
QPPV	Qualified Person Responsible for Pharmacovigilance
RMP	Risk Management Plan
RR	Relative Risk
RTU	Ready-to-Use
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SMR	Standardised Mortality Ratio
SOC	System Organ Class
SOHO	Schizophrenia Outpatient Health Outcomes
SSRI	Selective Serotonin Reuptake Inhibitor
SUD	Substance Use Disorder
TEAE	Treatment-Emergent Adverse Event
TRD	Treatment-Resistant Depression
UK	United Kingdom
US	United States
WHO	World Health Organization

1 PART I: PRODUCT(S) OVERVIEW

Table 1-1 Active Substance Information	
Active substance(s) (INN or common name)	Aripiprazole
Pharmacotherapeutic group(s) (ATC code):	Other antipsychotics (N05AX12)
Name of marketing authorisation	Otsuka Pharmaceutical Netherlands B.V.
Medicinal products to which this RMP refers:	2
Invented name of the product in the European Economic Area (EEA)	Abilify Abilify Maintena
Marketing authorisation procedure	Centralized: EMEA/H/C/000471 (Abilify), EMEA/H/C/002755 (Abilify Maintena)
Brief description of the product	Chemical class: Atypical antipsychotic
	Summary of mode of action: It has been proposed that aripiprazole's efficacy is mediated through a combination of partial agonism at dopamine D2 and serotonin 5-hydroxytryptamine-1a (5-HT1a) receptors and antagonism of serotonin 5-HT2a receptors. Aripiprazole exhibited antagonist properties in animal models of dopaminergic hyperactivity and agonist properties in animal models of dopaminergic hypoactivity. Aripiprazole exhibited high binding affinity in vitro for dopamine D2 and D3, serotonin 5-HT1a and 5-HT2a receptors and moderate affinity for dopamine D4, serotonin 5-HT2c and 5-HT7, α1-adrenergic and histamine H1 receptors. Aripiprazole also exhibited moderate binding affinity for the serotonin reuptake site and no appreciable affinity for muscarinic receptors. Interaction with receptors other than dopamine and serotonin subtypes may explain some of the other clinical effects of aripiprazole.
	Important information about its composition: Not applicable
eCTD link to the proposed product information, as appropriate	*Abilify: Sequence 0208* *Abilify Maintena: Sequence 0104*
Indications: approved and proposed	Abilify Approved: Oral use: Abilify is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older. Abilify is indicated for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment.

Table 1-1 Active Substance Information	
	Abilify is indicated for the treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older. Intramuscular use: Abilify solution for injection is indicated for the rapid control of agitation and disturbed behaviours in patients with schizophrenia or in patients with manic episodes in Bipolar I Disorder, when oral therapy is not appropriate. Treatment with aripiprazole solution for injection should be discontinued as soon as clinically appropriate and the use of oral aripiprazole should be initiated. Abilify Maintena Approved: Abilify Maintena is indicated for maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole
Dosage in the EEA	Abilify Approved: Oral use: Adults: Schizophrenia: the recommended starting dose for Abilify is 10 or 15 mg/day (i.e., 10 or 15 mL solution/day) with a maintenance dose of 15 mg/day administered on a once-a-day schedule without regard to meals. A calibrated measuring cup and a 2 mL calibrated dropper are included in the carton. Abilify is effective in a dose range of 10 to 30 mg/day (i.e., 10 to 30 mL solution/day). Enhanced efficacy at doses higher than a daily dose of 15 mg has not been demonstrated although individual patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg. Manic episodes in Bipolar I Disorder: the recommended starting dose for Abilify is 15 mg (i.e., 15 mL solution/day) administered on a once-a-day schedule without regard to meals as monotherapy or combination therapy. Some patients may benefit from a higher dose. The maximum daily dose should not exceed 30 mg (i.e., 30 mL solution/day). Recurrence prevention of manic episodes in Bipolar I Disorder: for preventing recurrence of manic episodes in patients, who have been receiving aripiprazole as monotherapy or combination therapy, continue therapy at the same dose. Adjustments of daily dosage, including dose

Table 1-1	**Active Substance Information**
	reduction should be considered on the basis of clinical status. Paediatric population: Schizophrenia in adolescents aged 15 years and older: the recommended dose for Abilify is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using Abilify oral solution 1 mg/mL) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. When appropriate, subsequent dose increases should be administered in 5 mg increments without exceeding the maximum daily dose of 30 mg. Abilify is effective in a dose range of 10 to 30 mg/day. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated although individual patients may benefit from a higher dose. Abilify is not recommended for use in patients with schizophrenia below 15 years of age due to insufficient data on safety and efficacy. Manic episodes in Bipolar I Disorder in adolescents aged 13 years and older: the recommended dose for Abilify is 10 mg/day administered on a once-a-day schedule without regard to meals. Treatment should be initiated at 2 mg (using Abilify oral solution 1 mg/mL) for 2 days, titrated to 5 mg for 2 additional days to reach the recommended daily dose of 10 mg. The treatment duration should be the minimum necessary for symptom control and must not exceed 12 weeks. Enhanced efficacy at doses higher than a daily dose of 10 mg has not been demonstrated, and a daily dose of 30 mg is associated with a substantially higher incidence of significant undesirable effects including extrapyramidal symptom (EPS) related events, somnolence, fatigue, and weight gain. Doses higher than 10 mg/day should therefore only be used in exceptional cases and with close clinical monitoring. Younger patients are at increased risk of experiencing adverse events (AEs) associated with aripiprazole. Therefore, Abilify is not recommended for use in patients below 13 years of age. Intramuscular use: The recommended initial dose for aripiprazole solution for injection is 9.75 mg (1.3 mL), administered as a single intramuscular injection. The effective dose range of aripiprazole solution for injection is 5.25 - 15 mg as a single injection. A

Table 1-1	**Active Substance Information**
	lower dose of 5.25 mg (0.7 mL) may be given on the basis of individual clinical status, which should also include consideration of medicinal products already administered either for maintenance or acute treatment. A second injection may be administered 2 hours after the first injection, on the basis of individual clinical status and no more than three injections should be given in any 24-hour period. The maximum daily dose of aripiprazole is 30 mg (including all formulations of aripiprazole). Abilify Maintena Approved: For patients who have never taken aripiprazole, tolerability with oral aripiprazole must occur prior to initiating treatment with Abilify Maintena. Titration of the dose for Abilify Maintena is not required. The starting dose can be administered by following one of two regimens: • One injection start: On the day of initiation, administer one injection of 400 mg Abilify Maintena and continue treatment with 10 mg to 20 mg oral aripiprazole per day for 14 consecutive days to maintain therapeutic aripiprazole concentrations during initiation of therapy. • Two injection start: On the day of initiation, administer two separate injections of 400 mg Abilify Maintena at separate injection sites, along with one 20 mg dose of oral aripiprazole. After the injection start, the recommended maintenance dose of Abilify Maintena is 400 mg. Abilify Maintena should be administered once monthly as a single injection (no sooner than 26 days after the previous injection). If there are adverse reactions with the 400 mg dosage, reduction of the dose to 300 mg once monthly should be considered.
	Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe Proposed: For patients who have never taken aripiprazole, tolerability with aripiprazole must occur prior to initiating treatment with Abilify Maintena. Titration of the dose for Abilify Maintena is not required. The starting dose can be administered by following one of two regimens: • One injection start: On the day of initiation, administer one injection of 960 mg Abilify Maintena and continue treatment with 10 mg to 20 mg oral aripiprazole per day for 14 consecutive days to maintain therapeutic

Table 1-1 Active Substance Information	
	aripiprazole concentrations during initiation of therapy. • Two injection start: On the day of initiation, administer one injection Abilify Maintena 960 mg and one injection Abilify Maintena 400 mg at two different injection sites (Abilify Maintena 720/960 mg is for gluteal intramuscular injection only), along with one 20 mg dose of oral aripiprazole. After the injection start, the recommended maintenance dose of Abilify Maintena is 960 mg. Abilify Maintena 720/960 mg should be administered once every two months as a single injection (56 days after the previous injection). If there are adverse reactions with the 960 mg dosage, reduction of the dose to 720 mg once every two months should be considered. Transitioning to Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe from Abilify Maintena When transitioning patients from Abilify Maintena 400 mg (once a month injection) to Abilify Maintena 960 mg (once every 2 months injection), Abilify Maintena 960 mg should be administered at the time of the next scheduled injection of Abilify Maintena (26 days after the previous injection). Abilify Maintena 960 mg should then be dosed once every 2 months (every 56 days). The first Abilify Maintena 960 mg injection may be administered in place of the second, or later injection of Abilify Maintena. Dosing Interval and Dosing Adjustments of Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe. Following the initial dose, administer Abilify Maintena 960 mg once every 2 months (56 days after the previous injection). Patients may be given the injection up to 2 weeks before or 2 weeks after the scheduled 2-month dose. If there are adverse reactions with the 960 mg dosage, consider reducing the dosage to 720 mg once every two months. <u>Missed doses</u> If less than 14 weeks have elapsed since the last injection, administer the next dose of Abilify Maintena 960 mg as soon as possible. The once every two-month schedule should be resumed. If more than 14 weeks have elapsed since the last injection, restart with the one or two injections start with the next administered injection of Abilify Maintena 960 mg.
Pharmaceutical Form(s)	Approved: Abilify Tablets; Abilify Orodispersible tablets;

Table 1-1 Active Substance Information	
	Abilify Oral solution; and Abilify Solution for injection Abilify Maintena powder and solvent for prolonged release suspension for injection; Abilify Maintena powder and solvent for prolonged-release suspension for injection in pre-filled syringe; Proposed: Abilify Maintena 960 mg prolonged-release suspension for injection in pre-filled syringe Abilify Maintena 720 mg prolonged-release suspension for injection in pre-filled syringe
Pharmaceutical Strength(s)	Approved: Abilify Tablets (5, 10, 15, 30 mg); Abilify Orodispersible tablets (10, 15, 30 mg); Abilify Oral solution (1 mg/mL); and Abilify Solution for injection (7.5 mg/mL) Abilify Maintena 300 mg powder and solvent for prolonged release suspension for injection; Abilify Maintena 400 mg powder and solvent for prolonged release suspension for injection; Abilify Maintena 300 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe; Abilify Maintena 400 mg powder and solvent for prolonged-release suspension for injection in pre-filled syringe. Proposed: Abilify Maintena 960 mg prolonged-release suspension for injection in pre-filled syringe Abilify Maintena 720 mg prolonged-release suspension for injection in pre-filled syringe
Is/will the product subject to additional monitoring in the EU?	No

2 PART II: SAFETY SPECIFICATION

2.1 Module SI: Epidemiology of the Indication and Target Populations

Brand Names of Concerned Products: Abilify, Abilify Maintena

The epidemiological trends and statistics associated schizophrenia and bipolar mania are summarized below. As applicable, information regarding the occurrence of agitation associated with schizophrenia, and bipolar mania has also been provided.

2.1.1 Indication #1 Schizophrenia

2.1.1.1 Incidence

Schizophrenia: Overall, schizophrenia occurs at a low frequency and has been relatively stable in epidemiological studies within regions for several decades. Across regions, there is variability in incidence rates which may be related to differences in reporting or to true differences in rates of schizophrenia that vary based on genetic or environmental factors.[1] Reported incidence rates have shown considerable heterogeneity in terms of gender, age, ethnic group, and study center.[2] The heterogeneity in reported incidence rates of schizophrenia is attributed to methodological differences between studies and difficulties inherent in designing studies to obtain a representative estimate; changes in diagnostic criteria over recent years (e.g., "restrictive" vs. "broad" definition in the diagnosis of schizophrenia); the method of case identification (e.g., assertive outreach vs. hospital-based services, or personal interview vs. chart diagnosis); the type of recruitment site (inpatient or outpatient setting); scope of coverage (e.g., all patients vs. inpatients only); and whether incidence was assessed based upon rates of first contact with a mental health center or on hospital admission rates.[3,4,5,6] Given this methodologic heterogeneity, the degree of international variability in estimates for the incidence rate of schizophrenia is not surprising. Large-scale studies have shown:

- A review of 16 international studies conducted from the 1930s through the 1970s: annual incidence rates for schizophrenia ranged from 17/100,000 (UK) to 69/100,000 (US).[7]
- A review of 13 studies conducted from 1946 through the 1990s in Europe, North America, Asia, and the Caribbean: annual incidence rates, for either broadly or narrowly defined schizophrenia diagnosis, ranged from 17/100,000 (Taiwan) to 54/100,000 (Germany).[4]

International variability was also found in a World Health Organization (WHO) schizophrenia study carried out across 10 countries (Colombia, Czech Republic, Denmark, India, Ireland, Japan, Nigeria, Russia, UK, US). The annual "first contact"

incidence rates for broadly-defined schizophrenia, from 9 per 100,000 population (Czech Republic) to 42 per 100,000 population (India); for narrowly-defined schizophrenia, from 2 per 100,000 population (Russia) to 14 per 100,000 population.[4]

- Systematic review (2002) of 8 international incidence studies published since 1980[8] found significant heterogeneity across 1-year incidence rates of schizophrenia (a variation of nearly 5-fold between the lowest and highest rates based on ICD diagnosis criteria): best estimate for the annual incidence: 11.1/100,000 (95% CI: 7.5-16.3/100,000).
- A systematic review including 68 incidence studies for schizophrenia drawn from 27 countries with 170 discrete incidence rates[9] found an asymmetric distribution of incidence rates: median value (10%-90% percentile, or central 80% of incidence rates): 15.2/100,000/year (range: 7.7 to 43/100,000/year).
- Reports of a decline in the incidence in recent years have been inconsistent. While some studies report significant declines in the incidence of schizophrenia[10] others have reported an increase in incidence.[1,4,9,11,12]

2.1.1.2 Prevalence

Schizophrenia: Numerous epidemiological studies have been conducted in various sites worldwide to assess the prevalence of schizophrenia.[6,13] There is substantial heterogeneity in reported estimates, which likely arises due to factors such as the age structure of the population, mortality rates, migration patterns within and between sites and operationalization of schizophrenia.[4,14]

- A systematic review of 188 studies from 46 countries published from 1965 to 2002[13] estimated median prevalence values (10%-90% quantile range) per 1,000 persons:
  - Point prevalence (≤1 month): 4.6 (1.9-10.0)
  - Period prevalence (>1 month and <12 months): 3.3 (1.3-8.2)
  - Estimated lifetime prevalence: 4.0 (1.6-12.1)
  - Lifetime morbid risk: 7.2 (3.1-27.1).
- A systematic review of 16 international prevalence studies[6] found significant differences across studies, but calculated best estimates (pooled rates) that were consistent with the above-mentioned analysis were:
  - 1-year prevalence: 0.34/100 (95% CI: 0.22-0.50)
  - Lifetime prevalence: 0.55/100 (95% CI: 0.37-0.8).

As of January 2022, new estimations of the prevalence of schizophrenia have been stable since the 1990s within the previously noted regional differences:

- The 2019-point prevalence of schizophrenia in Greenland was 0.7% according to a cross-sectional evaluation of mental health patient records.[15]

- The estimated (2020) prevalence of schizophrenia in the Valencia region of Spain was 0.62%.[16]
- A 2016 global systematic review of schizophrenia across 195 countries found a point prevalence of 0.28%.[17]

Agitation in Schizophrenia: Agitation, characterized by motor restlessness, heightened response to stimuli, irritability, excitement, hostility, aggressive and/or violent behaviour[14,18] most commonly occurs due to non-compliance with therapy or disease progression[19,20] and may be complicated by substance abuse.[19,21] It is related to the severity of "positive" symptoms[19,21], and violent behaviour, in particular, and is associated with hallucinatory symptoms.[19,19,22] The largest predictor of violent behaviour is a history of violence.[21]

Epidemiological data quantifying the prevalence of agitation in schizophrenia are limited. More often data on the occurrence of symptoms of agitation (specifically aggressive and/or violent behavior) come from studies with relatively small patient samples:

- The UK population-based AESOP study of incident cases of psychosis over 2- years: ~40% of first-episode schizophrenia patients displayed aggressive behaviour.[23]
- European Schizophrenia Cohort study of 1,208 schizophrenia patients in Germany, France, and the UK: 26% had experienced an episode of physical violence.[22]
- US-based National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness Study: 6-month prevalence of any violence among 1,410 schizophrenia patients in diverse treatment settings was 19.1%; 3.6% constituted serious violent behaviour.[24]
- WHO Determinants of Outcomes of Severe Mental Disorder studies conducted across 10 countries reported an incidence of assault at 20.6 per 100 patients with schizophrenia among the entire cohort of 1,017 first-contact schizophrenia patients.[24]
- A survey of 583 patients with schizophrenia or bipolar disorder in the UK, Germany, and Spain was conducted to evaluate the prevalence and characteristics of agitation, defined as uneasiness, restlessness, or nervousness. Patients experienced "moderate" or "moderate-intense" agitation events that were disruptive of day-to-day living an average of 22 times in the previous 12 months. "Severe" events, defined as agitation that would lead to hospitalization or violence were experienced an average of 2.9 times in the previous year.[25]

2.1.1.3 Incidence and Prevalence in Paediatric/Adolescent Populations

Early-onset schizophrenia (EOS, onset before the age of 15 years) has been estimated to be approximately 1%[26], and varies depending upon age group, being less prevalent in 5- to 9-year olds than in 10- to 15-year olds.[12] The prevalence appears to be higher in males than females, but the reported ratios vary from 1.4:1 to 4.5:1.[12,27] An evaluation of pediatric psychiatric care centers in France found that 8.9% of pediatric patients matched diagnostic criteria for schizophrenia.[28]

The incidence of early-onset schizophrenia is low (≤10/100,000 for age < 10 years), but increases sharply after the age of 12 or 13 years, and peaks between the ages of 15 and 20 years[9,29], where the observed rate of onset is approximately 35/100,000 to 55/100,000.[24]

Prognosis appears to be worse for early-onset disease[12,30] although EOS continues to be a controversial diagnosis that is associated with misdiagnosis. While both early-onset schizophrenia and very-early-onset schizophrenia (defined as onset before the age of 13 years) were associated with poor outcomes and severe symptomatology in one 2020 study (France), a separate study (Denmark) found that EOS and adult-onset schizophrenia did not differ in long-term hospitalization rates.[31,32]

2.1.1.4 Demographics of the Target Populations in Schizophrenia

Gender, ethnicity, migrant status, and urban versus rural settings all may impact the epidemiology of schizophrenia and may vary based on geographic locations.

Gender and Age of Onset Differences in Incidence

Findings have been inconsistent with regard to differences in the incidence of schizophrenia according to gender but generally suggest a higher incidence among males early in life and a narrower sex-based difference in lifetime prevalence due to relatively increased diagnosis later in life in women compared to men.[33]

Analyses of international studies provide evidence for a higher annual incidence rate for males:

- Meta-analysis conducted across 49 studies: male-to-female incidence risk ratio for schizophrenia = 1.42 (95% CI: 1.30-1.56).[34]

A 2-year (1997-1999) prospective population-based case-control study of 3 centers in the UK (AESOP study)[2] found that the risk of schizophrenia was greater for men than women at younger ages:

- Incidence rate ratio (IRR) for 20-24-year age band = 4.1.
- Incidence of schizophrenia for men was approximately 40/100,000/year, compared to approximately 10/100,000/year for women.[2]
- Differences disappeared with age.[2]

An incidence study in a catchment area of Melbourne, Australia conducted between 1997 and 2000 estimated that incidence rates for schizophrenia spectrum diagnoses (DSM-IV schizophrenia, schizophreniform disorder, schizoaffective disorder) were consistently approximately 2-fold higher for males than females across all age groups up to 29 years[5] with annual incidence for those 15-29 years of age 11.7-12.5/10,000 for males and 5.0-5.4/10,000 for females.

Evidence for the earlier onset of schizophrenia in males is well-established. Earlier onset of schizophrenia in males, as compared to females, has been widely reported with most studies reporting a 3-5 year difference.[29,35,36] Difference in age of onset between the genders persists irrespective of culture, diagnostic criteria used, definition of onset, or age distribution of the general population.[13,18]

Of note, the gender differences in age of onset appear to apply only to sporadic schizophrenia and *not* to familial cases; the age of onset is similar for both genders in instances where a patient has an affected first-degree relative (i.e., where there is "high genetic load").[13,29]

While most studies report a mean age of onset in the early 20s for males and in the mid-to-late 20s for females[13], evidence suggests that there may be age-specific peaks in disease incidence for each gender.[29,37]

- Males: early peak of onset in their late teens and early 20s, followed by a gradual decline
- Females: several peaks of onset, with the first in their 20s, another in late middle age, and another over the age of 65 years.[18,21]
- The annual incidence of schizophrenia for women >40 years old has been reported to be twice as high as for men, 8.9/100,000 as compared to 4.2/100,000, respectively.[38]

Hypotheses proposed to explain the differing age-at-onset distributions for men and women:

- An age-dependent protective effect of estrogen: antipsychotic and potent neuromodulatory activities of estrogen that result in a later age of onset for women[13,29]
  - May explain, at least in part, findings that women usually have a less severe course of disease and a better response to neuroleptic treatment[13,18,29]
  - Consistent with the late-adult-onset peak seen more frequently in women as estrogen levels fall in menopause[21,29]
- Slower neurodevelopment of males that may make them more prone to pre- and perinatal and childhood "insults," and hence, the development of neurophysiological disorders or abnormalities.[13,29]

Gender and Prevalence

Point prevalence studies suggest that the point prevalence of schizophrenia is higher among males compared to females. For example:

- Among the 56,000 inhabitants of Greenland, the point prevalence of schizophrenia was 2.5-fold higher in men compared to women.[15]
- Among the 4 million inhabitants of Valencia, Spain, the point prevalence of schizophrenia was 2-fold higher in men compared to women.[16]

Interestingly and in contrast, lifetime prevalence of schizophrenia is similar for males and females across all studies.[6,22] This unexpected finding might be explained by a shorter duration of illness or a higher mortality rate in males.[6]

Gender and Course of Illness and Treatment Responses

A better outcome for female schizophrenic patients has been traditionally reported[39] as well as a more favorable response to treatment among women compared to men.[13,18,29]

However, some more recent studies have questioned this dogma and suggested that, while overall clinical outcomes are indeed more favorable in female patients, female schizophrenia patients may face increased comorbidity:

- A study of 1,055 schizophrenia patients (74% male) in France found that female patients, compared to male patients, were more likely to be taking antidepressants, more likely to have a history of suicide attempts, have higher levels of self-stigma, and have lower satisfaction with their interpersonal relationships.[40]
- In Croatia, female patients were more likely to have physical comorbidities compared to male patients.[41]

Migrant vs. Native-born Differences in Incidence Rates and Prevalence

Evidence, although quite heterogeneous, consistently reveals that immigrant populations have a higher incidence of schizophrenia as compared to the host country native populations.[42,43,44] This elevated incidence is particularly apparent for migrants from developing countries relocating to European or westernized countries; and evidence has indicated that the level of economic development in the region of birth is significantly associated with a heightened risk.[42]

- A meta-analysis of studies for 5 countries (UK, Australia, Netherlands, Sweden, and Denmark) examined the risk of schizophrenia among immigrants, including those from the Caribbean, Africa, West Africa, Morocco, Eastern Europe, India, Pakistan, Asia, and the Middle East. The analysis found the mean relative risk of schizophrenia for first- and second-generation migrants compared to native-born individuals to be 2.9 (95% CI: 2.5-3.4), but there was significant heterogeneity in the effect sizes across the included studies.[44]
- IRR for all first-generation immigrants in the Netherlands, 15-54 years old, when compared to native Dutch people was 2.3 (95% CI: 1.7-3.0).[45]
- IRR for all first-generation immigrants in the Netherlands, 15-54 years old, and including those from non-Western countries, such as Morocco, Suriname, and the Caribbean, was 2.3 (95% CI: 1.7-3.0) compared to native Dutch people.[45]

Hypotheses to explain this migrant phenomenon include psychosocial factors, such as poor socioeconomic status, social marginalization or adversity, discrimination, and stress associated with integration into a different culture.[46] Interestingly, a study in Italy comparing international migrants, domestic migrants from areas of lower socioeconomic status in South Italy, and the general population found that risk for psychosis was equally elevated in both migrant groups.[47]

The wide range in the incidence estimates in migrant studies has been attributed to methodological issues in conducting such studies, including factors related to differential pathways to treatment. However, the reported effect sizes associated with migration are greater than those of many other risk factors that have been implicated in the etiology of schizophrenia and therefore, cannot be solely attributed to potential differences in treatment patterns, which merits continued consideration. Hypotheses to explain these observations include migration of those with a predilection for schizophrenia and social adversity faced by immigrants (discrimination, unemployment, separation from family and friends, language barriers, and more).

Urban vs. Rural Setting and Risk of Schizophrenia

Population-based studies (Denmark) have revealed an association between urban birth, upbringing, or residence and an increased risk of schizophrenia; however, the underlying causes of the urban-rural difference in the occurrence of schizophrenia are not known.[48]

Outcomes in Developed vs. Developing Nations

While there is study evidence from WHO to suggest better outcomes in schizophrenia for patients in developing countries compared to those in developed countries[49,50] other analyses of the study data do not strictly support this conclusion.[51,52]

2.1.1.5 Risk Factors for the Disease

Family history is a well-established risk factor for schizophrenia.[53] Potential risk factors include obstetric complications[54,55,56,57] parental age (both paternal and maternal)[58,59,60,61,62] urban vs. rural residence[48] prenatal infection[7,63] and below average pre-morbid intellectual performance.[64]

Comorbid substance use disorder (SUD) is common in patients with schizophrenia.[65] It is likely to also alter and exacerbate the clinical course of schizophrenia as well as the treatment of patients with schizophrenia:

- SUD is associated with an earlier age-of-onset of schizophrenia (Denmark).[65]
- A study of patient outcomes in an involuntary psychiatric unit found that patients that tested positive for tetrahydrocannabinol (a main active component of cannabis) were more likely to have a longer length of hospitalization and more likely to be prescribed benzodiazepines rather than antidepressants.[66]
- Cannabis use is associated with an increased frequency of psychotic experiences. A study of genetic risk in 109,308 UK Biobank patients found that patients with a higher PRS for schizophrenia had stronger associations between concurrent cannabis use and auditory hallucinations, visual hallucinations, and delusions of reference.[67]

2.1.1.6 Main Treatment Options

Treatment options for schizophrenia include atypical or typical antipsychotic agents.

Among antipsychotics, use of long-acting second generation/atypical antipsychotics including oral aripiprazole have been associated with a lower mortality in observational studies.[68] However, also in observational studies, use of antipsychotics have also been associated with an increased risk of important adverse cardiac events including cardiac arrest.[69]

2.1.1.7 Mortality and Morbidity (Natural History)

It has been estimated that globally, schizophrenia reduces life expectancy by an average of 10 years.[22] Increased mortality has been widely reported for schizophrenia, a finding that has been substantiated by 2 meta-analyses that included data from up to 9 countries.[70,71]

The causes of the observed excess mortality are believed to be due to the mental disorder itself, as well as to unhealthy lifestyle practices (poor diet, smoking, alcohol, or other substance abuse) among schizophrenic patients.[57,70]

Overall Mortality:

- Aggregate crude mortality rate from meta-analysis: 189 deaths/10,000 population/year.
- Aggregate all-cause SMR in meta-analysis ranged from 1.51 (95% CI: 1.48-1.54) to 1.57 (95% CI: 1.53-1.60), or a risk of death 1.6 times that expected.
- 10-year survival rate of 81%.[70]

Natural Death

- Eighty percent of people with schizophrenia die from natural causes, compared to 97% of the general population.[70]
- Natural death accounts for approximately 60% of the excess mortality of schizophrenia (meta-analysis).[71]
- Estimated aggregate SMR for natural death (meta-analysis) ranges from 1.34 (95% CI: 1.31-1.37) to 1.37 (95% CI: 1.34-1.41).[57,72]
- Deaths due to cardiovascular, respiratory, and infectious diseases, as well as from digestive system, endocrine, and mental disorders are all significantly higher than expected.[57,72]

Unnatural Deaths (accidents, suicide, homicide, other)

- These deaths were significantly increased for people with schizophrenia for both genders (meta-analysis).[71]
- Deaths from suicide and accident accounted for 38% to 41% of the total excess mortality of schizophrenia and the mortality risk from unnatural cause and were 4 times higher than expected: aggregate SMRs of 4.26 (95% CI: 4.02-4.51) and 4.34 (95% CI: 4.12-4.57), respectively.[71]
- Rate of death from accidents among people with schizophrenia was twice that of the general population (SMR: 2.16; 95% CI: 1.96-2.36) and accounted for approximately 12% of excess mortality.[71]

- Suicide constituted the largest single cause of excess mortality in schizophrenia:
  - Accounted for approximately 12% of all deaths and about 28% of excess mortality in schizophrenia
  - Reported aggregate SMRs of 8.38 (95% CI: 7.84-8.94) to 9.00 (95% CI: 8.42-9.62).[71]

Suicide was significantly higher among men than women and was found to occur at the highest rate in the year immediately following diagnosis.[57]

Other risk factors for increased mortality in schizophrenia patients include male gender, young age, the presence of physical comorbidities, no antipsychotic use, fewer outpatient psychiatric visits, and comorbid substance use disorders.[73] As of January 2022, studies have found that the most common causes of mortality in patients with schizophrenia have shifted in certain populations compared to past populations:

- In a Finnish follow-up study conducted from 1984 to 2014: the mean age of death in schizophrenia patients increased from 57.6 to 70.1 years old, compared to 70.9 to 77.5 years old in the general Finnish population. Mortality from suicide decreased over this time period, while mortality from cardiovascular disease and cancer increased among those with schizophrenia.[74]
- In Malaga, Spain (2021): among 1,418 schizophrenia patients followed on average for 13 years, the most common causes of death (in descending order) were "circulatory disease," cancer, and suicide.

Differences in the relative frequencies of causes of mortality are subject to socioeconomic and cultural factors specific to a given study population and recording of cause of death is challenging. Nonetheless, these studies and other evidence indicate a narrowing of the gap in mortality difference between those with schizophrenia versus the general population, likely with large gains in life-years coming as the result of decreasing rates of suicide and accident among people with schizophrenia.

2.1.1.8 Potential Health Risks

Premature death due to suicide and co-morbid conditions is a major health risk among patients with schizophrenia.

Suicide: The risk of suicide death was estimated at 9 times higher for schizophrenic patients than the general population.[57]

- Among those experiencing acute agitation, violent behavior presents a risk of harm to self, family members, and medical personnel. Moreover, violent or aggressive behavior in agitated patients is associated with suicidal tendency.[20]

Psychiatric Co-morbidities: Patients with schizophrenia may also experience anxiety, panic disorder, OCD, social phobia, PTSD, and depression. Psychiatric co-morbidities

are common among schizophrenic patients; however, epidemiological data are very limited, and most studies examining prevalence are based on small clinical samples. Moreover, reported rates vary greatly, most likely due to differences in patient samples and diagnostic methods/criteria used.[75,76,77,78] Comorbid depression in particular is highly prevalent among patients with schizophrenia:

- In a 2020 metanalysis spanning 18 studies: 32.6% of 6,140 schizophrenia patients had comorbid major depressive disorder.[79]
- In schizophrenia patients older than 55 years old in France, 78% of patients presented with subsyndromal or syndromal depressive symptoms.[80]

Medical Co-morbidities: Medical illness is more common among patients with psychiatric conditions than in the general population; however, prevalence data are limited for specific psychiatric diagnoses and there is limited data related to cardiovascular co-morbidities and other common medical co-morbidities. While several serious co-morbidities of schizophrenia have been found to be treatment-related or to be exacerbated by treatment, numerous co-morbidities are independent of drug effects. Cardiovascular disease is a significant cause of mortality in patients with schizophrenia - schizophrenia patients have been found to have higher rates of adverse cardiac events, including coronary artery disease, myocardial infarction, heart failure, arrythmias, and stroke.[69,81,82] Sexual dysfunction in both men and women is also associated with schizophrenia and its related depressive symptoms, negative symptoms, psychotic symptoms, and antipsychotic use.[83]

2.1.2 Indication #2 Bipolar Mania

2.1.2.1 Incidence

Bipolar Mania: Reported incidence rates of bipolar mania vary with type of populations studied, local variations, difficulty of establishing disease onset (i.e., time of first episode), and other factors. Reported incidence includes:

- First admission to psychiatric facilities: 3.0-8.3/100,000/year for males and from 2.0-10.7/100,000/year for females[84]
- Rates based on all referrals for treatment: 4.5-15.2/100,000/year for males and 4.8-32.5/100,000/year for females.[84]
- Lower incidence for mania vs. bipolar disorders: incidence of mania is about half that of all bipolar disorder.[85]

The age and pattern of incidence of bipolar disorder is heterogeneous across countries. The peak incidence of bipolar mania is typically understood to be highest during the late paediatric/young adult years, with variability based on how these years are classified. For

example, a 35-year study reported a peak incidence of 16 per 100,000 population/year during the 21 to 25 years age range[86] and another study reported a peak of 12 per 100,000 population/year during the slightly later 30 to 49 years age range.[85]

A 2021 meta-analysis spanning studies performed in North America, Europe, and Australia has suggested that bipolar mania incidence may follow a trimodal pattern with early (17-year-old), middle (26-year-old) and late (42-year-old) peaks. The early peak demonstrated the greatest incidence (45%, n=13,236).[84]

Agitation in Bipolar Mania: No epidemiological studies assessing the incidence of agitation in bipolar disorder or mania were identified.

2.1.2.2 Prevalence

Bipolar Mania: Reported prevalence rates for bipolar I disorder differ across studies due to local variations, use of different validated instruments, variation in the criteria that define a specific bipolar disorder, and because of the diverse manner in which bipolar I disorder manifests at any given time (chronic or recurrent). Reported prevalence rates include:

- Estimated international 1-year prevalence and lifetime prevalence rates: 0.7% - 1%.[87,88] and 0.8%[87,89] respectively.
- Higher lifetime prevalence rates have been reported: Netherlands: 1.8%; UK: 1.7%;[85] US: 1.6%;[90,91] Switzerland: 4.4%;[88,92] and Sweden 2.63%.[93]
- US National Epidemiological Catchment Area database mania lifetime prevalence: 0.8%; hypomania: 0.5%; when subsyndromal symptoms of mania are included, the lifetime prevalence for the bipolar manic spectrum is 6.4%.[94]

Agitation in Bipolar Mania:

The United Kingdom (UK) population-based Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) study of incident cases of psychosis over 2 years: approximately 60% of first-episode mania patients displayed aggressive behaviour.[23]

2.1.2.3 Incidence and Prevalence in Paediatric/Adolescent Populations

The diagnosis of paediatric bipolar I/mania, particularly among pre-adolescent patients, is complex and remains controversial.[95]

While there appears to be general agreement that uncomplicated classical manic depression (i.e., episodes of euphoric mania, depression, and normal mood states) is uncommon in pre-adolescent children, there is disagreement regarding whether or not children meet symptom criteria for a manic syndrome.[96]

Diagnosis of bipolar mania is complicated by the overlap of symptoms with other psychiatric conditions.[16,17] Some maintain that symptoms rarely meet criteria for mania before adolescence[25,28,31,95] while others contend that persistent and chronic mania may be part of the natural history of prepubertal and early adolescent bipolar disorder.[32,40]

Moreover, there are regional differences in the recognition and diagnosis of bipolar disorder/mania[41] and prevalence estimates are often not restricted to bipolar mania, but rather include all bipolar spectrum disorders (bipolar I disorder, bipolar II disorder, bipolar not otherwise specified (NOS)). For instance, US clinicians have been found to make significantly more diagnoses of mania than have UK clinicians.[47] Even for a given set of individuals within the same country, there can be significant variability in diagnostic coding by clinicians. For example, a random sample of 131 charts from Danish paediatric patients designating an International Classification of Diseases 10 (ICD-10) diagnosis of single hypomanic/manic episode or bipolar disorder had 55% of these diagnoses rejected upon re-evaluation by ICD-10 standards.[97]

As a result of the challenges and varying professional views regarding the diagnosis of bipolar mania in children, the reported incidence and prevalence of bipolar mania in children and adolescents varies widely and remains relatively uncertain.

Population-based estimates of bipolar disorder

Few population-based epidemiology studies have been conducted to assess the prevalence of paediatric or adolescent bipolar disorder and reported estimates vary internationally, ranging from < 1% to 2%:

- Lewinsohn et al.[28] reported that the lifetime prevalence of bipolar disorders among a representative community sample of 1,709 adolescents (aged 14 through 18 years) was approximately 1% (primarily bipolar II disorder and cyclothymia); only 0.12% met the full Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition Revised (DSM-III-R) criteria for a lifetime manic episode. The 1-year incidence was estimated to be 0.13%.
- Costello et al.[65] found no cases of bipolar mania among 4,500 randomly-selected children residing in a southeastern area of the US.
- The National Comorbidity Survey (US) estimated the lifetime prevalence of bipolar I disorder among adolescents to be approximately 0.5%.[98]
- A community-based (US) longitudinal study of 717 youths found the incidence rate of bipolar disorder to be 1.9%.[66]
- The 6-month prevalence of bipolar mania in a national sample representative of 13- to 18-year-olds from the Dutch general population was 1.9%.[67]

- A 2021 population-based Danish study found the prevalence of bipolar mania in 5- to 18- year-olds to be 0.019%.[97]
- A 2019 multiregional metanalysis covering studies from the US, South America, Central America, and Europe found the pooled prevalence of bipolar mania to be 0.6%.[87]

Estimates of bipolar disorder among a referral population

Higher prevalence rates have been reported for clinically referred (inpatient or outpatient) samples of children and adolescents, with international rates ranging from approximately 1% to 27%:

- A retrospective analysis of US community mental health clinics data 1999-2003 found that among 3,086 children and adolescents (4 to 18 years of age), approximately 6% were diagnosed with bipolar disorders, 51% of which (3% of the total sample) were bipolar I.[74]
- Among 1,468 consecutive new cases (7-16 years old) ascertained from US outpatient child psychiatry and paediatric facilities, 6.3% met DSM-IV criteria for bipolar mania.[16]
- Among 1,838 consecutive patients ≤18 years of age referred to a US academic psychiatry service from 1991-2002, 16% received a diagnosis of bipolar mania; 66% of these patients were ≤12 years of age.[40]
- Among child and adolescent psychiatric inpatients in Finland, the prevalence of bipolar disorder at the beginning of 2000 was 1.7%[79] and the annual incidence of first episode (1987-1994) was 1.7/100,000 (males: 0.6/100,000; females 0.9/100,000).[85]
- The frequency of bipolar mania among Danish psychiatric patients <15 years (1970-1986) was 1.2%.[80]
- The prevalence of bipolar disorder among a case series of psychiatric patients 15-18 years old in Spain was 4%.[41]
- The reported prevalence of bipolar disorder among outpatients <5 years in Brazil (1998-2001) was 7.2%.[81]
- Bipolar mania rates reported for children or adolescents in India ranged from 2.5% to 3.3%.[82,83]

The variability in the rate of bipolar mania among children and adolescents is also in part due to failure to diagnose bipolar disorder among children with manic features who have previously been diagnosed with attention deficit hyperactivity disorder (ADHD) and other conditions.[99]

- A retrospective analysis revealed that when 64 adolescents and children (7-18 years old) treated in a community setting were reassessed using formal DSM-IV criteria, bipolar disorder was under diagnosed, with only 38% of bipolar

disorder patients receiving a diagnosis of bipolar disorder, while 29% and 33% of bipolar disorder patients received a misdiagnosis of ADHD and MDD, respectively.[99]

Hence, the diagnosis of bipolar mania in children and adolescents varies, depending upon the instrument used to ascertain the diagnosis (e.g., structured interview or DSM criteria) and the criteria used to define mania (i.e., whether mania was defined according to adult criteria or according to an expanded criteria; or whether criteria were based upon severity, episode length, impairment of functioning, or some combination of criteria).[25,98,100,101,102]

Trends in the diagnosis of bipolar disorder

Although the diagnosis of paediatric (and particularly, pre-adolescent) bipolar mania remains challenging and controversial, evidence in the past several years has continued to accumulate, supporting the idea that bipolar mania may be more common at younger ages than previously recognized. This is reflected in the reported increase in utilization of both inpatient and outpatient mental health services.

- A study using the Danish Psychiatric Central Research Registry found that the incidence rate for bipolar disorder increased from 11.5 to 24.5 per 100,000 person-years during the years 1995 to 2010, and that these time trends were greatest among those <29 years old.[8]
- An analysis of a large nationwide (US) database of private health insurance claims (MarketScan) found a 65.4% increase in the likelihood of bipolar diagnosis among children <18 years old and that the prevalence of inpatient diagnosis for bipolar disorder among children <18 years old increased from 3.80/10,000 to 4.23/10,000 from 1995 to 2000.[103]
- A survey of approximately 1,000 representative community hospitals in the US for 1990-2000 found that the proportion of discharges among those patients <18 years old diagnosed with principal bipolar disorders rose 5-fold, from 2.9% to 15.1%.[104]
- Analysis of the National Hospital Discharge Survey indicated that the rate of diagnoses for bipolar disorder increased among both US children and adolescents during the 8-year study period:[105]
    - In 1996, there were 1.4 paediatric discharges with bipolar disorder diagnosis/10,000 children in the general population (US); by 2004, there were 7.3/10,000. This represented an increase from 10% to 34% in the proportion of bipolar diagnosis among the total psychiatric-related discharges for children.[105]
    - In 1996, there were 5.1 discharges with a primary diagnosis of bipolar disorder/10,000 adolescents; by 2004, there were 20.4 discharges/10,000 adolescents. This represented an increase from 10% to almost 26% in the

proportion of bipolar diagnosis among the total psychiatric-related discharges for adolescents.[105]

- The reported rates of outpatient diagnosis of bipolar disorder among children and adolescents have increased in recent decades:
  - According to data from the US National Ambulatory Medical Care Survey, the estimated annual number of office-based visits for youth with a diagnosis of bipolar disorder increased 40-fold, from 25/100,000 population (1994-1995) to 1,003/100,000 population (2002-2003).[106]

2.1.2.4 Demographics of the Target Populations in Bipolar Mania

Adult Patients: Bipolar disorder occurs with equal frequency among males and females.[87] The age of onset, although variable, appears to be earlier in males than in females.[97] Studies also suggest that clinical outcomes differ between men and women.[88,89] Men more commonly present at onset with mania and are more likely to have a comorbid substance use disorders.[88,89] Women are hospitalized more often for bipolar episodes and for longer periods of time.[88,89]

Incidence of mania peaks in early adult life, but there is evidence of early and later onset subgroups.[97] Early age of onset has been reported at a relatively high frequency among adult bipolar patients. In US studies, 15% - 28% of adults with bipolar disorder reported onset before the age of 13 years and 35% - 37% reported onset between the ages of 13-18 years.[107] Early-onset bipolar disorder is associated with a more severe disease course of illness.[108]

Racial differences in bipolar mania diagnosis have been identified in both Europe and the US. In the US, black patients have been observed to present more commonly with manic symptoms and hallucinations and are more likely to be misdiagnosed with another illness, such as schizophrenia.[90] Such diagnostic differences may also have ramifications in terms of therapeutic approach. In a UK study, black African and black Caribbean patients with bipolar mania were found to be less likely to receive cognitive behavioral therapy than their white English counterparts.[91]

Paediatric/Adolescent Patients: Bipolar mania appears to occur more frequently in males, particularly among pre-adolescent cases.[40,67,69,79,81,109,110,111]

2.1.2.5 Risk Factors for the Disease

Family history and male gender are recognized risk factors for bipolar disorder.

Family history of bipolar disorder represents the single greatest risk factor for developing bipolar mania, and early onset of bipolar disorder is associated with greater familial loading.[31,101,112,113] One study found that offspring of parents with bipolar disorder showed a 14-fold increase in the rate of bipolar spectrum disorders compared to offspring of control parents.[31] A comparative analysis of original data aggregated from 17 studies found that children of parents with bipolar disorder are 4 times more likely to develop an affective disorder than are offspring of parents with no mental disorder or no major mental disorder.[113]

Substance use is also associated with bipolar disorder, and the relationship between substance use and bipolar disorder may be bidirectional. A 2021 metanalysis found that nicotine, alcohol, cannabis, and cocaine have all been previously reported to increase risk for a subsequent diagnosis of bipolar mania. In particular, recent studies have identified cannabis use as a significant risk factor for bipolar mania; a history of cannabis use has also been associated with more intense symptoms.[92]

Childhood trauma and neurodevelopmental delay are relatively novel risk factors associated with bipolar disorder. In Sweden, a 2021 population-based study found that both childhood trauma and pre-existing neurodevelopmental disorders increase risk for bipolar mania.[93] A number of studies have attempted to generate polygenic risk scores (PRS) for bipolar mania as a means of predicting risk and age-of-onset as a supplement to clinical criteria; however, these efforts remain in the research realm and are not currently used for clinical purposes.[23,94]

2.1.2.6 Main Treatment Options

Treatment options for bipolar disorder include mood stabilizers (e.g., lithium), antidepressants, atypical antipsychotics, and anticonvulsants (e.g., sodium valproate; lamotrigine). In the EU and the developed world, atypical antipsychotics have become increasingly common.[100,101] The growth of use of second-generation antipsychotics has been well documented in the US population where use of second-generation antipsychotics expanded from 12% of all outpatient prescriptions for bipolar disorder during 1997 to 2000 to 51% during 2013 to 2016.[114]

2.1.2.7 Mortality and Morbidity (Natural History)

The overall mortality among patients with a pre-existing mental disorder exceeds that of the general population by roughly 2- to 3-fold. Suicide accounts for at least half of unnatural deaths in bipolar I populations. However, cardiovascular disease remains the leading natural cause of excess death reported among bipolar populations.[115,116]

Comorbid conditions such as smoking or other risky lifestyle behaviors may drive much of this excess long-term risk.

Reported mortality rates for bipolar disorder include:

- Meta-analysis all-cause standardised mortality ratio (SMR): 2.02 (95% CI: 1.88-2.17).[70]
- Danish population based all-cause SMR in all subgroups of affective disorder (including bipolar mania): 1.94 (95% CI: 11.91-1.98).[115]
- US-based study absolute mortality: 2.8%.[117]
- Swedish population-based 12-year study period all-cause SMR: 2.5 (95% CI: 2.4-2.6) for men and 2.7 (95% CI: 2.6-2.8) for women[116]; approximately 20% of deaths could be attributed to suicide.

As of 2021, the impact of the Coronavirus Disease 2019 pandemic on bipolar mania diagnosis and clinical course remains unclear.

2.1.2.8 Potential Health Risks

Suicide and co-morbidities are major health risks among bipolar patients.[118,119]

Suicide: Risk of suicide deaths is reported to be 10 to 30 times higher for bipolar disorder patients than the expected rate in the general population.[72,115,120]

- A 2019 case-control study conducted within the US Mental Health Research Network found a 13-fold increased risk for suicide mortality that was associated with bipolar disorder, more than was observed for depressive disorders (7-fold increased risk), anxiety (6-fold), or ADHD (2-fold).[10]
- In Europe, a 2021 study investigating suicide rates in bipolar mania found that comorbid post-traumatic stress disorder (PTSD) as well as comorbid personality disorders enhanced risk for death from suicide.[98]
- Tobacco smoking and other comorbid substance use disorders are associated with recurrent suicide attempts in bipolar mania.[96]

Psychiatric Co-morbidities: Patients with bipolar mania may also experience anxiety, panic disorder, obsessive-compulsive disorder (OCD), social phobia, PTSD, and depression.

Medical Co-morbidities*:* Medical illness is more common among patients with psychiatric conditions compared to the general population; however, prevalence data for comorbidities are primarily limited for specific psychiatric diagnoses. While several serious co-morbidities of bipolar I disorder have been found to be treatment-related or to be exacerbated by treatment, numerous co-morbidities are independent of drug effects.[3,121]

Increased risk for cardiovascular disease appears to drive a significant proportion of the excess mortality associated with bipolar disorder. Bipolar mania is associated with multiple cardiovascular disease risk factors, including elevated body mass index (BMI) and hypertension:

- A population-based cohort study from the US found that bipolar mania was associated with major adverse cardiovascular events. This association persisted after controlling for smoking, diabetes mellitus, hypertension, high-density lipoprotein cholesterol, and BMI.[95]
- A 2021 study from Denmark also found that bipolar mania is associated with a greater risk for out-of-hospital cardiac arrest.[69]
- In the Netherlands, a 2021 population-based study found that metabolic syndrome was more common in patients with bipolar mania than controls.[109]

These data suggest that the high observed rates of cardiovascular disease in those with bipolar disorder are likely in part related to shared comorbidities such as smoking. Recent studies have additionally suggested that predisposing genetic factors are shared between bipolar disorder and cardiovascular disease.[11] Reviewing this evidence, the American Heart Association has issued a consensus statement that bipolar disorder is associated with accelerated atherosclerosis and cardiovascular risk.[12]

2.2 Module SII: Nonclinical Part of the Safety Specification

The pharmacological activity of aripiprazole is mediated through a combination of partial agonism at dopamine D_2 and serotonin 5-HT_{1A} receptors and antagonism of serotonin 5-HT_{2A} receptors.

Abilify

The nonclinical pharmacology, pharmacokinetic, and drug safety evaluations performed with oral and intramuscular (IM) aripiprazole support the continued use for the treatment of schizophrenia and bipolar mania disorders. The nonclinical safety data demonstrated no special hazard for humans based on studies of safety pharmacology, repeat-dose toxicity in juvenile and adult animals, genotoxicity, reproductive toxicity, and carcinogenic potential.

Pharmacologically mediated central nervous system (CNS)-related clinical signs included impaired motor activity, hyporeactivity, tremors, catalepsy, and abnormal posture at low oral doses and exposures in monkeys (subtherapeutic to 3 times the mean steady-state area under the concentration-time curve [AUC] at the maximum recommended human dose [MRHD]). Other toxicologically important effects in repeat-dose oral toxicity studies (dose-dependent adrenocortical toxicity, increased adrenocortical carcinomas, and

combined adrenocortical adenomas/carcinomas in rats and hepatic cholelithiasis in monkeys) were observed only at doses markedly exceeding the maximum tolerated dose and/or exposures that were in excess of the maximum human dose or exposure, indicating that these effects were of limited or of no relevance to clinical use.

Based on results of a full range of genotoxicity tests, aripiprazole was considered nongenotoxic. Aripiprazole did not impair fertility in reproductive toxicity studies. Developmental toxicity, including delayed fetal ossification and vaginal opening, were observed in rats at doses resulting in subtherapeutic exposures (based on the AUC). In rabbits, increased embryo-fetal mortality and skeletal variations occurred at doses resulting in exposures 3 and 11 times the mean steady-state AUC at the MRHD. Developmental toxicity occurred only at doses that produced maternal toxicity.

The toxicity profile of aripiprazole in juvenile rats and dogs was comparable to that observed in adult animals, and there was no evidence of neurotoxicity or adverse effects on development.

Abilify Maintena

The toxicity profile for the aripiprazole IM depot formulation also relies on the nonclinical data developed following oral administration of aripiprazole as described above. Exposures, based on AUC values, following intramuscular injection of aripiprazole were lower than those following comparable doses with oral administration.

With intramuscular injection, microscopic findings at the injection site generally consisted of inflammation, hemorrhage, edema, and fibroplasia/fibrosis. Injection site changes were minimal in severity and attributed to the vehicle and mechanical trauma associated with repeated injections. There was, however, a slight exacerbation of the injection site injury in treated animals at all doses attributable to aripiprazole. All aripiprazole-related changes were reversible or showed a tendency towards reversibility. The toxicity profile for aripiprazole IM depot did not reveal any unique systemic toxicity.

Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe

Nonclinical pharmacokinetics (PK) and irritation studies conducted with the aripiprazole 2M RTU LAI formulation did not reveal any new or unexpected treatment related toxicities. In addition, the application of exercise, heat, and pressure, and the administration of an anti-inflammatory agent (diclofenac) had minimal effects on the PK of aripiprazole 2M RTU LAI after IM administration. Since the conditions used in these nonclinical studies represent a worst-case scenario and the changes were minimal, none

of these effects are expected to cause clinically significant changes in aripiprazole 2M RTU LAI exposure after IM administration.

Safety concerns identified in the nonclinical program are provided in Table 2.2-1.

Table 2.2-1 SII-1: Summary of Key Safety Findings from Nonclinical Studies and Relevance to Human Usage

Key safety findings (from nonclinical studies)	Relevance to human usage
Pharmacologically mediated CNS clinical signs: Impaired motor activity, hyporeactivity, tremors, catalepsy, and abnormal posture were observed in monkeys at 5 to 75 mg/kg/day (subtherapeutic to 3-times the mean steady-state AUC at the MRHD).	These findings in monkeys are due to exaggerated pharmacology and are not relevant at human exposure levels.
Adrenocortical toxicity: Lipofuscin pigment accumulation or parenchymal cell loss observed in rats after 26 weeks at 30 and 60 mg/kg/day or 104 weeks at 20 to 60 mg/kg/day (3- to 10-times the mean steady-state AUC at the MRHD).	Limited or no relevance to clinical use since effects were observed only at doses or exposures that were sufficiently in excess of the maximum human dose or exposure.
Adrenocortical adenomas/carcinomas: Increased adrenocortical carcinomas and combined adrenocortical adenomas/carcinomas observed in female rats at 60 mg/kg/day (10-times the mean steady-state AUC at the MRHD). The highest nontumorigenic exposure in female rats was 7-times the mean steady-state AUC at the MRHD.	Limited or no relevance to clinical use since effects were observed only at doses or exposures that were sufficiently in excess of the maximum human dose or exposure.
Hepatic cholelithiasis: Observed as a consequence of precipitation of sulphate conjugates of hydroxy metabolites of aripiprazole in the bile in monkeys after repeated oral dosing at 25 to 125 mg/kg/day (1- to 3-times the mean steady-state AUC at the MRHD).	Limited or no relevance to clinical use since the concentrations of the sulphate conjugates of hydroxy aripiprazole in human bile at the maximum recommended human dose were no more than 6% of the bile concentrations found in monkeys in the 39-week study and are well below their limits of solubility.
Developmental toxicity: Delayed fetal ossification and developmental effects in rats at 10 and 30 mg/kg/day (subtherapeutic exposures based on the mean steady-state AUC at the MRHD) and in rabbits at 30 and 100 mg/kg/day (3- and 11-times the mean steady-state AUC at the MRHD). Maternal toxicity occurred at doses eliciting developmental toxicity. Aripiprazole was excreted into maternal milk of rats during lactation.	It is not known whether aripiprazole can cause fetal harm when administered to a pregnant woman. Aripiprazole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus. Aripiprazole is excreted into human milk. Aripiprazole use in pregnancy and lactation are considered Important Missing Information for all formulations (see Section 2.7.3).
Aripiprazole IM depot Injection site reactions: Injection site changes in animals consisted of minimal inflammation, hemorrhage, edema and fibroplasia/fibrosis that were reversible. Changes attributed to the vehicle and mechanical trauma associated with repeated injections were reported. A slight exacerbation of the injection site injury was attributed to aripiprazole.	Injection site reactions (including erythema, induration, pruritus, injection site reaction, swelling, rash, inflammation, hemorrhage) have been reported.

2.2.1 Conclusions on Nonclinical Data

Of the toxicologically important nonclinical effects of aripiprazole described previously, none are considered to be toxicologically relevant at clinical doses. The aripiprazole-related developmental toxicity in rats and rabbits at maternally toxic doses is considered of unknown clinical significance. Moreover, aripiprazole use in pregnancy and lactation is considered Missing Information for all formulations (see Section 2.7.3).

2.3 Module SIII: Clinical Trial Exposure

2.3.1 Brief Overview of Development

Abilify (BMS-337039/OPC-14597) is a novel dopamine-serotonin system stabilizer discovered by Otsuka Pharmaceutical Company, Ltd. (OPC) and co-developed by Bristol-Myers Squibb (BMS) and OPC. Abilify Maintena is co-developed by H. Lundbeck A/S (Lundbeck) and Otsuka. The efficacy of aripiprazole is mediated through a combination of partial agonism (agonism/antagonism) at dopamine D2 and serotonin 5-HT1A receptors and antagonism at serotonin 5-HT2 receptors.

In adults, aripiprazole is indicated for the following (not all indications are approved in all countries):

- Treatment of schizophrenia (oral formulations and prolonged-release suspension for injection)
- Maintenance treatment of schizophrenia in adult patients stabilized with oral aripiprazole (Abilify Maintena)
- Treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy or adjunctive to lithium or valproate (oral formulations)
- Adjunctive treatment of MDD (oral formulations)
- Treatment of agitation associated with schizophrenia or bipolar mania (solution for injection for immediate release)

In paediatrics, the oral formulations of aripiprazole are indicated for:

- Treatment of schizophrenia
- Treatment of manic or mixed episodes associated with bipolar I disorder as monotherapy or adjunctive to lithium or valproate
- Treatment of irritability associated with autistic disorder
- Treatment of Tourette’s Disorder

Aripiprazole (Abilify and Abilify Maintena) is commercially available in the following formulations and strengths (not all formulations and strengths are approved or available in all countries).

- Abilify tablets: 1 mg, 2 mg, 3 mg, 5 mg, 6 mg, 10 mg, 12 mg, 15 mg, 20 mg and 30 mg
- Abilify orally disintegrating tablets: 3 mg, 5 mg, 6 mg, 10 mg, 12 mg, 15 mg, 20 mg, 24 mg and 30 mg
- Abilify oral solution: 1 mg/mL
- Abilify powder: 10 mg aripiprazole/1 g powder
- Abilify solution for injection (immediate release) for IM use: 7.5 mg/mL
- Abilify Maintena extended-release injectable suspension (powder and solvent for prolonged release suspension for injection) for IM use: 300 mg/vial or prefilled dual chamber syringe and 400 mg/vial or pre-filled dual chamber syringe

In the interval period since the approval of RMP v11.1, twelve company-sponsored clinical trials were completed, including 5 Phase 1 trials (031-201-00104, 031-201-00181, 031-201-00279, 031-403-00049, 031-403-00050), 5 Phase 3 trials (031-403-00048, 031-403-00106, 031-403-00107, 31-10-207, 31-14-204), 1 Phase 4 trial (031-409-00036), and 1 post-authorisation safety study (PASS, 15893N).

Two company-sponsored clinical trials are ongoing (031-402-00129, 031-402-00154). A review of safety findings currently available from these ongoing trials did not suggest any change to the established positive benefit-risk profile of aripiprazole.

Based on review of the data from the clinical trials completed during the reporting period, no significant efficacy and safety findings affecting the established positive benefit-risk profile of aripiprazole were identified.

The benefit-risk profile associated to the administration of aripiprazole in the authorised indications continues to be positive. The Company will continue to monitor suspected adverse reactions in association with the use of aripiprazole.

2.3.2 Clinical Trial Exposure

Abilify, Abilify Maintena, and Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe

Clinical investigation of aripiprazole has been underway since 05 Nov 1990. As of 30 Nov 2021, there have been 29,383 subjects who have been exposed to aripiprazole in clinical trials. Clinical trial exposure to Abilify, Abilify Maintena, and Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe by duration, age group and gender, dose, and race are provided in the following tables:

Table 2.3.2.1-1, Table 2.3.2.1-2, Table 2.3.2.1-3, Table 2.3.2.2-1, Table 2.3.2.2-2, Table 2.3.2.2-3, Table 2.3.2.3-1, Table 2.3.2.3-2, Table 2.3.2.3-3, Table 2.3.2.4-1, Table 2.3.2.4-2, and Table 2.3.2.4-3.

2.3.2.1 Duration of Exposure

Table 2.3.2.1-1 SIII.1-1: Clinical Trial Exposure to Abilify by Duration of Exposure (Cumulative and by Indication)

Duration of Exposure	Persons	Person Time (patient years)[1]
Cumulative for All Indications (Person Time)		
<= 1 month	8983	283.94
>= 3 months	13696	2960.47
>= 6 months	2656	1795.9
>= 12 months	2615	3204.8
>= 24 months	565	1290.15
>= 36 months	868	5262.52
Total person time	29383	14797.77
Schizophrenia		
<= 1 month	4345	163.55
>= 3 months	7589	1687.27
>= 6 months	1476	973.92
>= 12 months	1553	1948.39
>= 24 months	389	883.55
>= 36 months	830	5108.63
Total person time	16182	10765.31
Bipolar I Disorder		
<= 1 month	2084	74.15
>= 3 months	3778	847.54
>= 6 months	557	364.93
>= 12 months	321	396.77
>= 24 months	52	110.01
Total person time	6792	1793.4
Major Depressive Disorder		
<= 1 month	304	10.37
>= 3 months	1386	207.63
>= 6 months	230	171.36
>= 12 months	194	205.26
Total person time	2114	594.63
Autistic Disorder		
<= 1 month	47	1.77
>= 3 months	264	68.17
>= 6 months	96	70.62
>= 12 months	225	259.28
>= 24 months	17	40.3
>= 36 months	20	71.69
Total person time	669	511.84
Tourette's Disorder		
<= 1 month	112	4.68
>= 3 months	197	39.82
>= 6 months	98	73.02
>= 12 months	144	157.71

Table 2.3.2.1-1 SIII.1-1: Clinical Trial Exposure to Abilify by Duration of Exposure (Cumulative and by Indication)

Duration of Exposure	Persons	Person Time (patient years)[1]
Total person time	551	275.23
Alzheimer's Disease		
<= 1 month	215	5.25
>= 3 months	367	87.1
>= 6 months	195	139.92
>= 12 months	191	257.9
>= 24 months	112	267.57
Total person time	1080	757.74
Conduct Disorder		
<= 1 month	26	1.1
Total person time	26	1.1
Parkinson Disease		
<= 1 month	6	0.19
>= 3 months	5	0.88
>= 6 months	3	1.55
Total person time	14	2.62
Alcoholism		
<= 1 month	23	1
>= 3 months	123	24.82
Total person time	146	25.82
Healthy Volunteers		
<= 1 month	1823	21.99
Total person time	1823	21.99

[1] Patient years was calculated by computing the sum of all days subjects were exposed to the drug and dividing by 365.25.
*DLP: 30 Nov 2021

Table 2.3.2.1-2 SIII.1-2: Clinical Trial Exposure to Abilify Maintena by Duration of Exposure (Cumulative and by Indication)

Duration of Exposure	Persons	Person Time (patient years)[1]
Cumulative for All Indications (Person Time)		
<= 1 month	505	35.95
>= 3 months	1506	436.19
>= 6 months	664	481.24
>= 12 months	767	899.84
>= 24 months	138	329.04
>= 36 months	543	3098.19
Total person time	4123	5280.44
Schizophrenia		
<= 1 month	431	30.68
>= 3 months	1188	348.47
>= 6 months	499	364.02
>= 12 months	496	596.86
>= 24 months	121	292.7
>= 36 months	543	3098.19
Total person time	3278	4730.91

Table 2.3.2.1-2	**SIII.1-2: Clinical Trial Exposure to Abilify Maintena by Duration of Exposure (Cumulative and by Indication)**	
Duration of Exposure	**Persons**	**Person Time (patient years)[1]**
Bipolar I Disorder		
<= 1 month	74	5.27
>= 3 months	318	87.72
>= 6 months	165	117.22
>= 12 months	271	302.98
>= 24 months	17	36.34
Total person time	845	549.53

[1]Patient years was calculated by computing the sum of all days subjects were exposed to the drug and dividing by 365.25
*DLP: 30 Nov 2021

Table 2.3.2.1-3	**SIII.1-3: Clinical Trial Exposure to Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringeby Duration of Exposure (Cumulative and by Indication)**	
Duration of Exposure	**Persons**	**Person Time (patient years)[1]**
Cumulative for All Indications (Person Time)		
<= 1 month	44	3.13
>= 3 months	92	21.78
>= 6 months	104	63.2
Total person time	240	88.11
Schizophrenia		
<= 1 month	27	1.92
>= 3 months	70	15.26
>= 6 months	74	44.97
Total person time	171	62.15
Bipolar I Disorder		
<= 1 month	17	1.21
>= 3 months	22	6.52
>= 6 months	30	18.23
Total person time	69	25.96

[1]Patient years was calculated by computing the sum of all days subjects were exposed to the drug and dividing by 365.25.
*DLP: 30 Nov 2021

2.3.2.2 Age Group and Gender

Table 2.3.2.2-1	**SIII.2-1: Clinical Trial Exposure to Abilify by Age Group and Gender (Cumulative and by Indication)**			
	Persons		**Person Time (patient years)[1]**	
Age Group	**M**	**F**	**M**	**F**
Cumulative for All Indications (Person Time)				
Children (5 to 11 years)	685	162	438.65	92.45
Adolescents (12 to 17 years)	1025	599	929.92	598.94
Adults (18 to 64 years)	14196	11295	6382.65	5498.55

Table 2.3.2.2-1 SIII.2-1: Clinical Trial Exposure to Abilify by Age Group and Gender (Cumulative and by Indication)				
	Persons		**Person Time (patient years)[1]**	
Age Group	**M**	**F**	**M**	**F**
Elderly people	410	1008	188.54	666.71
- 65 to 74 years	165	259	65.87	125.5
- 75 to 84 years	163	366	84.26	274.65
- 85+ years	82	383	38.41	266.56
Age Not Available	2	1	0.97	0.38
Total	16318	13065	7940.73	6857.04
Schizophrenia				
Children (5 to 11 years)	1	0	0.03	0
Adolescents (12 to 17 years)	512	371	605.56	459.42
Adults (18 to 64 years)	9116	5989	5420.8	4210.35
Elderly people	81	110	20.34	47.88
- 65 to 74 years	70	93	19.36	40.51
- 75 to 84 years	8	15	0.56	7.26
- 85+ years	3	2	0.42	0.11
Age Not Available	1	1	0.54	0.38
Total	9711	6471	6047.27	4718.04
Bipolar I Disorder				
Children (5 to 11 years)	48	28	27.94	14.07
Adolescents (12 to 17 years)	135	132	90.41	75.54
Adults (18 to 64 years)	2692	3672	649.11	910.13
Elderly people	32	52	11.48	14.29
- 65 to 74 years	32	49	11.48	13.02
- 75 to 84 years	0	3	0	1.28
Age Not Available	1	0	0.43	0
Total	2908	3884	779.37	1014.03
Major Depressive Disorder				
Adults (18 to 64 years)	825	1232	217.31	351.22
Elderly people	20	37	9.25	16.85
- 65 to 74 years	15	26	6.18	12.88
- 75 to 84 years	5	11	3.06	3.98
Total	845	1269	226.56	368.07
Autistic Disorder				
Children (5 to 11 years)	414	73	311.46	52.27
Adolescents (12 to 17 years)	151	31	121.04	27.06
Total	565	104	432.51	79.33
Tourette's Disorder				
Children (5 to 11 years)	215	56	98.95	25.87
Adolescents (12 to 17 years)	215	63	112.39	36.85
Adults (18 to 64 years)	2	0	1.18	0
Total	432	119	212.52	62.72
Alzheimer's Disease				
Adults (18 to 64 years)	24	11	14.01	11.37
Elderly people	259	786	145.95	586.41
- 65 to 74 years	38	75	28.3	58.75
- 75 to 84 years	143	331	79.75	261.41
- 85+ years	78	380	37.9	266.25
Total	283	797	159.96	597.78

Table 2.3.2.2-1	**SIII.2-1: Clinical Trial Exposure to Abilify by Age Group and Gender (Cumulative and by Indication)**			
	Persons		**Person Time (patient years)[1]**	
Age Group	**M**	**F**	**M**	**F**
Conduct Disorder				
Children (5 to 11 years)	7	5	0.26	0.24
Adolescents (12 to 17 years)	12	2	0.52	0.08
Total	19	7	0.78	0.32
Parkinson Disease				
Adults (18 to 64 years)	1	1	0.1	0.02
Elderly people	5	7	1.49	1.01
- 65 to 74 years	1	2	0.52	0.09
- 75 to 84 years	3	4	0.88	0.72
- 85+ years	1	1	0.09	0.2
Total	6	8	1.59	1.03
Alcoholism				
Adults (18 to 64 years)	109	36	18.65	6.94
Elderly people	0	1	0	0.23
- 65 to 74 years	0	1	0	0.23
Total	109	37	18.65	7.16
Healthy Volunteers				
Adults (18 to 64 years)	1439	356	18.7	3.21
Elderly people	13	15	0.04	0.04
- 65 to 74 years	9	13	0.02	0.04
- 75 to 84 years	4	2	0.01	0.01
Total	1452	371	18.74	3.25

[1] Patient years was calculated by computing the sum of all days subjects were exposed to the drug and dividing by 365.25.
*DLP: 30 Nov 2021

Table 2.3.2.2-2	**SIII.2-2: Clinical Trial Exposure to Abilify Maintena by Age Group and Gender (Cumulative and by Indication)**			
	Persons		**Person Time (patient years)[1]**	
Age Group	**M**	**F**	**M**	**F**
Cumulative for All Indications (Person Time)				
Adults (18 to 64 years)	2360	1748	3013.51	2255.4
Elderly people	8	7	5.39	6.13
- 65 to 74 years	7	6	4.4	5.14
- 75 to 84 years	1	1	0.99	0.99
Total	2368	1755	3018.9	2261.54
Schizophrenia				
Adults (18 to 64 years)	2016	1252	2787.91	1935.39
Elderly people	5	5	3.18	4.43
- 65 to 74 years	4	4	2.19	3.44
- 75 to 84 years	1	1	0.99	0.99
Total	2021	1257	2791.09	1939.82
Bipolar I Disorder				
Adults (18 to 64 years)	344	496	225.6	320.01
Elderly people	3	2	2.21	1.7

Table 2.3.2.2-2	**SIII.2-2: Clinical Trial Exposure to Abilify Maintena by Age Group and Gender (Cumulative and by Indication)**			
	Persons		**Person Time (patient years)[1]**	
Age Group	**M**	**F**	**M**	**F**
- 65 to 74 years	3	2	2.21	1.7
Total	347	498	227.81	321.71
[1]Patient years was calculated by computing the sum of all days subjects were exposed to the drug and dividing by 365.25. *DLP: 30 Nov 2021				

Table 2.3.2.2-3	**SIII.2-3: Clinical Trial Exposure to Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe by Age Group and Gender (Cumulative and by Indication)**			
	Persons		**Person Time (patient years)[1]**	
Age Group	**M**	**F**	**M**	**F**
Cumulative for All Indications (Person Time)				
Adults (18 to 64 years)	159	81	58.86	29.25
Total	159	81	58.86	29.25
Schizophrenia				
Adults (18 to 64 years)	122	49	43.96	18.19
Total	122	49	43.96	18.19
Bipolar I Disorder				
Adults (18 to 64 years)	37	32	14.9	11.06
Total	37	32	14.9	11.06
[1] Patient years was calculated by computing the sum of all days subjects were exposed to the drug and dividing by 365.25. *DLP: 30 Nov 2021				

2.3.2.3 Dose

Table 2.3.2.3-1	**SIII.3-1: Clinical Trial Exposure to Abilify by Dose (Cumulative and by Indication)**	
Dose of Exposure	**Persons**	**Person Time (patient years)[1]**
Cumulative for All Indications (Person Time)		
<=7.5 mg	3914	1363.74
>7.5 - <=12.5 mg	5741	2665.23
>12.5 - <=17.5 mg	8049	3135.62
>17.5 - <=25 mg	5898	3405.24
>25 - <=32.5 mg	5198	4035.45
>32.5 mg	583	192.49
Total	29383	14797.77
Schizophrenia		
<=7.5 mg	1035	454.14
>7.5 - <=12.5 mg	2913	1691.06
>12.5 - <=17.5 mg	4560	2105.83
>17.5 - <=25 mg	4058	2826.7
>25 - <=32.5 mg	3336	3646.71

Table 2.3.2.3-1 SIII.3-1: Clinical Trial Exposure to Abilify by Dose (Cumulative and by Indication)		
Dose of Exposure	**Persons**	**Person Time (patient years)[1]**
>32.5 mg	280	40.87
Total	16182	10765.31
Bipolar I Disorder		
<=7.5 mg	119	19.04
>7.5 - <=12.5 mg	1229	300.87
>12.5 - <=17.5 mg	2500	726.68
>17.5 - <=25 mg	1465	380.1
>25 - <=32.5 mg	1468	364.07
>32.5 mg	11	2.64
Total	6792	1793.4
Major Depressive Disorder		
<=7.5 mg	1097	225.22
>7.5 - <=12.5 mg	686	230.17
>12.5 - <=17.5 mg	232	95.75
>17.5 - <=25 mg	86	37.77
>25 - <=32.5 mg	11	5.32
>32.5 mg	2	0.4
Total	2114	594.63
Autistic Disorder		
<=7.5 mg	287	185.57
>7.5 - <=12.5 mg	272	212.8
>12.5 - <=17.5 mg	110	113.46
Total	669	511.84
Tourette's Disorder		
<=7.5 mg	131	67.35
>7.5 - <=12.5 mg	103	44.48
>12.5 - <=17.5 mg	15	8.44
>17.5 - <=25 mg	13	6.43
>25 - <=32.5 mg	16	2.32
>32.5 mg	273	146.23
Total	551	275.23
Alzheimer's Disease		
<=7.5 mg	690	405.08
>7.5 - <=12.5 mg	182	156.98
>12.5 - <=17.5 mg	64	50.53
>17.5 - <=25 mg	143	143.11
>32.5 mg	1	2.04
Total	1080	757.74
Conduct Disorder		
<=7.5 mg	20	0.8
>7.5 - <=12.5 mg	3	0.12
>12.5 - <=17.5 mg	2	0.11
>17.5 - <=25 mg	1	0.07
Total	26	1.1
Parkinson Disease		
<=7.5 mg	13	2.27
>7.5 - <=12.5 mg	1	0.34
Total	14	2.62

Table 2.3.2.3-1 SIII.3-1: Clinical Trial Exposure to Abilify by Dose (Cumulative and by Indication)

Dose of Exposure	Persons	Person Time (patient years)[1]
Alcoholism		
<=7.5 mg	13	0.76
>7.5 - <=12.5 mg	16	1.74
>12.5 - <=17.5 mg	28	4.2
>17.5 - <=25 mg	57	11.75
>25 - <=32.5 mg	32	7.37
Total	146	25.82
Healthy Volunteers		
<=7.5 mg	509	3.51
>7.5 - <=12.5 mg	340	7.2
>12.5 - <=17.5 mg	542	5.07
>17.5 - <=25 mg	81	0.79
>25 - <=32.5 mg	335	5.11
>32.5 mg	16	0.31
Total	1823	21.99

[1] Patient years was calculated by computing the sum of all days subjects were exposed to the drug and dividing by 365.25.
*DLP: 30 Nov 2021

Table 2.3.2.3-2 SIII.3-2: Clinical Trial Exposure to Abilify Maintena by Dose of Exposure (Cumulative and by Indication)

Dose of Exposure	Persons	Person Time (patient years)[1]
Cumulative for All Indications (Person Time)		
15-50 mg	50	18.07
100-200 mg	32	4.19
300-400 mg	4041	5258.18
Total	4123	5280.44
Schizophrenia		
15-50 mg	50	18.07
100-200 mg	32	4.19
300-400 mg	3196	4708.65
Total	3278	4730.91
Bipolar I Disorder		
300-400 mg	845	549.53
Total	845	549.53

[1] Patient years was calculated by computing the sum of all days subjects were exposed to the drug and dividing by 365.25.
*DLP: 30 Nov 2021

Table 2.3.2.3-3	**SIII.3-3: Clinical Trial Exposure to Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe by Dose of Exposure (Cumulative and by Indication)**	
Dose of Exposure	**Persons**	**Person Time (patient years)[1]**
Cumulative for All Indications (Person Time)		
420 mg	72	13.29
780 mg	18	2.66
810 mg	1	0.31
960 mg	131	69.2
1200 mg	18	2.66
Total	240	88.11
Schizophrenia		
420 mg	43	7.97
780 mg	18	2.66
960 mg	92	48.86
1200 mg	18	2.66
Total	171	62.15
Bipolar I Disorder		
420 mg	29	5.32
810 mg	1	0.31
960 mg	39	20.33
Total	69	25.96

[1] Patient years was calculated by computing the sum of all days subjects were exposed to the drug and dividing by 365.25.
*DLP: 30 Nov 2021

2.3.2.4 Race

Table 2.3.2.4-1	**SIII.4-1: Clinical Trial Exposure to Abilify by Race (Cumulative and by Indication)**	
Race	**Persons**	**Person Time**
Cumulative for All Indications (Person Time)		
White	16811	8870
Black	4227	1178.04
Asian	6246	2204.33
Other	1456	566.14
Race Not Available	643	1979.26
Total	29383	14797.77
Schizophrenia		
White	8578	6109.77
Black	2555	799.57
Asian	3612	1477.6
Other	836	437.14
Race Not Available	601	1941.22
Total	16182	10765.31
Bipolar I Disorder		
White	4683	1300.22
Black	1055	212.51
Asian	794	207.55

Table 2.3.2.4-1 SIII.4-1: Clinical Trial Exposure to Abilify by Race (Cumulative and by Indication)		
Race	**Persons**	**Person Time**
Other	259	72.97
Race Not Available	1	0.15
Total	6792	1793.4
Major Depressive Disorder		
White	993	353.03
Black	93	33.68
Asian	998	196.96
Other	30	10.96
Total	2114	594.63
Autistic Disorder		
White	375	236.86
Black	110	70.97
Asian	160	185.49
Other	24	18.52
Total	669	511.84
Tourette's Disorder		
White	313	171.27
Black	49	16.77
Asian	136	44.26
Other	12	5.04
Race Not Available	41	37.89
Total	551	275.23
Alzheimer's Disease		
White	856	665.11
Black	69	38.44
Asian	130	35.47
Other	25	18.72
Total	1080	757.74
Conduct Disorder		
White	14	0.55
Black	11	0.51
Other	1	0.04
Total	26	1.1
Parkinson Disease		
White	13	2.6
Asian	1	0.02
Total	14	2.62
Alcoholism		
White	123	22.63
Black	18	2.48
Asian	2	0.38
Other	3	0.33
Total	146	25.82
Healthy Volunteers		
White	875	10.39
Black	268	2.85
Asian	414	6.32

Table 2.3.2.4-1	**SIII.4-1: Clinical Trial Exposure to Abilify by Race (Cumulative and by Indication)**	
Race	**Persons**	**Person Time**
Other	266	2.42
Total	1823	21.99

[1] Patient years was calculated by computing the sum of all days subjects were exposed to the drug and dividing by 365.25.
*DLP: 30 Nov 2021

Table 2.3.2.4-2	**SIII.4-2: Clinical Trial Exposure to Abilify Maintena by Race (Cumulative and by Indication)**	
Race	**Persons**	**Person Time (patient years)[1]**
Cumulative for All Indications (Person Time)		
White	1759	2998.96
Black	1147	794.25
Asian	1085	1104.93
Other	130	381.84
Race Not Available	2	0.47
Total	4123	5280.44
Schizophrenia		
White	1286	2689.95
Black	934	670.29
Asian	950	1004.26
Other	107	366.18
Race Not Available	1	0.24
Total	3278	4730.91
Bipolar I Disorder		
White	473	309.01
Black	213	123.97
Asian	135	100.67
Other	23	15.66
Race Not Available	1	0.23
Total	845	549.53

[1] Patient years was calculated by computing the sum of all days subjects were exposed to the drug and dividing by 365.25.
*DLP: 30 Nov 2021

Table 2.3.2.4-3	**SIII.4-3: Clinical Trial Exposure to Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe by Race (Cumulative and by Indication)**	
Race	**Persons**	**Person Time (patient years)[1]**
Cumulative for All Indications (Person Time)		
White	55	19.7
Black	178	65.46
Asian	3	1.82
Other	4	1.13
Total	240	88.11

Table 2.3.2.4-3	**SIII.4-3: Clinical Trial Exposure to Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe by Race (Cumulative and by Indication)**	
Race	**Persons**	**Person Time (patient years)[1]**
Schizophrenia		
White	31	9.49
Black	139	52.05
Other	1	0.61
Total	171	62.15
Bipolar I Disorder		
White	24	10.21
Black	39	13.41
Asian	3	1.82
Other	3	0.52
Total	69	25.96

[1] Patient years was calculated by computing the sum of all days subjects were exposed to the drug and dividing by 365.25.
*DLP: 30 Nov 2021

2.4 Module SIV: Populations Not Studied in Clinical Trials

2.4.1 SIV.1: Exclusion Criteria in Pivotal Clinical Studies Within the Development Programme

Exclusion criteria across the development programme from pivotal clinical studies with Abilify, Abilify Maintena, and Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe are itemized in Table 2.4.1-1. Hypersensitivity to the active substance or to any of the excipients is the only contraindication that is labelled in all summaries of product characteristics (SmPCs).

Table 2.4.1-1	**SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies**		
Exclusion Criterion	**Reason(s) for Exclusion**	**Is it considered to be included as missing information?**	**Rationale(s)**
Allergies and Adverse Drug Reactions (ADRs) • Participants who are known to be allergic, intolerant, or unresponsive to prior treatment with aripiprazole or other quinolinones • Participants with a history of hypersensitivity to antipsychotic agents • Participants with a history of neuroleptic malignant syndrome (NMS) or clinically	• To protect participant safety • Limit risk to study participants with new formulation being tested	No	• Contraindication as labelled in SmPC Section 4.3 Contraindications

Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies			
Exclusion Criterion	**Reason(s) for Exclusion**	**Is it considered to be included as missing information?**	**Rationale(s)**
significant tardive dyskinesia at screening • Participants deemed intolerant of receiving injectable treatment			
Reproductive status exception • Sexually active males who were not practicing double-barrier birth control or who will not remain abstinent during the study and for 180 days following the last dose of study medication • Sexually active females of childbearing potential who are not practicing double-barrier birth control or who will not remain abstinent during the study and for 150 days following the last dose of study medication • If employing birth control, two of the following precautions must be used: vasectomy, tubal ligation, vaginal diaphragm, intrauterine device, birth control pill, birth control implant, condom, or sponge with spermicide • Females who were breast-feeding and/or who have a positive serum pregnancy test result prior to receiving study drug	• Concerns raised in animal reproductive studies	Yes	• Addressed in the SmPC in Section 4.6 Fertility, pregnancy and lactation • Lack of clinical data to support animal reproductive studies
Target disease: schizophrenia • Participants with a current DSM-5 diagnosis other than schizophrenia, including schizoaffective disorder, major depressive disorder, bipolar disorder, delirium, dementia, amnestic or other cognitive disorders. Participants with borderline, paranoid, histrionic, schizotypal, schizoid or antisocial personality disorder	• Limit study population to schizophrenia only due to heterogeneity of psychosis • Limit study population to non-affective participants to minimise bias in results • Participants who are refractory to antipsychotic treatment will not	No	• Post-marketing experience will assess responses in other populations that are exposed over time

Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies			
Exclusion Criterion	**Reason(s) for Exclusion**	**Is it considered to be included as missing information?**	**Rationale(s)**
• Participants experiencing acute depressive symptoms within the past 30 days that requires treatment with an antidepressant according to the investigator's opinion • Participants with schizophrenia that is considered resistant/refractory to antipsychotic treatment by history • Participants with a history of failure to clozapine treatment or response to clozapine treatment only	respond to drug under study • Participants who fail clozapine treatment will be considered treatment resistant (see above)		
Target disease: bipolar I disorder • Participants with a current Axis I (DSM-5) diagnosis other than bipolar I disorder, including schizophrenia, schizoaffective disorder, major depressive disorder, attention deficit/hyperactivity disorder, delirium, dementia, amnestic, or other cognitive disorders. Also, participants with borderline, paranoid, histrionic, schizotypal, schizoid, or antisocial personality disorder • Participants who have experienced 9 or more mood episodes within the past year • Participants who have not experienced at least one previous manic episode of sufficient severity to require hospitalization and/or treatment with a mood stabilizer or antipsychotic agent, excluding their current manic episode • Participants with a current manic episode with a duration of > 2 years • Participants who are currently experiencing a mixed or a	• Limit study population to bipolar I disorder only due to heterogeneity of disease • To ensure heterogeneity of disease population and minimise bias in results, exclude participants with patterns of rapid-cycling and without primary symptoms of mania • Participants who are refractory to antipsychotic treatment will not respond to drug under study • Participants who fail clozapine treatment will be considered treatment resistant (see above)	No	• Post-marketing experience will assess responses in other populations that are exposed over time.

Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies			
Exclusion Criterion	**Reason(s) for Exclusion**	**Is it considered to be included as missing information?**	**Rationale(s)**
depressive episode (per DSM-5 criteria) • Participants with bipolar I disorder who are considered resistant/refractory to treatment for manic symptoms by history • Participants unresponsive to clozapine for treatment of mania or who only respond to clozapine for treatment of mania			
Medical history and concurrent disease • Participants below 18 years and above 65 years of age • Participants who require or may need any other antipsychotic medications during the course of the trial (other than allowed rescue medication if applicable) • Participants with a significant risk of violent behavior or a significant risk of committing suicide based on history or investigator's judgment or who had an answer of "yes" on questions 4 or 5 (current or over the last 30 days) on the Baseline/Screening version of the C-SSRS. • Participants who met DSM-5 criteria for substance dependence including alcohol and benzodiazepines, but excluding caffeine and nicotine • Participants with known hypothyroidism or hyperthyroidism (unless condition had been stabilised with medications for at least the past 90 days) • Participants with a history or evidence of a medical condition that would expose them to an undue risk of a significant AE or interfere	• Limit risk to young and old participants in the study with new formulation being tested • Limit risk of comorbidity due to unstable medical/neurological diagnoses (noted in screening assessments), substance dependence, etc. • Limit risk to participants in the study with new formulation being tested	• Use in elderly patients above 65 years of age considered missing information	• Age below 18 and above 65 addressed in SmPC Section 4.2 Posology and method of administration • Addressed in SmPC Section 4.4 Special warnings and precautions for use

Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies			
Exclusion Criterion	**Reason(s) for Exclusion**	**Is it considered to be included as missing information?**	**Rationale(s)**
with assessments of safety or efficacy during the course of the trial, including but not limited to hepatic, renal, respiratory, cardiovascular, endocrine, neurologic, hematologic, or immunologic disease as determined by the clinical judgment of the investigator • Participants with epilepsy or a history of seizures, except for a single childhood febrile seizure, post traumatic, alcohol withdrawal, etc. • Participants who have had recent electroconvulsive therapy (i.e., within 2-3 months of administration of IMP) • Participants with a history of NMS or clinically significant tardive dyskinesia as assessed by the investigator • Participants with insulin dependent diabetes mellitus. Participants with an established diagnosis of diabetes mellitus being treated with medications other than insulin are eligible for the study if their glucose control is stable for at least 30 days before entering the study			
Physical and laboratory test findings • Participants with two positive drug screens for cocaine. Two positive drug screens for other drugs of abuse must be discussed with the Medical Monitor prior to entry into Phase 2 unless the subject satisfied criteria for dependence, in which case the subject should excluded from the study • The following laboratory test, vital sign, and	• Limit risk to subjects in the study with new formulation being tested • Limit risk of comorbidity due to unstable medical/neurological diagnoses (noted in screening assessments), substance dependence, etc.	No	• Drug screening not applicable for inclusion in SmPC • QT considerations addressed in SmPC in Section 4.4 Special warnings and precautions for use

Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies			
Exclusion Criterion	**Reason(s) for Exclusion**	**Is it considered to be included as missing information?**	**Rationale(s)**
electrocardiogram (ECG) results are exclusionary: 1. Platelets ≤ 75,000/mm^3 2. Hemoglobin ≤ 9 g/dL 3. Neutrophils, absolute ≤ 1,000/mm^3 4. Aspartate aminotransferase > 3x upper limit of normal 5. Alanine aminotransferase > 3x upper limit of normal 6. Creatinine ≥ 2 mg/dL 7. Diastolic blood pressure > 105 mmHg 8. QTc > 475 msec on either QTcB (Bazett) or QTcF (Fridericia) corrections on 2 of 3 timepoints of triplicate ECGs performed • Participants should be excluded if they have any other abnormal laboratory tests, vital sign results, or ECG findings which in the investigator's judgment is medically significant and that would impact the safety of the participant or the interpretation of the study results. Abnormal results for laboratory parameters or vital signs should be repeated to ensure reproducibility of the abnormality before excluding a participant based on the criteria noted above. The central ECG service will provide the corrections for the three ECGs done approximately five minutes apart (each ECG result reported is derived from the average of the triplicate ECG done at each time point). Based on the QTcB or QTcF corrections reported by the central service, a subject will be excluded if *either* of the			

Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies			
Exclusion Criterion	**Reason(s) for Exclusion**	**Is it considered to be included as missing information?**	**Rationale(s)**
corrections exceeds 475 msec for two of the three time points of triplicate ECGs done. If only one triplicate ECG time point has a corrected QTc greater than 475 msec on either correction factor, and this is not reproduced at the other two time points, this subject can be included in the study. In addition, participants should be excluded if they have any other abnormal ECG finding at screening that, in the investigator's judgment, is medically significant in that it would impact the safety of the participant or the interpretation of the trial results			
Prohibited therapies and/or medications • Participants likely to require prohibited concomitant therapy during the trial • Participants receiving CYP2D6 or CYP3A4 inhibitors or CYP3A4 inducers at screening or anticipated use of such agents during the trial • Participants who received any investigational agent in a clinical trial within 30 days prior to screening or who were randomized into a clinical trial with aripiprazole IM depot at any time. Participants who have discontinued at any phase of the study are not eligible and cannot be rescreened to enter the study	• Limit risk to participants in the study with new formulation being tested • To avoid confounding factors on efficacy and safety as aripiprazole is metabolized through these 2 metabolic pathways • To protect safety of participants	No	• Addressed in SmPC Section 4.5. Interactions with other medicinal products and other forms of interaction

Table 2.4.1-1 SIV.1-1: Exclusion Criteria in Pivotal Clinical Studies			
Exclusion Criterion	**Reason(s) for Exclusion**	**Is it considered to be included as missing information?**	**Rationale(s)**
Other exclusion criteria • Prisoners or participants who were compulsorily detained (involuntarily incarcerated) for treatment of either a psychiatric or physical (e.g., infectious disease) illness must not be enrolled	• Unethical to use involuntary participants for clinical research • Limit risk to participants in the study with new formulation being tested • To exclude confounding factors on efficacy and safety • To protect safety of subjects	No	• Not applicable to be addressed in SmPC

The clinical program for Abilify Maintena includes the following clinical studies:

Studies in Adults with Schizophrenia: CN138-020, 031-07-002, 031-08-003, 031-13-005, 31-05-244, 31-11-289, 31-08-008, 31-07-246, 31-07-247, 31-08-248, 31-10-002, 31-10-270, 31-11-283, 31-11-284, 31-11-290, 31-12-291, 31-12-297, 31-12-298, 14724A, 14724B

Studies in Adults with Bipolar I Disorder: 31-08-250, 31-08-252

The clinical program for Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe includes the following clinical studies:

Studies in Adults with Schizophrenia: 031-201-00104, 031-201-00181, 031-201-00279

Studies in Adults with Bipolar I Disorder: 031-201-00181, 031-201-00279

2.4.2 SIV.2: Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

Abilify

Limitations common to Abilify clinical trials to detect adverse reactions of special interest are presented in Table 2.4.2-1.

Table 2.4.2-1 SIV.2-1 Limitations Common to All Abilify Clinical Trials		
Ability to detect adverse reactions	**Limitation of trial program**	**Discussion of implications for target population**
Reproductive status	• Women of childbearing potential who are nursing or who are unwilling or unable to use an adequate method to avoid pregnancy for the entire study period	Due to insufficient safety information in humans, and concerns raised by animal reproductive studies, aripiprazole should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the fetus. Neonates exposed to aripiprazole during the third trimester of pregnancy are at risk of adverse reactions, including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.
Lactation	• Women who were lactating	Aripiprazole is excreted in human breast milk. Patients should be advised not to breast feed if they are taking aripiprazole.
Suicidal behavior	• Patients who represent a significant risk of suicidal behavior	The occurrence of suicidal behavior is inherent in psychotic illnesses and mood disorders, and in some cases, has been reported early after initiation or switch of antipsychotic therapy, including treatment with aripiprazole. Close supervision of high-risk patients should accompany antipsychotic therapy. Results of an epidemiological study suggested that there was no increased risk of suicidality with aripiprazole compared to other antipsychotics among patients with schizophrenia or bipolar disorder.
Seizure disorder	• Patients with history of seizure disorder other than infantile or febrile seizures	In clinical trials, uncommon cases of seizure were reported during treatment with aripiprazole. Therefore, aripiprazole should be used with caution in patients who have a history of seizure disorder or have conditions associated with seizures.
Neuroleptic Malignant Syndrome (NMS)	• Patients with a history of NMS	NMS is a potentially fatal symptom complex associated with antipsychotic medicinal products. In clinical trials, rare cases of NMS were reported during treatment with aripiprazole. If a patient develops signs and symptoms indicative of NMS, aripiprazole must be discontinued.
Medical history and concurrent diseases	• History or evidence of a medical condition that would have exposed the patient to an undue risk of a significant AE • Any clinically important abnormal laboratory test results, vital signs, or ECG • Allergic or hypersensitivity to aripiprazole	No expected implication; exclusion criterion applied generally to clinical trials and real-world practice.

Abilify Maintena

Limitations of the Abilify Maintena clinical trials to detect adverse reactions of special interest are presented in Table 2.4.2-2.

Table 2.4.2-2 SIV.2-2 Limitations Common to All Abilify Maintena Clinical Trials

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Rare ADRs (≥1/10,000 to <1/1,000).	As of the data cut-off, a total of 3,624 patients have been exposed in the clinical programs of aripiprazole IM depot in schizophrenia and bipolar I disorder. In the clinical program of aripiprazole IM depot, no rare ADRs occurred.	Rare ADRs may not be observed in the clinical program of aripiprazole IM depot but may be reported through post-marketing experience to detect important rare adverse drug reactions.
ADRs which have a long latency, such as tardive dyskinesia	The long-term exposure data showed that treatment-emergent adverse events (TEAEs) decreased in frequency over the time course of exposure or remained stable at the same frequency as reported at the start of treatment.	ADRs which have a long latency will likely be observed with long-term exposure to aripiprazole, including any changes of frequency over time. Post-marketing experience will detect important adverse drug reactions that emerge due to long-term exposure.

Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe

Limitations of the Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe clinical trials to detect adverse reactions of special interest are presented in Table 2.4.2-3.

Table 2.4.2-3 SIV.2-3 Limitations of Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe Clinical Trials

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Rare ADRs (≥1/10,000 to <1/1,000).	As of the data cut-off, a total of 240 patients have been exposed in the clinical programs of aripiprazole 2M RTU LAI in participants with schizophrenia and bipolar I disorder.	Rare ADRs may not be observed in the clinical program of aripiprazole IM depot but may be reported through post-marketing experience to detect important rare adverse drug reactions.

Table 2.4.2-3	**SIV.2-3 Limitations of Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe Clinical Trials**	
Ability to detect adverse reactions	**Limitation of trial program**	**Discussion of implications for target population**
	In the clinical program of aripiprazole 2M RTU LAI, no rare ADRs occurred.	
ADRs due to cumulative effects.	No ADRs or TEAEs due to cumulative effects have been observed in the clinical program with aripiprazole 2M RTU LAI No organ-specific toxicity or cumulative effects been observed in the clinical program with aripiprazole 2M RTU LAI.	Not applicable.
ADRs which have a long latency, such as tardive dyskinesia	The long-term exposure data showed that TEAEs decreased in frequency over the time course of exposure or remained stable at the same frequency as reported at the start of treatment.	ADRs which have a long latency will likely be observed with long-term exposure to aripiprazole, including any changes of frequency over time. Post-marketing experience will detect important adverse drug reactions that emerge due to long-term exposure.

2.4.3 SIV.3: Limitations in Respect to Populations Typically Underrepresented in Clinical Trial Development Programmes

2.4.3.1 Children

Abilify

For the purposes of this RMP, there has been no experience with aripiprazole treatment in children <13 years of age with schizophrenia or children or adolescents <10 years of age with bipolar mania.

Completed Studies

In the context of the Type II variation for an extension of indication to treat adolescent patients with schizophrenia (EMEA/H/C/471/II/048), the marketing authorisation holder (MAH) agreed and completed the following studies/safety data analyses which were also listed in the paediatric investigation plan (PIP, 000235 PIP02 10 M01) as well as in the RMP:

- An open-label, multicenter study (31-09-267) to evaluate the safety and tolerability of flexible dose oral aripiprazole as maintenance treatment in paediatric 10 to <18 years of age with bipolar I disorder or schizophrenia. Type II Variation with clinical study report (CSR) submitted on 03-Mar-2015. Procedure

is ongoing. Response to second request for supplementary information submitted to Committee for Medicinal Products for Human Use (CHMP) in April 2016.

- A double-blind, randomized, multicenter placebo-controlled study (31-09-266) to evaluate the long-term efficacy, safety, and tolerability of aripiprazole as maintenance treatment in adolescents 13 to < 18 years of age with schizophrenia. Type II Variation with CSR submitted on 11-Jun-2014. Outcome: No label change, but the MAH submitted as agreed the results from the open label extension study 31-09-267 in 2015.

In the context of the Type II variation for an extension of indication of treatment up to 12 weeks of moderate to severe manic episodes in bipolar I disorder in adults and adolescents aged 13 years and older, the MAH updated the RMP for identified or potential safety concerns in this particular population and completed the following safety study:

- PASS to assess the effectiveness of the educational program (e.g., whether the educational material effectively communicates and reinforces the core safety messages conveyed in the SmPC and Patient Information Leaflet to carefully consider the indicated age range, dose, and duration of treatment before considering aripiprazole for patients with paediatric bipolar disorder).

Completed Safety Data Analyses

- To provide the results of a pooled analysis on prolactin levels, height, weight, lipid parameters, glucose, insulin and ECGs of the following studies performed in adolescent schizophrenia patients (13-17 years) for up to 2 years: 31-03-239, 31-03-241, and 31-05-243; and of the following studies performed in children and adolescents (10-17 years) with bipolar I disorder for up to 32 weeks: 31-03-240 and 31-03-241. This safety analysis was submitted to the European Medicines Agency (EMA) on 02-Dec-2009.
- To provide data analysis on prolactin levels, height, weight, lipid parameters, glucose, insulin, ECGs and Tanner staging for Study CN138180 conducted in children and adolescents (6-17 years) with autistic disorder for up to 1 year. Submitted to the EMA on 21-Dec-2009.
- An epidemiological cohort study to assess suicide in paediatric/adolescent patients (<18 years of age) using aripiprazole (CN138598-ST). Final CSR submitted to the EMA on 04-July-2012.

<u>Abilify Maintena</u>

No clinical studies have been conducted in the paediatric population with aripiprazole IM depot. A full PIP waiver has been granted by the Paediatric Committee (PDCO)/EMA for all IM formulations for all subsets of the paediatric population (Paediatric Investigational Plan EMEA 000235-PIP02-10-M01; EMA/PDCO/283777/2012).

Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe

No clinical studies have been conducted in the paediatric population with aripiprazole 2M RTU LAI.

2.4.3.2 Elderly

Abilify

Per CHMP guidance[122] bipolar mania is not typical for elderly patients and no special studies in the elderly are necessary for the indication of "treatment of acute manic episode" and "prevention of recurrence."

Elderly patients typically were not excluded from adult bipolar mania or schizophrenia aripiprazole studies. However, due to the limited number of patients >65 years old in the short-term bipolar mania or schizophrenia studies, a >50-year-old cohort was utilized for summaries to assess safety and efficacy in older patients. No clinically relevant differences were observed in the safety parameters (overall AE incidence rates, laboratory measurements, ECGs including QTc, and vital signs) between the 2 cohorts in the safety parameters of these studies.

The effectiveness of Abilify in the treatment of bipolar mania or schizophrenia in patients 65 years of age or older has not been established. Owing to the greater sensitivity of this population, a lower starting dose should be considered when clinical factors warrant it.

There are no differences in the PK of aripiprazole between healthy elderly and younger adult subjects, nor was there any detectable effect of age in a population PK analysis in schizophrenic patients.

In elderly patients with psychosis associated with Alzheimer's disease, safety data from 3 placebo-controlled aripiprazole trials (n=938; mean age: 82.4 years; range: 56-99 years) indicated that patients treated with aripiprazole were at increased risk of death compared to placebo. The rate of death in aripiprazole-treated patients was 3.5% compared to 1.7% in the placebo group. Although the causes of deaths were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

In the same trials, cerebrovascular AEs (e.g., stroke, transient ischemic attack), including fatalities, were reported in elderly patients (mean age: 84 years; range: 78-88 years). Overall, 1.3% of aripiprazole-treated patients reported cerebrovascular AEs compared with 0.6% of placebo-treated patients in these trials. This difference was not statistically

significant. However, in one of these trials, a fixed-dose trial, there was a significant dose-response relationship for cerebrovascular AEs in patients treated with aripiprazole.

Abilify Maintena

In clinical trials evaluating the clinical safety and efficacy of aripiprazole IM depot in schizophrenia and bipolar I disorder, elderly patients above 65 years of age were excluded.

Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe

In clinical trials evaluating the clinical safety and efficacy of aripiprazole 2M RTU LAI in schizophrenia, elderly patients above 65 years of age were excluded.

2.4.3.3 Pregnant or Breast-Feeding Women

Pregnancy

There are no adequate and well-controlled trials of aripiprazole in pregnant women. Congenital anomalies have been reported; however, causal relationship with aripiprazole could not be established. Animal studies could not exclude potential developmental toxicity. Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during treatment with aripiprazole. Due to insufficient safety information in humans and concerns raised by animal reproduction studies, this medicinal product should not be used in pregnancy unless the expected benefit clearly justifies the potential risk to the fetus. Neonates exposed to antipsychotics (including aripiprazole) during the third trimester of pregnancy are at risk of adverse reactions, including EPS and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully.

Lactation

Aripiprazole is excreted in human breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue aripiprazole, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

In clinical trials conducted with aripiprazole IM depot and aripiprazole 2M RTU LAI, no pregnant or lactating women were included. Pregnancy, positive pregnancy test, and breast-feeding were part of the exclusion criteria. Women who became pregnant during a clinical trial were withdrawn from the trial and treatment was discontinued.

2.4.3.4 Patients with Hepatic Impairment

Abilify

Results from subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) in a single-dose PK study after oral administration of aripiprazole did not reveal an important effect of hepatic impairment on the PK of aripiprazole and dehydro-aripiprazole. However, the study included only 3 patients with Class C liver cirrhosis, which is insufficient to draw conclusions on their metabolic capacity.

No dosage adjustment after oral administration of aripiprazole is required for patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the data available are insufficient to establish recommendations. In these patients, dosing should be managed cautiously. However, the maximum daily dose of 30 mg should be used with caution in patients with severe hepatic impairment.

Abilify Maintena

The effect of hepatic impairment was obtained from oral aripiprazole studies. A single-dose study with oral administration of aripiprazole to subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) did not reveal a significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and dehydro-aripiprazole, but the study included only 3 patients with Class C liver cirrhosis, which is insufficient to draw conclusions on their metabolic capacity.

Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe

The effect of hepatic impairment was obtained from oral aripiprazole studies. A single-dose study with oral administration of aripiprazole to subjects with varying degrees of liver cirrhosis (Child-Pugh Classes A, B, and C) did not reveal a significant effect of hepatic impairment on the pharmacokinetics of aripiprazole and dehydro-aripiprazole, but the study included only 3 patients with Class C liver cirrhosis, which is insufficient to draw conclusions on their metabolic capacity.

2.4.3.5 Patients with Renal Impairment

Abilify

The PK characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to young healthy patients after oral administration of aripiprazole. No dosage adjustment is required in patients with renal impairment.

Abilify Maintena

The effect of renal impairment was obtained from oral aripiprazole studies. In a single-dose study with oral administration of aripiprazole, the pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to that in young healthy subjects.

Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe

The effect of renal impairment was obtained from oral aripiprazole studies. In a single-dose study with oral administration of aripiprazole, the pharmacokinetic characteristics of aripiprazole and dehydro-aripiprazole were found to be similar in patients with severe renal disease compared to that in young healthy subjects.

2.4.3.6 Patients with Other Relevant Co-Morbidity

Subjects who had a history or evidence of a medical condition that would expose them to an undue risk of a significant AE or interfere with assessments of safety or efficacy were excluded from all clinical trials.

2.4.3.7 Patients with a Disease Severity Different from the Inclusion Criteria in the Clinical Trial Population

No studies were conducted in patients with disease severity different from that studied in the aripiprazole clinical trials. Likewise, in aripiprazole IM depot and aripiprazole 2M RTU LAI studies, no patients with disease severity different from that studied in clinical trials were included.

2.4.3.8 Sub-Populations Carrying Known and Relevant Polymorphisms

Abilify

Following a single oral administration of aripiprazole, CYP2D6 poor metaboliser (PM) subjects had 41% lower clearance compared to CYP2D6 extensive metaboliser (EM) subjects. Plasma concentrations of the active metabolite dehydro-aripiprazole were decreased by 34% in CYP2D6 PM subjects compared to CYP2D6 EM subjects. In CYP2D6 PMs, concomitant use of potent inhibitors of CYP3A4 may result in higher plasma concentrations of aripiprazole compared to that in CYP2D6 EMs. When considering concomitant administration of ketoconazole or other potent CYP3A4 inhibitors with aripiprazole, potential benefits should outweigh the potential risks to the patient. When concomitant administration of ketoconazole with oral aripiprazole occurs, the aripiprazole dose should be reduced to approximately one-half of its prescribed dose. Other potent inhibitors of CYP3A4, such as itraconazole and human immunodeficiency

virus (HIV) protease inhibitors, may be expected to have similar effects and similar dose reductions should therefore be applied.

Abilify Maintena

PK evaluation of aripiprazole IM depot showed that aripiprazole plasma concentrations in CYP2D6 PMs were approximately twice the concentrations observed in CYP2D6 EMs. Due to the expected higher aripiprazole concentrations in these subjects, a reduction of the dose of aripiprazole IM depot 400 mg to 300 mg, administered once monthly, is recommended in subjects who are known to be CYP2D6 PMs. In subjects who are known to be CYP2D6 PMs and who are receiving a monthly aripiprazole IM depot dose of 300 mg, a dose reduction from 300 mg to 200 mg should be considered when long term (more than 14 days) co-administration of a strong CYP3A4 inhibitor is required.

Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe

In subjects who are known to be CYP2D6 PMs, the total body clearance of aripiprazole was approximately 50% lower compared to subjects who are CYP2D6 EMs. A dose reduction of aripiprazole 2M RTU LAI from 960 mg to 720 mg for CYP2D6 PM subjects would result in median steady-state aripiprazole concentrations that are within the therapeutic window and comparable to that following Abilify Maintena 300 mg. Therefore, a comparable 25% lower dose of aripiprazole 2M RTU LAI (960 mg to 720 mg), as recommended for Abilify Maintena (400 mg to 300 mg), is also recommended for CYP2D6 PM subjects. Aripiprazole 2M RTU LAI is not recommended for known CYP2D6 PMs who are also taking CYP3A4 inhibitors.

2.4.3.9 Patients of Different Racial and/or Ethnic Origin

Abilify

Patients were not excluded from the pivotal registrational studies on the basis of race or ethnic origin. Bipolar mania subpopulations by race and ethnicity were evaluated; however, in general, the subgroups were too small for meaningful analysis. Population PK evaluations in schizophrenic patients administered oral aripiprazole demonstrated no evidence of clinically important race-related differences in the PK of aripiprazole.

Abilify Maintena

In clinical studies performed with aripiprazole IM depot, patients were not excluded on the basis of race or ethnic origin. Overall, there were no clinically relevant differences with regard to AEs, laboratory values, or vital signs. Population PK evaluation of

aripiprazole IM depot showed no evidence of race-related differences in the PK of aripiprazole.

Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe

In clinical studies performed with aripiprazole 2M RTU LAI, patients were not excluded on the basis of race or ethnic origin. Overall, there were no clinically relevant differences with regard to AEs, laboratory values, or vital signs. Population PK evaluation of aripiprazole 2M RTU LAI showed no evidence of race-related differences in the PK of aripiprazole.

Table 2.4.3.9-1 SIV.9-1: Exposure of Special Populations Included or not in Clinical Trial Development Programmes - Abilify, Abilify Maintena, Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe

Type of Special Population	Exposure
Abilify	
Patients with Hepatic Impairment*	Persons: 19 Person Time: 0.05
Patients with Renal Impairment*	Persons: 6 Person Time: 0.02
Patients with Poor Cytochrome P450 Metabolizer Phenotype	Persons: 74 Person Time: 19.20
Patients with Extensive/Ultrarapid Cytochrome P450 Metabolizer Phenotype	Persons: 1067 Person Time: 404.68
Abilify Maintena	
Patients with Poor Cytochrome P450 Metabolizer Phenotype	Persons: 57 Person Time: 122.32
Patients with Extensive/Ultrarapid Cytochrome P450 Metabolizer Phenotype	Persons: 869 Person Time: 2003.90
Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe	
Patients with Poor Cytochrome P450 Metabolizer Phenotype	Persons: 1 Person Time: 0.15
Patients with Extensive/Ultrarapid Cytochrome P450 Metabolizer Phenotype	Persons: 23 Person Time: 3.40
*Data captured when reported; these data may have been reported in Phase 2 and Phase 3 studies and not collected.	

2.5 Module SV: Postauthorisation Experience

2.5.1 SV.1: Postauthorisation Exposure

2.5.1.1 SV.1.1: Method Used to Calculate Exposure

Estimates of patient exposure are based on the availability of monthly sales and “free goods” distribution figures per product by region and formulation. Due to the limitations of this approach, it is not possible to precisely determine the number of patients treated with marketed aripiprazole. The methods described below were used to arrive at an estimation of the number of patients treated with each respective aripiprazole formulation.

Abilify

Using the average dose and duration of treatment as described in the prescribing information for Abilify, the estimated mg sold can be used to calculate an estimated number of patients treated. Keeping in mind that the dose and duration of therapy may depend on several factors (e.g., age, hepatic function, renal function, specific treatment indication, therapeutic response), the following assumptions were used to arrive at an estimation of the number of patients treated with Abilify:

- Each patient received an average defined dose of 15 mg Abilify daily
- Each patient received this dose for a duration of 26 weeks
- Each patient received a total dose of 2,730 mg

Abilify Maintena

Using the average dose and duration of treatment as described in the prescribing information for Abilify Maintena, the estimated mg sold can be used to calculate an estimated number of patients treated. Keeping in mind that the dose and duration of therapy may depend on several factors (e.g., age, hepatic function, renal function, specific treatment indication, therapeutic response), the following assumptions were used to arrive at an estimation of the number of patients treated with Abilify Maintena:

- Each patient received an average defined dose of 300 mg or 400 mg monthly
- Each patient received this dose for 6 months
- For patients taking 300 mg monthly, each patient received a total dose of 1,800 mg
- For patients taking 400 mg monthly, each patient received a total dose of 2,400 mg

Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe

This product is not currently marketed in any country worldwide.

The estimates of patients exposed to aripiprazole in the post-marketing setting should be interpreted with caution, taking into account the above-mentioned assumptions and the limitations of the available sales data.

2.5.1.2 SV.1.2: Exposure

Abilify

Based on sales data through 30 Nov 2021, an estimated 71,727,716,789 mg of Abilify have been sold worldwide. Using the methods described in Section 2.5.1.1, the estimated number of patients who received Abilify and estimated cumulative worldwide exposure to Abilify are as follows:

- 71,727,716,789 mg ÷ 2,730 mg/patient = 26,273,889 patients exposed
- 26,273,889 patients × 180 days exposure = 4,729,300,008 patient days exposure
- 4,729,300,008 patient days ÷ 365 days/year = 12,956,986 patient years exposure

A summary of the worldwide postmarketing distribution of Abilify cumulatively until 30 Nov 2021 is presented in Table 2.5.1.2-1.

Table 2.5.1.2-1 SV.1.2-1: Estimated Abilify Postmarketing Exposure by Country/Region

Country/Region	Exposure (Persons)	Exposure (Person Years)
Algeria	CCI	CCI
Australia		
Austria		
Belgium		
Brazil		
Bulgaria		
Canada		
China		
Cyprus		
Czech Republic		
Denmark		
Egypt		
Estonia		
Finland		
France		
French Guiana		
French Polynesia		
Germany		
Greece		
Guadeloupe		
Hong Kong		
Hungary		
Iceland		
Indonesia		
Ireland		
Italy		
Japan		
Lithuania		
Luxembourg		
Martinique		
Mayotte		

Table 2.5.1.2-1	**SV.1.2-1: Estimated Abilify Postmarketing Exposure by Country/Region**	
Country/Region	**Exposure (Persons)**	**Exposure (Person Years)**
Mexico	CCI	CCI
Netherlands		
New Caledonia		
Northern Ireland		
Norway		
Philippines		
Poland		
Portugal		
Réunion		
Romania		
San Marino		
Singapore		
Slovakia		
Slovenia		
South Africa		
South Korea		
Spain		
Sweden		
Switzerland		
Taiwan		
Thailand		
Tunisia		
Turkey		
United Kingdom		
United States		
BMS Historical Sales		
Total	**26,273,889**	**12,956,986.30**

Abilify Maintena

Based on sales data, an estimated 5,173,187,500 mg of Abilify Maintena have been sold worldwide: 598,976,700 mg of the 300 mg formulation and 4,574,210,800 mg of the 400 mg formulation. Using the methods described in Section 2.5.1.1, the estimated number of patients who received Abilify Maintena and estimated cumulative worldwide exposure to Abilify Maintena are as follows:

- 300 mg formulation: 598,976,700 mg ÷ 1,800 mg/patient = 332,764 patients
- 400 mg formulation: 4,574,210,800 mg ÷ 2,400 mg/patient = 1,905,921 patients
- (332,764 + 1,905,921) patients × ½ year = 1,119,343 patient years exposure

A summary of the worldwide postmarketing distribution of Abilify Maintena cumulatively until 30 Nov 2021 is presented in Table 2.5.1.2-2.

Table 2.5.1.2-2 SV.1.2-2: Estimated Abilify Maintena Postmarketing Exposure by Country

Country	Exposure (Persons)	Exposure (Person Years)
Australia	CCI	CCI
Austria		
Bahrain		
Belgium		
Bulgaria		
Canada		
Croatia		
Czech Republic		
Denmark		
Estonia		
Finland		
France		
Germany		
Greece		
Hong Kong		
Hungary		
Iceland		
Indonesia		
Ireland		
Israel		
Italy		
Japan		
Kuwait		
Lebanon		
Lithuania		
Malaysia		
Netherlands		
Northern Ireland		
Norway		
Philippines		
Poland		
Portugal		
Qatar		
Romania		
San Marino		
Saudi Arabia		
Singapore		
Slovakia		
Slovenia		
South Africa		
South Korea		
Spain		
Sweden		
Switzerland		
Taiwan		
Thailand		
Turkey		
United Arab Emirates		

Table 2.5.1.2-2 SV.1.2-2: Estimated Abilify Maintena Postmarketing Exposure by Country		
Country	**Exposure (Persons)**	**Exposure (Person Years)**
United Kingdom	CCI [redacted]	CCI [redacted]
United States		
Total	**2,238,686**	**1,119,343.01**

Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe

This product is not currently marketed in any country worldwide.

2.6 Module SVI: Additional EU Requirements for the Safety Specification

2.6.1 Potential for Misuse for Illegal Purposes

Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. In physical dependence studies in monkeys, withdrawal symptoms were reported upon abrupt cessation of dosing. While the clinical trials did not demonstrate any tendency for drug-seeking behavior, these observations were not systematic, and it is not possible to predict on the basis of this limited experience, the extent to which a CNS-active drug will be misused, diverted, or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be monitored closely for signs of aripiprazole misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

2.7 Module SVII: Identified and Potential Risks

2.7.1 SVII.1: Identification of Safety Concerns in the Initial RMP Submission

2.7.1.1 SVII.1.1: Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

Reason(s) for not including an identified or potential risk in the list of safety concerns in the RMP:

Not applicable.

2.7.1.2 SVII.1.2: Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

2.7.2 SVII.2: New Safety Concerns and Reclassification with a Submission of an Updated RMP

No new safety concerns have been identified since the last EU RMP update. Section 2.7.3 reflects the current important identified risks and important potential risks after a reclassification of risks in 2018 (RMP version 11.1). Additionally, there were no new safety findings that have a significant impact on an existing safety concern.

2.7.3 SVII.3: Details of Important Identified Risks, Important Potential Risks, and Missing Information

Abilify

In the Abilify clinical trials and post-authorization experience, the following safety concerns are presented below:

- Important identified risks: EPS, including tardive dyskinesia
- Important potential risks: Orthostatic hypotension
- Missing information: Use in pregnancy and lactation

Abilify Maintena

In Abilify Maintena clinical trials and post-authorization experience, the following safety concerns are presented below:

- Important identified risks: EPS, including tardive dyskinesia
- Important potential risks: Orthostatic hypotension
- Missing information: Use in pregnancy and lactation, Use in elderly patients above 65 years of age

The safety profile of Abilify Maintena 720/960mg is similar to that of Abilify Maintena 300/400mg.

2.7.3.1 SVII.3.1: Presentation of Important Identified Risks and Important Potential Risks

Details of Important Identified and Important Potential Risks

Table 2.7.3.1-1	**SVII.3.1-1: Details of Important Identified Risk: EPS, including tardive dyskinesia**
MedDRA Terms	The search criteria included the following: SMQ Extrapyramidal syndrome (broad) and additional PTs of Myotonia, Nuchal rigidity, Asterixis, Essential tremor, Clumsiness, Fumbling, Head titubation, Huntington's disease, Myoclonus, and Clonus (MedDRA version 24.1).

Table 2.7.3.1-1 SVII.3.1-1: Details of Important Identified Risk: EPS, including tardive dyskinesia	
Potential Mechanisms	Exaggerated pharmacology: altered central acetylcholine and dopamine neurotransmission, principally in the basal ganglia of the brain.
Evidence Sources and Strength of Evidence	EPS, including tardive dyskinesia is an important identified risk based upon data from the aripiprazole clinical development program, post-marketing experience, and the therapeutic drug class.
Characterisation of the Risk	The characterization of EPS, including tardive dyskinesia is well-established based upon the following data: **<u>Epidemiology of EPS, including tardive dyskinesia</u>** **EPS** Extra-pyramidal side effects (EPSEs), encompassing both EPS and tardive dyskinesia, are common in schizophrenia and related conditions that are treated with antipsychotics. Two recent meta-analyses have investigated the relationship between atypical antipsychotic use and EPSEs in patients diagnosed with psychiatric disorders: • A 2021 metanalysis of EPSEs from antipsychotics (typical and/or atypical) reported a pooled prevalence of 37% including antipsychotic-induced parkinsonism (20% pooled prevalence), akathisia (11%), and tardive dyskinesia (7%).[97] • A 2020 metanalysis of 177 studies across 58,069 patients found that patients treated with atypical antipsychotics were at greater risk for akathisia (composite rate of 2.9 to 13%) compared to placebo (3.7%). Higher doses of antipsychotics were associated with increased risk.[87] ***Schizophrenia*** The baseline prevalence of EPS was 38% among over 9,000 EU schizophrenia patients who participated in the Schizophrenia Outpatient Health Outcomes (SOHO) study and were treated in routine clinical settings.[133] As of January 2022, one study was identified that focused on the incidence of EPS among patients with schizophrenia treated with atypical antipsychotics. In 11,642 patients with schizophrenia who filled prescriptions for atypical antipsychotics, 21.2% experienced EPS within the first year. These patients were Medicaid patients in the U.S. identified through the MarketScan Multistate Medicaid database.[84] Additionally, Lauriello et al. investigated the long-term adverse effects of aripiprazole lauroxil in patients with schizophrenia (n = 478). In the first year of treatment, 12.8% of patients developed EPS. Rates of adverse effects including EPS did not change past 52 weeks until the end of study follow-up (130 weeks).[85]

Table 2.7.3.1-1	**SVII.3.1-1: Details of Important Identified Risk: EPS, including tardive dyskinesia**
	Bipolar Mania No population-based epidemiologic studies have been conducted to quantify the incidence/prevalence of EPS in patients with bipolar mania. • Incidence of EPS-related AEs from bipolar clinical trials: atypical antipsychotic treatment: 0.9% to 35%; other neuroleptic regimens: 6% to 63%.[134] • Prevalence of EPS from bipolar disorder observational studies: 1.5% to 52%.[135,136,137] ***Paediatrics*** EPS has been reported to occur in 50 to 73% of paediatric or adolescent schizophrenia patients treated with typical antipsychotic agents.[138,139,140] No large studies reporting the incidence or prevalence of EPS among children/adolescents with bipolar mania, autism, or depression were identified. EPS includes AEs that vary in severity, associated risk factors, time to onset, duration, clinical presentation, and persistence.[149] Treatment-resistant EPS may increase the risk of developing NMS, thus imposing a greater risk of morbidity and mortality among patients.[150] **Epidemiology of Tardive Dyskinesia** The incidence of tardive dyskinesia among general psychiatric patients treated with typical antipsychotics in an observational setting, including both in-patient and outpatients has been reported at 3% to 5% per year of exposure.[141,142,143,144] A 2017 metanalysis of 41 studies reported a global mean prevalence for tardive dyskinesia of 25%. There was significant variation between studies; however, rates of tardive dyskinesia were significantly lower in patients treated with atypical antipsychotics (21%, n = 5103) compared to those treated with first generation antipsychotics (30%, n = 5062). Included subjects were under treatment for a variety of psychiatric disorders, but schizophrenia was the predominant diagnosis.[90] ***Bipolar Mania*** No population-based epidemiologic studies have quantified the incidence/prevalence of tardive dyskinesia in those with bipolar mania. • In observational studies, the prevalence of tardive dyskinesia among those with bipolar disorder has been reported at 9.2% to 64%.[135,136,137,145,146,147]

Table 2.7.3.1-1	**SVII.3.1-1: Details of Important Identified Risk: EPS, including tardive dyskinesia**
	Schizophrenia The incidence of tardive dyskinesia was 3.0% (95% CI: 2.6-3.4) in the SOHO study, a prospective, observational health outcomes study of >9,000 schizophrenia patients in Europe.[133] An observational study comparing aripiprazole and haloperidol found that the annualized rate of new-onset tardive dyskinesia was 0.5% for schizophrenia patients taking aripiprazole and 9% for schizophrenia patients treated with haloperidol.[148] The baseline prevalence of tardive dyskinesia was 9% among participants in the SOHO study.[133] In 2019, a French study of 674 patients with schizophrenia recruited through the FACE-SZ program reported an overall prevalence of tardive dyskinesia of 8%, assessed using the Abnormal Involuntary Movement Scale.[88] A U.S. case-control study investigated the risk for tardive dyskinesia in 77,022 adults hospitalized for mood disorders or schizophrenia, who were age-matched to subjects drawn from the general population. Patients with schizophrenia or bipolar disorder had 4-fold higher odds of tardive dyskinesia than the general population.[89] ***Paediatrics*** The reported estimate of tardive dyskinesia in treated paediatric psychiatric patients (including schizophrenia, bipolar, autism, and Tourette's Disorder) varies widely, with frequencies ranging from 6% to 38%. **<u>Abilify Clinical Trials</u>** **Bipolar mania** ***Adults*** • 12-week active-controlled studies: CN138008 A Multicenter, Randomized, Double-blind Study of Aripiprazole and Haloperidol in the Maintained Response to Treatment for an Acute Manic Episode (23.4% aripiprazole vs. 60.9% haloperidol); CN138162 A Multicenter, Randomized, Double-blind, Placebo-controlled Study of Aripiprazole Monotherapy in the Treatment of Acutely Manic Patients with Bipolar 1 Disorder (23.5% aripiprazole vs. 53.3% haloperidol); CN138135 A Multicenter, Randomized, Double-Blind, Placebo Controlled Study of Aripiprazole Monotherapy in the Treatment of Acutely Manic Patients with Bipolar I Disorder (26.6% aripiprazole vs. 17.6% lithium) • CN138189 (52-week, placebo-controlled study of aripiprazole adjunctive to lithium or valproate): 11.4% aripiprazole vs. 4.2% placebo.

Table 2.7.3.1-1	**SVII.3.1-1: Details of Important Identified Risk: EPS, including tardive dyskinesia**
	• CN138392 (52-week, placebo-controlled study of aripiprazole in combination with lamotrigine): 15.9% aripiprazole vs. 9.1% placebo. ***Paediatrics*** • 31-03-240 (30-week, placebo-controlled study of aripiprazole in children and adolescent patients with bipolar I disorder): 31.5% aripiprazole vs. 7.2% placebo for acute phase and 34.5% aripiprazole vs. 8.2% placebo for combined acute + extension phase • 31-03-241 (6-month, open-label study of aripiprazole in children and adolescent patients with bipolar mania, manic or mixed episode with or without psychotic features): 12.8% aripiprazole. **Schizophrenia** ***Adults*** • 31-97-301 (52-week haloperidol-controlled study): 10.0% aripiprazole vs. 21.0% haloperidol. • CN138002 (26-week olanzapine-controlled study): 5.0% aripiprazole vs. 5.0% olanzapine. Five cases of tardive dyskinesia (1 mild and 4 moderate) were reported in the bipolar mania program; all events resulted in discontinuation and were coded as continuing beyond the end of the study. Of the 18 cases of tardive dyskinesia reported in the aripiprazole schizophrenia program, none was considered serious and or resulted in discontinuation. Of the 4 cases of tardive dyskinesia reported in the aripiprazole MDD program, none was considered serious and 2 resulted in discontinuation. In the adult studies, no deaths due to EPS-related AEs were reported in the aripiprazole MDD, bipolar mania, or schizophrenia programs; rates of discontinuations in these studies are described above. ***Paediatrics*** In paediatric studies, the majority of EPS-related AEs were mild to moderate in intensity; few were severe. In the bipolar mania controlled paediatric studies, there were no deaths due to EPS. In the paediatric studies, no cases of tardive dyskinesia were reported.

Table 2.7.3.1-1	**SVII.3.1-1: Details of Important Identified Risk: EPS, including tardive dyskinesia**
	Abilify Maintena Clinical Trials ***Paediatrics*** No studies have been conducted in paediatrics with aripiprazole IM depot because a waiver has been granted from PDCO for all IM formulations for all subsets of the paediatric population. **EPS-related TEAEs (including tardive dyskinesia)** • 031-07-002 (Single-dose, open-label PK trial): 3/26 (11.5%). • 31-11-289 (Single-dose, open-label trial): 9/60 (15.0%). • 31-11-290 (Single-dose PK trial): 11/35 (31.4%). • 31-12-291 (12-week, double-blind, placebo-controlled trial in acute schizophrenia): 32/167 (19.2%) aripiprazole IM depot 400 mg/300 mg group and 14/172 (8.1%) placebo group. • 31-05-244 (20-week, open-label PK trial): 8/39 (20.5%). • 31-10-002 (20-week, open-label, PK trial): 6/18 (21.4%) • 31-12-298 (20-week, open-label PK trial): 20/138 (14.5%). • 31-07-246 (52-week, placebo-controlled trial): single-blind stabilization phase 90/576 (15.6%) cases; double-blind randomization phase: 40/269 (14.9%) cases in the aripiprazole IM depot 400 mg/300 mg vs. 13/134 (9.7%) cases in the placebo group. • 31-08-003 (52-week, active-controlled trial vs Abilify tablets): 41/229 (17.9%) in the aripiprazole IM depot group and 32/227 (14.1%) in the tablet group. • 31-07-247 (38-week active-controlled trial): 58/265 (21.9%) aripiprazole IM depot 400 mg/300 mg vs. 31/266 (11.7%) oral aripiprazole 10-30 mg vs. 16/131 (12.2%) aripiprazole IM depot 50 mg/25 mg. • 31-08-248 (52-week, open-label trial): 97/1081 (9.0%). • 31-11-283 (6-month, open-label trial of hospitalization rates of subjects treated prospectively with IM depot in schizophrenics compared with a 6-month retrospective assessment of oral standard of care): 5/431 (13.7%). • 31-12-297 (26-week, open-label extension trial): 12/74 (16.2%). • Overall study population: 483/2824 (17.1%). The majority of EPS-related TEAEs were of mild or moderate intensity. The following frequencies per severity grade were reported in the overall study population: • Akathisia events: Mild 163/2824 (5.8%), Moderate 67/2824 (2.4%), Severe 4/2824 (0.1%). • Dyskinetic events: Mild 37/2824 (1.3%), Moderate 14/2824 (0.5%), Severe 1/2824 (~0.0%).

Table 2.7.3.1-1	**SVII.3.1-1: Details of Important Identified Risk: EPS, including tardive dyskinesia**
	• Dystonic events: Mild 65/2824 (2.3%), Moderate 22/2824 (0.8%). • Parkinsonism events: Mild 155/2824 (5.5%), Moderate 32/2824 (1.1%), Severe 2/2824 (0.1%). The discontinuation rates due to EPS with aripiprazole IM depot are approximately the same as those observed in clinical studies conducted with oral aripiprazole (oral 0.6%. vs. IM depot 0.5%). ***Tardive Dyskinesia TEAEs*** • 31-11-290 (Single-dose PK trial): 2/35 (5.7%). • 31-12-291 (12-week, double-blind, placebo-controlled trial in acute schizophrenia): 1/167 (0.6%) case of tardive dyskinesia was reported in the aripiprazole IM depot compared to no cases in the placebo group. • 31-05-244 (20-week, open-label PK trial): 1/39 (2.6%) in the aripiprazole 200 mg group. • 31-10-002 (20-week, open-label, PK trial): 1/28 (3.6%) • 31-07-246 (52-week, placebo-controlled trial): single-blind stabilization phase 5/576 (0.9%) cases; double-blind randomization phase 2/269 (0.7%) in aripiprazole IM depot 400 mg/300 mg group compared to 2/134 (1.5%) case in the placebo group. • 31-07-247 (38-week active-controlled trial): 7/265 (2.6%) aripiprazole IM depot 400 mg/300 mg, 3/266 (1.1%) in oral aripiprazole 10-30 mg, and 1/131 (0.8%) in the aripiprazole IM depot 50 mg/25 mg group. • 31-08-248 (52-week, open-label trial): 10/1081 (0.9%). • 31-11-283 (6-month, open-label trial of hospitalization rates of subjects treated prospectively with IM depot in schizophrenics compared with a 6-month retrospective assessment of oral standard of care): 5/431 (1.2%) • 31-12-297 (26-week, open-label extension trial): 1/74 (1.4%). • Overall study population: 52/2824 (1.8%). In total, there were 52 cases of tardive dyskinesia reported in the clinical program for the aripiprazole IM Depot formulation: 37/2824 (1.3%) cases were of mild intensity, 14/2824 (0.5%) cases were of moderate intensity, and 1/2824 (~0%) case was of severe intensity. **<u>Clinical Trial Safety Data</u>** **Methodology** A review of the Otsuka clinical trials database was performed cumulatively up to 30 Nov 2021. The search criteria included standardised MedDRA query (SMQ, broad) of extrapyramidal

Table 2.7.3.1-1	**SVII.3.1-1: Details of Important Identified Risk: EPS, including tardive dyskinesia**
	syndrome, and additional PTs of Myotonia, Nuchal rigidity, Asterixis, Essential tremor, Clumsiness, Fumbling, Head titubation, Huntington's disease, Myoclonus, and Clonus (MedDRA version 24.1) occurring in Otsuka-sponsored trials for all formulations of aripiprazole, excluding Abilify MyCite (tablet with ingestible event marker). **Abilify Results** Review of the Otsuka clinical trials database identified a total of 11,285 events (6,733 cases). The most frequently reported PTs included akathisia, (n=3,422), tremor (n=1,864), restlessness (n=1,547), extrapyramidal disorder (n=782), musculoskeletal stiffness (n=572), muscle spasms (n=370), muscle rigidity (n=342), dyskinesia (n=330), dystonia (n=243), and gait disturbance (n=221). Out of the 11,285 events, 77 events were assessed as serious, and 11,192 events were assessed as non-serious, and in the remaining 16 events, event seriousness was not reported. The investigator considered causality of events as definite (n=23), probable (n=13), probably related (n=8), related (n=5994), possible (n=9), possibly related (n=4110), unlikely related (n=580), not related (n=539), not likely (n=1), and unknown (n=8). Event outcome was reported as resolved in 2,909 events, resolved with sequelae in 42 events, resolving in 176 events, not resolved in 430 events, and unknown in 7,728 events. **Demographics** Out of the 6,733 cases, 3,297 were female subjects and 3,436 were male subjects with ages ranging from 6 to 97 years. The mean age (standard deviation) reported was 38.8 (±16.4). The median age (interquartile range) reported was 38.0 (27-48). **Analysis** Evaluation of the 11,285 events revealed that 900 events were confounded by underlying medical conditions (extrapyramidal disorder, tardive dyskinesia, akathisia, dyskinesia, tremor, muscle spasms, musculoskeletal stiffness, restlessness, trismus, oculogyric crisis, gait disturbance, and parkinsonism), 4,702 events were confounded by concomitant medications (quetiapine, olanzapine, venlafaxine, divalproex sodium, risperidone, haloperidol, escitalopram, citalopram, duloxetine, lamotrigine, sertraline, paroxetine, fluoxetine, clozapine, zotepine, amisulpride, lithium carbonate, asenapine), 549 events were confounded by both underlying medical conditions and concomitant medications. There were 6,232 events where a possible role of aripiprazole could not be excluded. Out of these 6,232 events, in 236 events the drug was either discontinued or

Table 2.7.3.1-1	**SVII.3.1-1: Details of Important Identified Risk: EPS, including tardive dyskinesia**
	dose was reduced and the event outcome was either resolved or resolving. **Abilify Maintena Results** Review of the Otsuka clinical trials database identified a total of 1,527 events (988 cases). The most frequently reported PTs included akathisia, (n=546), tremor (n=245), restlessness (n=142), extrapyramidal disorder (n=84), dyskinesia (n=70), musculoskeletal stiffness (n=61), dystonia (n=56), muscle spasms (n=45), parkinsonism (n=31), and muscle rigidity (n=25). Out of the 1,527 events, 7 events were assessed as serious, and 1,520 events were assessed as non-serious. The investigator considered causality of events as definite (n=9), definitely related (n=39), probable (n=14), probably related (n=20), related (n=849), possible (n=41), possibly related (n=410), unlikely related (n=36) not related (n=93), irrelevant (n=10), not likely (n=3), possibly unrelated (n=1), and unrelated (n=3). Event outcome was reported as resolved in 1,010 events, resolved with sequelae in 14 events, resolving in 143 events, not resolved in 334 events, and unknown in 26 events. **Demographics** Out of the 988 cases, 453 were female subjects and 535 were male subjects with ages ranging from 18 to 79 years. The mean age (standard deviation) reported was 40.5 (±11.7). The median age (interquartile range) reported was 41.0 (31-50). **Analysis** Evaluation of the 1,527 events revealed that 256 events were confounded by underlying medical conditions (extrapyramidal disorder, tardive dyskinesia, akathisia, dyskinesia, tremor, muscle spasms, musculoskeletal stiffness, restlessness, trismus, oculogyric crisis, gait disturbance, and parkinsonism), 983 events were confounded by concomitant medications (quetiapine, olanzapine, venlafaxine, divalproex sodium, risperidone, haloperidol, escitalopram, citalopram, duloxetine, lamotrigine, sertraline, paroxetine, fluoxetine, clozapine, zotepine, amisulpride, lithium carbonate, asenapine), 147 events were confounded by both underlying medical conditions and concomitant medications. There were 435 events where a possible role of aripiprazole could not be excluded. Out of these 435 events, in 50 events the drug was either discontinued or dose was reduced and the event outcome was either resolved or resolving. **Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe Results** Review of the Otsuka clinical trials database identified a total of 49 events (40 cases). The most frequently reported PTs included

Table 2.7.3.1-1	**SVII.3.1-1: Details of Important Identified Risk: EPS, including tardive dyskinesia**
	akathisia, (n=21), restlessness (n=6), dyskinesia (n=4), extrapyramidal disorder (n=3), muscle spasms (n=3), muscle twitching (n=2), musculoskeletal stiffness (n=2), oromandibular dystonia (n=2), trismus (n=2), and bradykinesia (n=1). Out of the 49 events, 1 event was assessed as serious and the remaining 48 events were assessed as non-serious. The investigator considered causality of 42 events as related and for the remaining 7 events as unrelated. Event outcome was reported as resolved in 41 events, and not resolved in 8 events. **Demographics** Out of the 40 cases, 18 were female subjects and 22 were male subjects with ages ranging from 21 to 63 years. The mean age (standard deviation) reported was 46.2 (±11.3). The median age (interquartile range) reported was 51.0 (36-55). **Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe Analysis** Evaluation of the 49 events revealed that 7 events were confounded by underlying medical conditions (extrapyramidal disorder, akathisia, tremor, essential tremor, and muscle spasms), 45 events were confounded by concomitant medications (quetiapine, olanzapine, venlafaxine, divalproex sodium, risperidone, haloperidol, duloxetine, lamotrigine, sertraline, paliperidone, fluoxetine, clozapine, lithium carbonate, and brexpiprazole), 6 events were confounded by both underlying medical conditions and concomitant medications. There were 3 events where a possible role of aripiprazole could not be excluded. The safety profile of aripiprazole 2M RTU LAI is similar to that of Abilify Maintena. EPS, including tardive dyskinesia is well-characterized for Abilify Maintena and applies to aripiprazole 2M RTU LAI. **<u>Post-Marketing Safety Data</u>** **Methodology** A review of the Otsuka safety database was performed cumulatively up to 30 Nov 2021. The search criteria included SMQ (broad) of extrapyramidal syndrome, and additional PTs of myotonia, nuchal rigidity, asterixis, essential tremor, clumsiness, fumbling, head titubation, Huntington's disease, myoclonus, and clonus (MedDRA version 24.1) reported in cases from clinical, literature, and spontaneous (including health authority) sources for all formulations of aripiprazole, excluding Abilify MyCite (tablet with ingestible event marker). **Abilify Results** Review of the Otsuka safety database identified a total of 30,306 events (24,771 cases). The most frequently reported PTs included

Table 2.7.3.1-1	**SVII.3.1-1: Details of Important Identified Risk: EPS, including tardive dyskinesia**
	akathisia (n=4,987), restlessness (n=4,875), tremor (n=4,658), tardive dyskinesia (n=2,370), extrapyramidal disorder (n=2,269), dyskinesia (n=1,985), dystonia (n=1,301), parkinsonism (n=987), musculoskeletal stiffness (n=799), and muscle spasms (n=6,580). Out of the 24,771 cases, 17,940 cases were from spontaneous reports, 975 cases were from spontaneous literature, 5,854 cases were from clinical trial, and 2 cases were from clinical literature. The event onset date range was from 1 to 4756 days. Out of the 30,306 events, 4,667 events were assessed as serious, and 25,639 events were assessed as non-serious. The overall causality of 30,108 events was assessed as related and the remaining 198 events were assessed as not related. The event outcome was reported as resolved in 6,620 events, resolving in 2,898 events, resolved with sequelae in 81 events, not resolved in 3,289 events, unknown in 17,386 events, and fatal in 32 events (all these 32 events were confounded by either concomitant medications or experienced co-reported events like asphyxia, completed suicide, seizure, cardiac failure, neuroleptic malignant syndrome, overdose, malignant hyperthermia, ketoacidosis, ischemic heart disease which resulted in fatal outcome; 17 events occurred in elderly patients). **Demographics** Out of the 24,771 cases, 13,651 were female patients, 8,612 were male patients (gender was unknown in the remaining 2,508 cases) with ages ranging from 1 day to 110 years. The mean age (standard deviation) reported was 49.704 (±28.807). The median age (interquartile range) reported was 49.5 (25.25-73.75). **Analysis** Evaluation of the 30,306 events revealed that 1,827 events were confounded by underlying medical conditions (extrapyramidal disorder, tardive dyskinesia, akathisia, dyskinesia tremor, muscle spasms, musculoskeletal stiffness, trismus, restlessness, gait disturbance, balance disorder, psychomotor hyperactivity, oculogyric crisis, Parkinson's disease, and parkinsonism), 10,757 events were confounded by concomitant medications (quetiapine, olanzapine, venlafaxine, desvenlafaxine, divalproex sodium, risperidone, haloperidol, escitalopram, citalopram, duloxetine, lamotrigine, sertraline, paroxetine, fluoxetine, clozapine, levomepromazine, bupropion, zotepine, amisulpride, lithium carbonate, brexpiprazole, paliperidone, asenapine, aripiprazole lauroxil), 924 events were confounded by both underlying medical conditions and concomitant medications, and 18,433 events had limited information, which precluded a meaningful medical assessment of the events. There were 213 events where a possible role of aripiprazole could not be excluded. Out of these 213 events, 19 were positive dechallenge events.

Table 2.7.3.1-1	**SVII.3.1-1: Details of Important Identified Risk: EPS, including tardive dyskinesia**
	Abilify Maintena Results Review of the Otsuka safety database identified a total of 3,308 events (2,619 cases). The most frequently reported PTs included akathisia (n=849), tremor (n=439), restlessness (n=305), extrapyramidal disorder (n=262), dyskinesia (n=175), musculoskeletal stiffness (n=136), tardive dyskinesia (n=124), dystonia (n=106), gait disturbance (n=104), and parkinsonism (n=93). Out of the 2,619 cases, 2,044 cases were from spontaneous reports, 59 cases were from spontaneous literature, and 516 cases were from clinical trial. The event onset date range was from 1 to 5,086 days. Out of the 3,308 events, 606 events were assessed as serious, and 2,702 events were assessed as non-serious. The overall causality of 3,263 events was assessed as related and the remaining 45 events were assessed as not related. The event outcome was reported as resolved in 746 events, resolving in 344 events, resolved with sequelae in 15 events, not resolved in 689 events, unknown in 1507 events, and fatal in 7 events (five events occurred in elderly patients who also experienced co-reported events such as cardiac arrest, neuroleptic malignant syndrome, pneumonia aspiration which resulted in fatal outcome; one event occurred in an adult patient with unknown therapy duration and experienced co-reported events of hematemesis, endotracheal intubation, cardiac arrest, hepatic failure which resulted in fatal outcome; one event had limited information and also patient completed suicide). **Demographics** Out of the 2,619 cases, 1,209 were female patients, 1,139 were male patients (gender was unknown in the remaining 271 cases) with ages ranging from 15 to 90 years. The mean age (standard deviation) reported was 50.77 (±21.375). The median age (interquartile range) reported was 50.5 (32.75-68.25). **Analysis** Evaluation of the 3,308 events revealed that 339 events were confounded by underlying medical conditions (extrapyramidal disorder, tardive dyskinesia, akathisia, dyskinesia, essential tremor, tremor, muscle spasms, musculoskeletal stiffness, trismus, restlessness, gait disturbance, psychomotor hyperactivity, oculogyric crisis, Parkinson's disease, and parkinsonism), 808 events were confounded by concomitant medications (quetiapine, olanzapine, venlafaxine, desvenlafaxine, divalproex sodium, risperidone, haloperidol, escitalopram, citalopram, duloxetine, lamotrigine, sertraline, paroxetine, fluoxetine, clozapine, levomepromazine, bupropion, zotepine, amisulpride, lithium carbonate, brexpiprazole, paliperidone, asenapine, aripiprazole lauroxil), 96 events were confounded by both underlying medical conditions and concomitant

Table 2.7.3.1-1	**SVII.3.1-1: Details of Important Identified Risk: EPS, including tardive dyskinesia**
	medications, and 2,171 events had limited information, which precluded a meaningful medical assessment of the events. There were 86 events where a possible role of aripiprazole could not be excluded. Out of these 86 events, 10 were positive dechallenge events. **<u>Study 31-10-270 Results</u>** This open label, multi center, rollover, long term study of aripiprazole intramuscular depot in patients with schizophrenia to evaluate the risk of EPS related events during treatment with aripiprazole IM depot was completed. In this study, EPS related TEAEs were reported in 49/709 (6.9%) of patients. The most frequently reported EPS related TEAEs were tremor (n=19), akathisia (n=9), muscle spasms (n=6), dyskinesia (n=5), tardive dyskinesia (n=3), muscle twitching (n=3), and parkinsonism (n=3). EPS-related TEAEs in this study were non-serious and did not result in discontinuation of aripiprazole IM depot. The incidence of akathisia and other EPS related TEAEs was low, and comparable to that observed in prior short-term and long-term schizophrenia trials. There were no clinically relevant findings with regard to mean changes in EPS. **<u>PASS Study 15893N Results</u>** This European, multinational historical cohort study, using longitudinal administrative claims databases, to assess the risk of EPS-related events linked to the use of Abilify Maintena in routine clinical practice was completed. In this study, incidence rates of EPS-related events per 100 patient years were IR=3.4 (95% CI 2.4; 4.6) in Germany, IR=7.7 (95% CI 5.8; 10.2) in Sweden, and IR=18.4 (95% CI 15.3-22.1) in Italy. The regional variation is most likely attributable to different prescribing habits for anticholinergic drugs, which is in line with previous findings. **Germany** The incidence of EPS-related events based on dispensations of antiparkinsonian medication appears lower than in the clinical trials. The onset of EPS-related events was accumulated to the beginning of the 2-year period after initiating Abilify Maintena, which was expected based on literature and information from clinical trials **Sweden** The detected incidence rate of EPS-related events among patients dispensed Abilify Maintena in Sweden, defined by dispensed anticholinergic drugs, appears lower than in clinical trials, and thus does not raise a safety concern. The onset of EPS-related events was accumulated to the beginning of the 2-year period after initiating Abilify Maintena, which was expected considering the frequency of acute EPS events in clinical trials on aripiprazole. Incident EPS-related events were also detected

Table 2.7.3.1-1	**SVII.3.1-1: Details of Important Identified Risk: EPS, including tardive dyskinesia**
	during the entire 2-year follow-up, suggesting that some EPS-events had onset beyond the acute treatment initiation phase. However, the occurrence of EPS-related events throughout the 2-year period was likely contributed by the use of dispensations of anticholinergic drugs as the event definition and by inpatient or outpatient use of antipsychotics other than Abilify Maintena. Among users of Abilify Maintena in Sweden, most of the studied risk factors were not associated with the occurrence of EPS-related events, with the exception of typical antipsychotic use 5 years prior to initiating Abilify Maintena, strengthening the previous evidence that the risk of EPS-related events increases when typical antipsychotics are used. **Italy** Results from this cohort study among adult new users of Abilify Maintena indicated that the absolute risk of EPS at 2 years after the index date among patients initiating Abilify Maintena was 27.8%, while the competing risk of death was below 1%. The most important risk factors for EPS events were older age at the index date, diagnosis of depression, use of antipsychotics in the 5 years before the index date, the concomitant use of some typical but no atypical antipsychotics (other than Abilify) within the 45 days before the index date, and the concomitant use of antidepressants and lithium within the 45 days before the index date. In this population, the crude IR of EPS-related events for the 2 years of follow-up was 18.4 per 100 person-years. The highest IR of EPS events was during the first month of treatment, with 56.7 EPS-related events per 100 person-years.
Risk Groups or risk factors	***EPS Risk Factors*** Established risk factors for EPS include exposure to antipsychotic treatments (with risk varying according to the agent type and dose), advanced age, male gender, alcohol and substance abuse, use of concomitant medications, and diabetes.[151] ***Tardive Dyskinesia Risk Factors*** Established risk factors for tardive dyskinesia include antipsychotic treatment, the presence or history of EPS, advanced age, cognitive difficulties, alcohol, and substance abuse, use of concomitant medications, and diabetes.[143,152,153,154]
Preventability	**EPS** Mitigation strategies include lowering the antipsychotic dose and adding anticholinergic drugs. If signs and symptoms of other EPS appear in a patient treated with aripiprazole, dose reduction and close clinical monitoring should be considered. **Tardive dyskinesia** Mitigation strategies may include more conservative use of antipsychotic drugs or more limited dosing duration. If signs and

Table 2.7.3.1-1	**SVII.3.1-1: Details of Important Identified Risk: EPS, including tardive dyskinesia**
	symptoms of tardive dyskinesia appear in a patient treated with aripiprazole, dose reduction or discontinuation may be considered.
Impact on the Risk-benefit Balance of the Product	Atypical antipsychotics have been associated with EPS, including tardive dyskinesia. Results from the completed PASS 15893N and Study 31-10-270 established that EPS, including tardive dyskinesia was further characterised and the impact on the risk-benefit balance of aripiprazole is minimal. EPS, including tardive is a well-established known risk based upon the therapeutic drug class and additional risk minimisation measures.
Public Health Impact	Absolute risk cannot be calculated since the size of the target population is unknown. However, the risk for EPS, including tardive dyskinesia remains minimal given that results from the PASS 15893N have concluded that the cumulative incidences of EPS, including tardive dyskinesia were lower or similar to the incidence of EPS adverse events in RCTs and support the established safety profile of Abilify Maintena as characterized in clinical trials.

Table 2.7.3.1-2	**SVII.3.1-2: Details of Important Potential Risk: Orthostatic hypotension**
MedDRA Terms	The search criteria included the following: PTs Dizziness postural, Orthostatic hypotension and Syncope (MedDRA version 24.1)
Potential Mechanisms	Aripiprazole is an α1-adrenergic receptor antagonist and postural hypotension is common after the initial dose of an α1-adrenergic receptor antagonist.
Evidence Sources and Strength of Evidence	Orthostatic hypotension is an important potential risk based upon data from the aripiprazole clinical development program, and post-marketing experience.
Characterisation of the Risk	**<u>Epidemiology of Orthostatic Hypotension</u>** The incidence of orthostatic (postural) hypotension in the general population is not known, but the prevalence of orthostatic hypotension has been estimated to be 5 to 30% (age-dependent) and is believed to be common in the elderly (usually defined as those aged 65 years or more).[123] Orthostatic hypotension appears to increase with advancing age (e.g., > 65 years: 20%; > 75 years: 30%)[124] and is also common in acute care settings and nursing homes.[124,125] There are no population-based studies describing the epidemiology of orthostatic hypotension either in the elderly or among those with psychiatric disorders. A 2018 study of 82 geriatric outpatients presenting with late life depression evaluated for orthostatic hypotension by an upright tilt table test and a questionnaire found that 28% of participants had appositive tilt table test and 57% reported symptoms suggestive of orthostatic hypotension. Women were more likely than men to have orthostatic hypotension.[126]

Table 2.7.3.1-2	**SVII.3.1-2: Details of Important Potential Risk: Orthostatic hypotension**
	Few studies have investigated exposure to antipsychotics and orthostatic hypotension. A respective cohort study (N = 8640) was found reporting that children and adolescents treated with antipsychotics had a higher prevalence of orthostatic hypotension (OR = 1.64) compared to those who did not receive antipsychotics.[127] A study of geriatric patients in Nigeria investigated the relationship between falls and "fall risk increasing drugs" (FRIDs) including antipsychotics. They found an overall prevalence of falls of 45% in patients taking FRIDs. Falls were associated with antipsychotic use. The study notes that orthostatic hypotension is a common contributor to falls in patients taking FRIDs, which are commonly made up of cardiovascular and psychotropic medications.[128] A 2021 metanalysis of 27,079 subjects across 69 RCTs found that, in addition to alpha blockers and SGLT2 inhibitors, antipsychotics were associated with 2-fold increased odds of orthostatic hypotension compared to placebo.[129] **<u>Abilify Clinical Trial Data</u>** **Bipolar Mania** ***Adults*** Incidence of at least 20-mm Hg decrease and at least 25-bpm increase in heart rate (supine to standing): • CN138135 (3-week placebo-controlled trial): 0.6% aripiprazole vs. 0.6% placebo • CN138162 (3-week placebo-controlled trial): 0.6% aripiprazole vs. 0% placebo Incidence of orthostatic-related AEs: • CN139009 (3-week placebo-controlled trial): syncope (0% aripiprazole vs. 1.6% placebo), and orthostatic hypotension (1.6% aripiprazole vs. 0% placebo) • CN138189 (52-week, placebo-controlled study of aripiprazole adjunctive to lithium or valproate): 0% aripiprazole vs. 1.5% placebo. • CN138392 (52-week, placebo-controlled study of aripiprazole in combination with lamotrigine): syncope (0.6% aripiprazole vs. 0% placebo). In Study CN138392, orthostatic hypotension (mild) was reported in 1/176 aripiprazole patients (0.6%) vs. 0/165 placebo patients. ***Paediatrics*** Incidence of at least 20-mm Hg decrease and at least 25-bpm increase in heart rate (supine to standing): • 31-03-240 A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Two Fixed Oral Doses of Aripiprazole (10 mg and 3 0 mg) in the Treatment of Child and Adolescent Patients, Ages 10-17 Years, with Bipolar I Disorder, Manic or Mixed Episode with or without Psychotic Features: 2 patients in the aripiprazole 10 mg group

Table 2.7.3.1-2	**SVII.3.1-2: Details of Important Potential Risk: Orthostatic hypotension**
	• 31-03-241: 5/86 aripiprazole patients (5.8%). Incidence of orthostatic-related AEs: • 31-03-240: 1.0%, 0.0%, and 2.1% in the aripiprazole 10 mg, aripiprazole 30 mg, and placebo groups, respectively • 31-03-241: none. In the pediatric studies, 1 patient (1%) in Study 31-03-240 on aripiprazole 10 mg had moderate orthostatic hypotension. **Schizophrenia** ***Adults*** Incidence of at least 20-mm Hg decrease and at least 25-bpm increase in heart rate (supine to standing) in 4-6-week placebo-controlled trials: 9.0% aripiprazole vs. 7.6% placebo. Incidence of orthostatic-related AEs: • CN138047 (26-week placebo-controlled trial: orthostatic hypotension): 0.7% aripiprazole vs. 0% placebo. Thirty-one orthostatic-related events were reported in placebo-controlled schizophrenia studies (5 moderate and 26 mild). ***Paediatrics*** • 031-09-003 (4-6-week placebo-controlled pediatric schizophrenia trial): all events were in the aripiprazole group: postural dizziness (1%), syncope (0.5%), and orthostatic hypotension (1.5%) • 031-09-004 (26-week open-label pediatric schizophrenia trial: all events were in the aripiprazole group): orthostatic hypotension (1.7%) and postural dizziness (0.7%). In pediatric schizophrenia studies, 6 mild orthostatic-related events were reported (3 orthostatic hypotension, 2 postural dizziness, and 1 syncope). All events resolved. **<u>Abilify Maintena Clinical Trial Data</u>** • 31-12-291 (12-week, double-blind, placebo-controlled trial in acute schizophrenia): 1/167 (0.6%) case in the aripiprazole IM depot 400 mg/300 mg group and 2/172 (1.2%) cases in the placebo group. • 31-05-244 (20-week, open-label PK trial): 1/39 (2.6%) case. • 31-07-246 (52-week, placebo-controlled trial): single-blind stabilization phase 4/576 (0.7%) cases; double-blind randomized phase 0/269 (0%) aripiprazole IM depot 400 mg/300 mg vs. 0/134 (0%) placebo. • 31-07-247 (38-week active-controlled trial): 2/265 (0.8%) cases in the aripiprazole IM depot 400 mg/300 mg group vs. 2/266 (0.8%) cases in the oral aripiprazole 10-30 mg group vs. 1/131 (0.8%) cases aripiprazole IM depot 50 mg/25 mg group. • 31-08-248 (52-week, open-label trial): 7/1081 (0.6%) cases.

Table 2.7.3.1-2	**SVII.3.1-2: Details of Important Potential Risk: Orthostatic hypotension**
	• 31-11-283 (6-month, open-label trial of hospitalization rates of subjects treated prospectively with IM depot in schizophrenics compared with a 6-month retrospective assessment of oral standard of care): 5/431 (1.2%). • Overall study population: 21/2824 (0.7%) cases. In the placebo-controlled trials, the incidence of at least 20-mm Hg decreases and at least 25-bpm increase in heart hate (supine to standing) was 3.0% aripiprazole vs. 2.3% placebo. The incidence of orthostatic-related AEs was postural dizziness (0.2% aripiprazole vs. 0.5% placebo), syncope (0.4% aripiprazole vs. 0% placebo), and orthostatic hypotension (0.6% aripiprazole vs. 0% placebo). All TEAEs related to orthostasis were of mild or moderate intensity. The following frequencies per severity grade were reported in the overall study population: mild severity 14/2824 (0.5%) and moderate severity 7/2824 (0.2%). The preferred terms are listed below: • Blood pressure orthostatic abnormal: Mild 1/2824 (~0%). • Dizziness postural: Mild 4/2824 (0.1%). • Orthostatic hypotension: Mild 3/2824 (0.1%), Moderate 1/2824 (~0%). • Presyncope: Mild 1/2824 (~0%), Moderate 2/2824 (0.1%). • Syncope: Mild 6/2824 (0.2%), Moderate 4/2824 (0.1%). Of the 6 orthostatic-related events reported in placebo-controlled Solution for Injection studies, 2 were severe (1 postural dizziness and 1 orthostatic hypotension), 1 was moderate, and 3 were mild. ***Paediatrics*** No studies have been conducted in pediatrics with aripiprazole IM depot because a waiver has been granted from PDCO for all IM formulations for all subsets of the pediatric population. **<u>Clinical Trial Safety Data</u>** **Methodology** A review of the Otsuka clinical trials database was performed cumulatively up to 30 Nov 2021. The search criteria included PTs Dizziness postural, Orthostatic hypotension and Syncope (MedDRA version 24.1) occurring in Otsuka-sponsored trials for all formulations of aripiprazole, excluding Abilify MyCite (tablet with ingestible event marker). **Abilify Results** Review of the Otsuka clinical trials database identified a total of 741 events (588 cases). The most frequently reported PTs included Dizziness postural (n= 282), Orthostatic hypotension (n= 292) and Syncope (n= 167). Out of the 741 events, 35 events were assessed as serious and remaining 706 events were assessed as non-serious. There were 387 events considered related, 241 events considered possibly related, 58 events considered not related, 53 events

Table 2.7.3.1-2	**SVII.3.1-2: Details of Important Potential Risk: Orthostatic hypotension**
	considered unlikely related, one event considered probable and remaining one event considered unknown by the investigator. The event outcome was reported as resolved in 365 events, not reported and/or unknown in 352 events, not resolved in 16 events, resolving in five events, resolved with sequelae in two events and the remaining one fatal event reported PT syncope in an PPD -year-old PPD . The fatal event was assessed as not related by the investigator. **Demographics** Out of the 588 cases, 227 were female subjects and 361 were male subjects with ages ranging from 9 to 90 years. The mean age (standard deviation) reported was 37.0 (±17.2). The median age (interquartile range) reported was 34 (24-45). **Analysis** Evaluation of the 741 events revealed that 83 events were confounded by underlying medical conditions including orthostatic hypotension, syncope, diabetes mellitus, hypertension, alcohol use and tobacco use, 236 events were confounded by concomitant medications including quetiapine, olanzapine, risperidone, trazodone, sertraline, citalopram, lithium carbonate, lithium, fluoxetine, lamotrigine, valsartan, furosemide, biperiden, paroxetine, lisinopril, clonidine, mirtazapine, zolpidem, venlafaxine, amlodipine, prednisolone, atenolol, perindopril, prednisolone, valproic acid, bupropion, ziprasidone and paliperidone, 58 events were confounded by both underlying medical conditions and concomitant medications. There were 480 events where a possible role of aripiprazole could not be excluded. Out of these 480 events, 12 were positive dechallenge events. **Abilify Maintena Results** Review of the Otsuka clinical trials database identified a total of 34 events (31 cases). The most frequently reported PTs included Dizziness postural (n= 10), Orthostatic hypotension (n= 11) and Syncope (n= 13). All 34 events were assessed as non-serious. There were 11 events considered related, 11 events considered not related, seven events considered possibly related, and remaining five events considered as unlikely related by the investigator. The events outcome was reported as resolved in 26 events, not resolved in seven events and remaining one event outcome reported as resolving. **Demographics** Out of the 31 cases, 18 were female subjects and 13 were male subjects with ages ranging from 18 to 60 years. The mean age (standard deviation) reported was 36.5 (±10.2). The median age (interquartile range) reported was 39.0 (28-45). **Analysis** Evaluation of the 34 events revealed that 10 events were confounded by underlying medical conditions including syncope, diabetes mellitus, hypertension, alcohol use and tobacco use, 20

Table 2.7.3.1-2	**SVII.3.1-2: Details of Important Potential Risk: Orthostatic hypotension**
	events were confounded by concomitant medications including quetiapine, olanzapine, clozapine, trazodone, sertraline, citalopram, lithium carbonate, lithium, fluoxetine, lamotrigine, carbamazepine, risperidone, mirtazapine, zolpidem, venlafaxine, tramadol, oxcarbazepine, escitalopram, biperiden, bupropion, ziprasidone and paliperidone, seven events were confounded by both underlying medical conditions and concomitant medications. There were 11 events where a possible role of aripiprazole could not be excluded. **Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe Results** Review of the Otsuka clinical trials database identified a total of one event (one case) reporting PT Orthostatic hypotension. The event was assessed as non-serious and considered unlikely related by the investigator. The outcome of the event was resolved. **Demographics** One case reported a PPD-year-old PPD subject. The mean age (standard deviation) reported was PPD (±0). The median age (interquartile range) reported was PPD . **Analysis** Evaluation of the one event revealed that it was confounded by concomitant medications including duloxetine and quetiapine. **<u>Post-Marketing Safety Data</u>** **Methodology** A review of the Otsuka safety database was performed cumulatively up to 30 Nov 2021. The search criteria included PTs Dizziness postural, Orthostatic hypotension and Syncope (MedDRA version 24.1) reporting in cases from clinical, literature, and spontaneous (including health authority) sources for all formulations of aripiprazole, excluding Abilify MyCite (tablet with ingestible event marker). **Abilify Results** Review of the Otsuka safety database identified a total of 624 events (602 cases). The most frequently reported PTs included Dizziness postural (n= 61), Orthostatic hypotension (n= 189) and Syncope (n= 374). Out of the 602 cases, 507 cases reported from spontaneous sources, 67 cases reported from clinical trial sources, 26 reported from spontaneous literature sources and remaining two cases reported from clinical literature sources. Out of the 624 events, 279 events were assessed as serious and remaining 345 events were assessed as non-serious. There were 601 events considered related and 23 events considered not related. The events outcome was reported as unknown in 317 events, resolved in 228 events, not resolved in 47 events, resolving in 26 events, resolved with sequelae in four events, and fatal in the remaining two events. Out of two fatal events, one fatal event reported PTs syncope and hypertrophic cardiomyopathy in a PPD-year-old PPD and the cause of death was attributed to hypertrophic

Table 2.7.3.1-2	**SVII.3.1-2: Details of Important Potential Risk: Orthostatic hypotension**
	cardiomyopathy. The remaining one fatal event reported PTs shock, dyspnoea, pulmonary embolism, syncope, seizure and circulatory collapse in a PPD-year-old PPD. The causes of death were attributed to shock, dyspnoea, pulmonary embolism, seizure and circulatory collapse. The onset date ranges from 1 day to 2740 days. **Demographics** Out of the 602 cases, 318 were female patients, 238 were male patients and 46 cases reported unknown gender with ages ranging from 5 to 96 years. The mean age (standard deviation) reported was 45.33 (±23.58). The median age (interquartile range) reported was 45 (25.5-64.5). **Analysis** Evaluation of the 624 events revealed that 109 events were confounded by underlying medical conditions including orthostatic hypotension, syncope, diabetes mellitus, hypertension, alcohol use, tobacco use and/or historical medications (quetiapine, olanzapine, risperidone, clozapine, haloperidol), 238 events were confounded by concomitant medications including quetiapine, olanzapine, risperidone, clozapine, trazodone, oxcarbazepine, escitalopram, bendroflumethiazide, venlafaxine, pregabalin, sertraline, dextroamphetamine, citalopram, duloxetine, lithium carbonate, metamizole, fluoxetine, lamotrigine, valsartan, topiramate, carbamazepine, furosemide, xylometazoline, biperiden, tramadol, paroxetine, lisinopril, clonidine, perindopril, mirtazapine, oxymorphone, zolpidem, meloxicam, amlodipine, prednisolone, nebivolol, atenolol, valproic acid, bupropion, ziprasidone, paliperidone and brexpiprazole, 65 events were confounded by both underlying medical conditions and concomitant medications and 156 events had limited information, which precluded a meaningful medical assessment of the events. There were 186 events where a possible role of aripiprazole could not be excluded. Out of these 186 events, 29 were positive dechallenge events, 3 positive dechallenge and positive rechallenge events, and remaining one positive rechallenge event. **Abilify Maintena Results** Review of the Otsuka safety database identified a total of 60 events (60 cases). The most frequently reported PTs included Dizziness postural (n= 02), Orthostatic hypotension (n= 21) and Syncope (n= 37). Out of the 60 cases, 52 cases reported from spontaneous sources and eight cases reported from clinical trial sources. Out of the 60 events, 24 events were assessed as serious and remaining 36 events were assessed as non-serious. There were 56 events considered related and 4 events considered not related. The events outcome was reported as unknown in 25 events, resolved in 26 events, and remaining nine events outcomes reported as not resolved. The onset date ranges from 1 day to 540 days.

Table 2.7.3.1-2	**SVII.3.1-2: Details of Important Potential Risk: Orthostatic hypotension**
	Demographics Out of the 60 cases, 29 were female patients, 28 were male patients and three cases reported unknown gender with ages ranging from 18-75 years. The mean age (standard deviation) reported was 42.23 (±17.06). The median age (interquartile range) reported was 40.5 (27.5-56.75). **Analysis** Evaluation of the 60 events revealed that 11 events were confounded by underlying medical conditions including orthostatic hypotension, syncope, diabetes mellitus, hypertension, alcohol use, nicotine dependence, tobacco use and/or historical medications (paliperidone palmitate, olanzapine), 16 events were confounded by concomitant medications including lamotrigine, lurasidone, biperiden, codeine, clozapine, methylphenidate, bupropion, lisdexamfetamine, topiramate, levomilnacipran, rivaroxaban, duloxetine, quetiapine, sertraline, amisulpride, acamprosate, atenolol, moxonidine, paroxetine, trazodone, lithium, brexpiprazole, paliperidone palmitate and olanzapine, three events were confounded by both underlying medical conditions and concomitant medications and 15 events had limited information, which precluded a meaningful medical assessment of the events. There were 21 events where a possible role of aripiprazole could not be excluded. Out of these 21 events, three were positive dechallenge events.
Risk Groups or risk factors	Established risk factors for orthostatic hypotension are listed below: • Advanced age • Use of psychotropic medications (e.g., dopaminergic drugs, antidepressants, neuroleptic agents)[125] • Use of antianginal drugs or antihypertensive and vasodilator therapy[124] • Medical conditions, including hypovolemia, defects of vasomotor reflexes, and autonomic nervous system dysfunction (as may occur in diabetes and Parkinsonism). Drug-induced orthostatic hypotension remains a concern[125,130] • Prolonged and severe orthostatic hypotension has been associated with stroke and myocardial infarction[131] • Drug-induced orthostatic hypotension and elderly patients: o Orthostatic hypotension is associated with significant morbidity and mortality, especially elderly patients in acute-care settings[124] ranging from mild symptoms (dizziness) to severe symptoms, such as syncope (leading to fractures or other injuries and immobility)[131] o Approximately one third of all falls in nursing homes are attributed to psychotropic drug use.[132]
Preventability	Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or

Table 2.7.3.1-2	**SVII.3.1-2: Details of Important Potential Risk: Orthostatic hypotension**
	ischemic heart disease, heart failure, or conduction abnormalities), cerebrovascular disease, or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Blood pressure, pulse, respiratory rate, and level of consciousness should be monitored regularly.
Impact on the Risk-benefit Balance of the Product	The incidence rates of orthostatic hypotension presented in clinical and post-marketing data remain low and mild in nature. The benefits of aripiprazole outweigh the risk for orthostatic hypotension.
Public Health Impact	Absolute risk cannot be calculated since the size of the target population is unknown. There is no health risk posed except to those of the at-risk group (e.g., elderly, those in acute-care settings, or those receiving certain medications, including antipsychotics).

2.7.3.2 SVII.3.2: Presentation of the Missing Information

Details of Missing Information

Table 2.7.3.2-1	**SVII.3.2-1: Details of Missing Information: Use in Pregnancy and Lactation**
MedDRA Terms	The following MedDRA terms were used: SMQ: Pregnancy, labour and delivery complications and risk factors (excluding abortions and stillbirth) SMQ: Neonatal exposures via breast milk
Evidence Source(s)	**<u>Epidemiology</u>** Pregnancy is a period with higher risk for relapse and recurrence of psychotic disorders, particularly following abrupt discontinuation of treatment.[155,156,157,158,159,160,161] Additionally, maternal obstetric complications could be potential environmental contributors to schizophrenia risk.[161] At least 50% of women with bipolar disorder who interrupt therapy became symptomatic during pregnancy.[157,160] Furthermore, women with bipolar disorder are at high risk for symptom exacerbation during the immediate postpartum period and recurrence rates for bipolar disorder within the first 3 to 6 postpartum months are extremely high, in the range of 67 to 82% according to one review.[156] Expert consensus opinion holds that the risks associated with psychotropics to both the mother and the fetus must be balanced against the benefits, with the decision individualized for each woman; the appropriate use of psychotropic medication during pregnancy substantially reduces the risk of relapse among women with bipolar disorder.[162] In patients with schizophrenia, antipsychotic discontinuation was associated with a 13-fold increase of relapse risk within three months.[163] Importantly, The American College of Obstetrics and Gynecology (ACOG)

Table 2.7.3.2-1	**SVII.3.2-1: Details of Missing Information: Use in Pregnancy and Lactation**
	guideline notes that untreated or inadequately treated maternal mental illness "may result in poor compliance with prenatal care, inadequate nutrition, exposure to additional medications or herbal medicines, increased alcohol and tobacco use, deficits in mother-infant bonding, and disruptions within the family environment." **Psychosis during pregnancy** • A 2020 metanalysis of 152 studies including many conducted within the EU found that risk factors for psychosis during the prenatal and perinatal period include: maternal age younger than 20 years old, paternal age younger than 20 years old, paternal age older than 35 years old, any psychopathology in either parent, a history of maternal psychosis or affective disorder, three or more past pregnancies, prenatal infections, and obstetric complications.[164] These same factors—e.g., maternal age, perinatal infection—are established as risks for adverse neonatal outcome and may explain in part the increased risk for birth defects traditionally associated with psychosis. • Similarly, severe mental illness has been associated with smoking, alcohol use, drug abuse, poor nutrition and non-compliance with prenatal care, which are considered to be independent risk factors that may be associated with adverse pregnancy and birth outcomes, such as congenital malformation, preterm birth, low birth weight, and perinatal death.[156,165,166] **Fetal complications among those with psychosis or mood disorders** • Schizophrenia has been associated with placental abruption and hemorrhage and fetal complication (low birth weight, congenital cardiac anomalies and fetal distress), although environmental factors and maternal comorbidities are likely to impact this relationship.[161] • Results from several population-based studies have suggested that infants born to women with a psychiatric disease diagnosis are more likely to have a low birth weight or small size for gestational age compared to infants born to mothers from the general population without psychiatric illness.[161,165,167,168,169,170,171] • Schneid-Kofman et al. (2008)[167] conducted a large retrospective population-based study of deliveries (1988-2005) that compared women with and without psychiatric illness in Israel. They collected data from 181,479 deliveries; of these 607 (0.3%) women reported psychiatric illness including depressive and anxiety disorders (39%), schizophrenia (11%), or other psychiatric illness (50%). Obstetrical risk factors such as hypertensive disorders or gestational and pregestational diabetes were more prevalent among patients with psychiatric illness compared to those who did not report psychiatric problems. Psychiatric illness during pregnancy (compared to no psychiatric illness)

Table 2.7.3.2-1	**SVII.3.2-1: Details of Missing Information: Use in Pregnancy and Lactation**
	represented an independent risk factor for perinatal mortality (odds ratio (OR) 2.4, 95% CI 1.5-3.7, P<0.001), congenital malformations (OR 1.4, 95% CI 1.01-1.9, P=0.03), Apgar score of less than 7 at 1 minute (7.3% vs. 4.3%, P<0.001), low birth weight (15.8% vs. 9.6%; P<0.001) and a higher rate of fetal distress (3.5% vs. 1.8%, P=0.003). **Use of antipsychotics during pregnancy** • Boden et al. (2012)[172] investigated the risks of adverse pregnancy and birth outcomes for treated and untreated women with bipolar disorder. They conducted a population-based cohort study using data from a national Swedish cohort of 332,137 mothers. Women with a recorded diagnosis of bipolar disorder and a filled prescription for mood stabilizers (lithium, antipsychotics or anticonvulsants) during pregnancy were assigned to the "treated" group (n=320) and those without a recorded prescription were assigned to the "untreated" (n=554) group. Both groups were compared with the rest of the women giving birth (n=331,263). The results showed the risks of preterm birth to be increased by 50% for both treated and untreated women. In addition, women with untreated bipolar disorder (3.9% n=542) had an increased risk of giving birth to an infant with a congenital malformation (microcephaly) compared with 2.3% (324 844) of the women without bipolar disorder (OR 1.68, 95% CI 1.07-2.62). The corresponding values for the treated women were 3.3% (n=311) (OR 1.26, 95% CI 0.67-2.37). Furthermore, similar trends were observed for risks of newborns being small for gestational age. This study analysis of variations in outcomes did not support any significant differences between treated and untreated women. Several studies have investigated associations between adverse maternal and fetal outcomes and use of aripiprazole or other atypical antipsychotics treatment during pregnancy: • In a large Australian registry-based study (2005-2012)[173] 13% of the study cohort was exposed to aripiprazole in the first trimester, but none of the observed congenital anomalies were associated with aripiprazole use. • In a U.S. cohort study from the Medicaid Analytic Extract database (2000-2010), after adjusting for other factors, there was no overall association between maternal exposure to atypical antipsychotics and any fetal malformations (RR 1.05, 95% CI 0.96-1.16) or specifically with fetal cardiac malformations (RR 1.06, 95% CI 0.90- 1.24), remaining elevated only for risperidone.[174] • In a Canadian cohort study (2005-2009), there was no association between maternal exposure to aripiprazole and fetal malformations.[175]

Table 2.7.3.2-1	**SVII.3.2-1: Details of Missing Information: Use in Pregnancy and Lactation**
	• In the U.S. National Birth Defects Prevention Study (1997-2011), there was an association (cOR = 2.0) between early pregnancy use of atypical antipsychotics and conotruncal heart defects. No analyses were performed with regards specifically to aripiprazole exposure.[176] • In a French prospective multicenter cohort study (2004-2011) including 258 pregnant women, there was no statistically significant association between exposure to aripiprazole during embryogenesis (4-10 gestational weeks) and fetal malformations or fetal loss. However, because the study included relatively few outcomes, there was a low degree of confidence in the estimates of association (OR 2.30, 95% CI 0.32-16.7) for major malformations, (OR 1.66, 95% CI 0.63-4.38) for miscarriage. There was a significant association between maternal exposure to aripiprazole and prematurity (OR 2.57, 95% CI 1.06-6.27) and with foetal growth retardation (OR 2.97, 95% CI 1.23-7.16). The authors concluded that this study failed to demonstrate a significant association between aripiprazole exposure during the embryonic period and risk of major malformations.[177] Several studies have investigated whether aripiprazole is associated with an increased risk for gestational diabetes but, thus far, there has been no evidence of significant risk is present. • A U.S. study of non-diabetic pregnant women on Medicaid (2000-2010) who had at least 1 antipsychotic medication dispensed during the 3 months before pregnancy found no association with gestational diabetes. In this study women with 2 dispensings for antipsychotic medications during pregnancy were considered "continuers," while women with no dispensings during pregnancy were considered discontinuers. 4.8% of continuers for aripiprazole were eventually diagnosed with gestational diabetes compared to 4.5% in discontinuers.[178] • A 2017 study of 303 women exposed to atypical antipsychotics during their first trimester compared to 149 controls did not find any significant differences in risk for gestational diabetes.[179] **Pre-Clinical Program** • Pregnant rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (1 times, 3 times, and 10 times the oral MRHD of 30 mg/day on a mg/m2 body surface area) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 mg/kg and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased body weights (10 mg/kg and 30 mg/kg), and increased incidences of hepatodiaphragmatic

Table 2.7.3.2-1	**SVII.3.2-1: Details of Missing Information: Use in Pregnancy and Lactation**
	nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg. Postnatally, delayed vaginal opening was seen at 10 mg/kg and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg; however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity. • In pregnant rats receiving aripiprazole injection intravenously (3 mg/kg/day, 9 mg/kg/day, and 27 mg/kg/day) during the period of organogenesis, decreased fetal weight and delayed skeletal ossification were seen at the highest dose, which also caused some maternal toxicity. • Pregnant rabbits were treated with oral doses of 10 mg/kg/day, 30 mg/kg/day, and 100 mg/kg/day (2 times, 3 times, and 11 times human exposure at the oral MRHD of 30 mg/day based on AUC and 6 times, 19 times, and 65 times the oral MRHD of 30 mg/day based on mg/m2 body surface area) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 mg/kg and 100 mg/kg), increased incidence of a skeletal abnormality (fused sternebrae at 30 mg/kg and 100 mg/kg), and minor skeletal variations (100 mg/kg). • In pregnant rabbits receiving aripiprazole injection intravenously (3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day) during the period of organogenesis, the highest dose, which caused pronounced maternal toxicity, resulted in decreased fetal weight, increased fetal abnormalities (primarily skeletal), and decreased fetal skeletal ossification. The fetal no-effect dose was 10 mg/kg, which produced 5 times the human exposure at the oral MRHD based on AUC and is 6 times the oral MRHD of 30 mg/day based on mg/m2 body surface area. • In a study in which rats were treated with oral doses of 3 mg/kg/day, 10 mg/kg/day, and 30 mg/kg/day (1 times, 3 times, and 10 times the oral MRHD of 30mg/day on a mg/m^2 body surface area) of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths and decreases in pup weight (persisting into adulthood) and survival were seen at this dose. • In rats receiving aripiprazole injection intravenously (3 mg/kg/day, 8 mg/kg/day, and 20 mg/kg/day) from day 6 of gestation through day 20 postpartum, an increase in stillbirths was seen at 8 mg/kg and 20 mg/kg and decreases

Table 2.7.3.2-1	**SVII.3.2-1: Details of Missing Information: Use in Pregnancy and Lactation**
	in early postnatal pup weights and survival were seen at 20 mg/kg. These doses produced some maternal toxicity. There were no effects on postnatal behavioral and reproductive development. **Clinical Program** • In clinical trials conducted with aripiprazole, no pregnant or lactating women have been included. Pregnancy, or positive pregnancy test or breast-feeding was part of the exclusion criteria. Women who became pregnant during a clinical trial were withdrawn from the trial and treatment was discontinued. **Clinical Trial Safety Data** **Methodology** A review of the Otsuka clinical trials database was performed cumulatively up to 30 Nov 2021. The search criteria included PTs: SMQ: Pregnancy, labour and delivery complications and risk factors (excluding abortions and stillbirth), SMQ: Neonatal exposures via breast milk (MedDRA version 24.1) occurring in Otsuka-sponsored trials for all formulations of aripiprazole, excluding Abilify MyCite (tablet with ingestible event marker). **Abilify Results** Review of the Otsuka clinical trials database identified a total of 14 mother-associated events (12 cases). The most frequently reported mother-associated PTs included Pregnancy (n=4), Breast engorgement (n=3), Abortion induced (n=2), Abortion missed (n=1), Abortion spontaneous (n=1), Chloasma (n=1), Jaundice neonatal (n=1) and Unwanted pregnancy (n=1). Out of the 14 mother-associated events, 7 events were assessed as serious, and 7 events were assessed as non-serious. There were 3 mother-associated events considered related, 1 mother-associated event considered possible, 1 event considered possibly related, 2 events considered unlikely related, and 7 events considered not related by the investigator. The mother-associated events outcome was reported as recovered/resolved in 7 events, recovering/resolving in 1 event, not recovered/not resolved in 2 events, and the outcome was unknown/not reported in 4 events. Review of the Otsuka clinical trials database identified a total of 5 child-associated events (4 cases). The most frequently reported child-associated PTs included Gilbert's Syndrome (n=3) and Tourette's Disorder (n=2). Out of the 5 child-associated events, 3 events were assessed as serious, and 2 events were assessed as non-serious. There were 4 child-associated events considered not related and 1 event considered unlikely related by the investigator. The child-associated events outcome was reported as recovered/resolved in 2 events, not recovered/not resolved in 2 events, and recovered/resolved with sequelae in 1 event. **Demographics** Out of the 12 mother-associated cases, all 12 were female subjects with ages ranging from 21 to 48 years old. The mean age

Table 2.7.3.2-1	**SVII.3.2-1: Details of Missing Information: Use in Pregnancy and Lactation**
	(standard deviation) reported was 38.00 (±7.63). The median age was reported was 35. Out of the 4 child-associated cases, all 4 were male subjects with ages ranging from 12 to 16 years old. The mean age (standard deviation) reported was 13.75 (±1.71). The median age was reported was 13.5. **Analysis** Evaluation of the 14 mother-associated events revealed that 2 of the events were confounded by underlying medical conditions including a history of steatocystoma multiplex. A total of 3 of the mother-associated events were confounded by concomitant medications including bromperidol, brotizolam, lithium and quetiapine. A total of 9 of the mother-associated events had limited information which precluded a meaningful medical assessment of the events. Evaluation of the 5 child-associated events revealed that 3 child-associated events were confounded by concomitant medications including allopurinol, ziprasidone, clonazepam and quetiapine. Evaluation of 2 of the child-associated events had limited information. **Abilify Maintena Results** Review of the Otsuka clinical trials database identified a total of 5 mother-associated events (4 cases). The most frequently reported mother-associated PTs included Abortion spontaneous, (n=2), Steatocytoma multiplex (n=2) and Breast Engorgement (n=1). Out of the 5 mother-associated events, 2 events were assessed as serious, and 3 events were assessed as non-serious. There was 1 mother- associated event considered possibly related, 1 event unlikely related, 3 events considered not related by the investigator. The mother-associated events outcome was reported as recovered/resolving in 4 events and recovering/resolving in 1 event. Review of the Otsuka clinical trials database identified no child-associated events. **Demographics** Out of the 4 mother-associated cases, all 4 were female subjects with ages ranging from 23 to 49 years old. The mean age (standard deviation) reported was 36.5 years (±12.07). The median age was reported was 37 years. **Analysis** Evaluation of the 5 mother-associated events revealed that 2 of the events were confounded by underlying medical conditions including a history of steatocystoma multiplex. A total of 3 of the mother-associated events were confounded by concomitant medications including bromperidol, brotizolam, lithium and quetiapine.

Table 2.7.3.2-1	**SVII.3.2-1: Details of Missing Information: Use in Pregnancy and Lactation**
	Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe Results Review of the Otsuka clinical trials database identified no mother-associated or child-associated events. **<u>Post-Marketing Safety Data</u>** **Methodology** A review of the Otsuka clinical trials database was performed cumulatively up to 30 Nov 2021. The search criteria included PTs: SMQ: Pregnancy, labour and delivery complications and risk factors (excluding abortions and stillbirth), SMQ: Neonatal exposures via breast milk (MedDRA version 24.1) occurring in Otsuka-sponsored trials for all formulations of aripiprazole, excluding Abilify MyCite (tablet with ingestible event marker). **Abilify Results** A cumulative search of the safety database through 30 Nov 2021 identified a total of 2,296 mother-associated events (1,649 cases). The most frequently reported events were maternal exposure during pregnancy (n=1,555), caesarean section (n=168), premature delivery (n=97), exposure during pregnancy (n=73), gestational diabetes (n=59), pre-eclampsia (n=31), premature labour (n=26), morning sickness (n=25), twin pregnancy (n=25), premature rupture of membranes (n=22), maternal exposure before pregnancy (n=19), induced labor (n=15) and threatened labour (n=13). A cumulative search of the safety database through 30 Nov 2021 identified a total of 517 child-associated events (419 cases). The most frequently reported events were foetal exposure during pregnancy (n=385), exposure via breast milk (n=61), large for dates baby (n=22), breech presentation (n=15), maternal exposure during pregnancy (n=6), maternal exposure during breastfeeding (n=6) and paternal exposure time unspecified (n=4). **Demographics** Out of the 2,296 mother-associated events, all were female subjects with ages ranging from 12 to 64 years old. The mean age (standard deviation) was reported as 31.6 years (±6.55). The median age reported was 30.8 years. Out of the 1,066 child-associated events, there were a total of 313 females, 512 males, and 241 where the sex was not reported with ages ranging from 0 to 10 years old. The mean age (standard deviation) was reported as 3.72 years (±1.06). The median age reported was 1.12 years. **Analysis** Of the 2,296 mother-associated events, 553 events were assessed as serious and 1,743 were assessed as non-serious. There were 1,102 events assessed as related and 1,194 events assessed as not related by the investigator. The events were reported from 1,789 spontaneous sources, 414 clinical trial sources, and 93 literature sources. Event outcome was reported as not recovered/not

Table 2.7.3.2-1	**SVII.3.2-1: Details of Missing Information: Use in Pregnancy and Lactation**
	resolved in 11 events, recovered/resolved in 536 events, recovering/resolving in 7 events and unknown/not reported in 1,742 events. Of the 517 child-associated events, 85 events were assessed as serious, and 432 events were assessed as non-serious. There were 254 events assessed as related and 263 events assessed as not related by the investigator. The events were reported from 439 spontaneous sources, 75 clinical trial sources, and 3 literature sources. Event outcome of the 517 child-associated events was reported as not recovered/not resolved in 2 events, recovered/resolved in 45 events and unknown/not reported in 470 events. Evaluation of the 2,296 mother-associated events revealed 206 events were confounded by underlying medical history including tobacco abuse, type I diabetes mellitus, type II diabetes mellitus, hypertension, hyperthyroidism, porphyria, hypothyroidism, alcohol use, substance abuse, cerebrovascular accident, carcinoma, road traffic accident, rheumatoid arthritis, listeriosis, hyperprolactinemia, coagulation factor V level abnormal and thrombocytopenia and 675 events were confounded by concomitant medications including alprazolam, methylphenidate, risperidone, quetiapine, lithium, olanzapine, haloperidol, and heparin. There were 1,363 events which had limited information, which precluded a meaningful medical assessment of the events. In 51 of the 2,296 mother-associated events, the drug was either discontinued or the dose was reduced, and the event outcome was either resolved or resolving. There was 1 positive rechallenge where the role of aripiprazole could not be excluded. Evaluation of the 517 child-associated events revealed 22 were confounded by underlying medical history including obesity, alcohol use, substance abuse, tobacco use, type 1 diabetes mellitus, type II diabetes mellitus, anemia, coagulation disorder and metabolic disorder. There were 64 events which were confounded by concomitant medication including flunitrazepam, lithium, olanzapine, quetiapine, and risperidone. There were 427 events with limited information, which precluded a meaningful medical assessment of the events. In 4 of the 517 child-associated events, the drug was either discontinued or the dose reduced, and the event outcome was either resolved or resolving. There was no positive rechallenge events. **Abilify Maintena Results** A cumulative search of the safety database through 30 Nov 2021 identified a total of 353 mother-associated events (310 cases). The most frequently reported PTs included maternal exposure during pregnancy (n=274), exposure during pregnancy (n=29), maternal exposure before pregnancy (n=8), premature delivery (7) and premature labor (n=7). Out of the 353 events, 28 events were assessed as serious, and 325 events were assessed as non-serious. There were 55 events considered related and 298 events

Table 2.7.3.2-1	**SVII.3.2-1: Details of Missing Information: Use in Pregnancy and Lactation**
	considered not related by the investigator. Event outcome was reported as recovered/resolved in 33 events, not recovered/not resolved in 6 events, recovering/resolving in 1 event and outcome unknown/not reported in 313 events. A cumulative search of the safety database through 30 Nov 2021 identified a total of 42 child-associated events (26 cases). The most frequently reported events were foetal exposure during pregnancy (n=15), exposure via breast milk (n=7), maternal exposure during breastfeeding (n=1), large for dates baby (n=1), umbilical cord around neck (n=1), exposure via father (n=1) and forceps delivery (n=1). Of the 42 child-associated events, 12 were assessed as serious and 30 events were assessed as non-serious. There were 19 events assessed as related and 23 events assessed as not related by the investigator. The events were reported from 30 spontaneous sources, 9 clinical trial sources, and 3 literature sources. Event outcomes of the 42 child-associated events were reported as fatal in 1 event, not recovered/not resolved in 4 events, recovered/resolved in 5 events and unknown in 32 events. **Demographics** Out of the 353 mother-associated cases, all were female subjects with ages ranging from 15 to 50 years old. The mean age (standard deviation) reported was 30.5 (±6.67). The median age reported was 27. Out of the 42 child-associated events, there were a total of 7 females, 18 males, and 17 where the sex was not reported with ages ranging from less than 1 to 6 years old. The mean age (standard deviation) was reported as 2.27 (±1.80). The median age reported was 2.82. **Analysis** Evaluation of the 353 mother-associated events revealed 58 were confounded by underlying medical history including trauma during pregnancy, hepatitis C, HIV, sickle cell anemia, obesity, alcohol use, substance abuse, tobacco use, pancreatitis acute, type 1 diabetes mellitus, type II diabetes mellitus, coagulation disorder, and metabolic disorder. There were 57 events which were confounded by concomitant medication including buprenorphine, divalproex, haloperidol, lithium, olanzapine, quetiapine, and risperidone. There were 289 events with limited information which precluded a meaningful medical assessment of the events. In 11 of the 415 mother-related events, the drug was either discontinued or the dose reduced, and the event outcome was either resolved or resolving. There were no positive rechallenge events.

Table 2.7.3.2-1	**SVII.3.2-1: Details of Missing Information: Use in Pregnancy and Lactation**
	Evaluation of the 42 child-associated events revealed 2 were confounded by underlying medical history including alcohol use, substance abuse, and tobacco use. There were 2 events which were confounded by concomitant medication including haloperidol and clozapine. There were 35 events with limited information, which precluded a meaningful medical assessment of the events. In 3 of the 42 child-related events, the drug was either discontinued or the dose reduced, and the event outcome was either resolved or resolving. There was no positive rechallenge events. The comprehensive review of clinical trials data, post marketing data and available literature did not show evidence supporting a causal relationship between exposure to aripiprazole and development of congenital malformations. Due to insufficient safety information in humans and concerns raised by animal product studies, use in pregnant women is not recommended as discussed in Section 4.6 of the current SmPC and Section 2 of Package leaflet for Abilify and Abilify Maintena and CCDS. The MAH will continue to monitor reports of exposure during pregnancy and lactation as part of routine pharmacovigilance activities.

Table 2.7.3.2-2	**SVII.3.2-2: Details of Missing Information: Use in Elderly Patients Above 65 Years of Age (Abilify Maintena only)**
MedDRA Terms	The search criteria was defined as any cases reporting elderly as the age group or any cases with patients 65 years and older.
Evidence Source(s)	**Abilify Maintena and Other Long-Acting Injectable Formulations of Antipsychotics** There is little evidence for a difference in effectiveness or a difference in the side of effect profile of long-acting antipsychotics compared to their shorter-acting counterparts. Direct comparisons of long- and short-acting antipsychotics are challenging because baseline risk factors are likely to differ comparing those prescribed long- compared to short-acting antipsychotics (e.g., severity of psychosis, social/environmental factors, non-adherence). **Among younger patients** • Llácer et al. 2019 studied the relationship between hyperprolactinemia and LAI formulations of various antipsychotics in 165 patients (67 patients 18 to 45 years old, 38 patients 45+ years old) with psychosis. LAI paliperidone and risperidone presented with the highest levels of hyperprolactinemia. No cases of hyperprolactinemia were found among patients treated with aripiprazole.[180] • Fernández-Miranda et al. 2021 performed a 5-year follow-up of patients with severe schizophrenia (n = 688, mean age: 43 years old, SD: 11.4 years) treated with LAI vs. oral antipsychotics. They found that both treatment retention and the number of subsequent hospital admissions improved in patients on LAI antipsychotics compared to those on oral

Table 2.7.3.2-2	**SVII.3.2-2: Details of Missing Information: Use in Elderly Patients Above 65 Years of Age (Abilify Maintena only)**
	formulations. The study did not report any specific findings with regards to aripiprazole.[181] • Taipale et al. 2018 investigated the association between treatment type and all-cause mortality in schizophrenia patients between the ages of 16 and 64 in Sweden (n=4,603). The lowest cumulative mortality was observed in patients treated with LAI atypical antipsychotics compared to those using LAI first generation antipsychotics, oral atypical antipsychotics, oral first-generation antipsychotics, or those not treated with antipsychotics. The study did not report any findings with regards to aripiprazole.[182] • Yan et al. 2018 compared the use of various LAI antipsychotics in patients with bipolar I disorder (mean age: 38 years old, SD: 14.8 years). The odds for hospitalization were significantly lower in patients treated with LAI aripiprazole compared to those treated with either LAI haloperidol or LAI risperidone.[183] • Calabrese et al. 2018 found that LAI aripiprazole increased time to hospitalization for mood-related episodes in patients with bipolar I disorder compared to placebo (n = 266, age range 18 to 65 years old).[184] • Fleischhacker et al. 2014 performed a 38-week non-inferiority RCT comparing LAI aripiprazole to oral aripiprazole in patients ages 18 to 60 years old. They concluded that LAI aripiprazole was non-inferior to oral aripiprazole.[185] • Schöttle et al. 2020 studied schizophrenia patients after switching from oral aripiprazole to LAI aripiprazole (n=243, mean age: 43.1 years old, SD: 15.1 years). They found that patients younger than 35 years old reported greater subjective improvements in well-being compared to those older than 35 years old.[186] • Lauriello et al. 2015 investigated long-term adverse effects of aripiprazole lauroxil in patients with schizophrenia (mean age: 39 years old, age range 18 to 79 years old). In the first year, 12.8% of patients developed EPS. Rates of adverse effects did not change past 52 weeks until the follow-up end at 130 weeks. The study did not report any findings stratified by age.[187] **Among patients 65 years old or more** • Lin et al. (2020) studied the effectiveness of LAI antipsychotics versus oral antipsychotics in elderly patients (over 60 years old) with schizophrenia for 1 year after hospital discharge. Patients treated with LAI antipsychotics had a lower rehospitalization rate and a longer time to rehospitalization compared to those treated with oral antipsychotics. The study did not report any findings with regards to aripiprazole.[188]

Table 2.7.3.2-2	**SVII.3.2-2: Details of Missing Information: Use in Elderly Patients Above 65 Years of Age (Abilify Maintena only)**
	• Suzuki and Hibino (2021) performed a retrospective cohort study of patients with schizophrenia who received LAI antipsychotics between 2009 and 2017 at Fukui Kinen Hospital (n = 68, mean age 65 to 70 years old). LAI aripiprazole had a significantly higher treatment continuation rate than LAI risperidone.[189] • Targum et al. (2017) performed a 12-week RCT comparing LAI aripiprazole to placebo and stratified the response by age group (< 30 years old, 30 to 39 years old, 40 to 49 years old, 50 to 69 years old). Patients treated with LAI aripiprazole showed improvement in Positive and Negative Syndrome Scale (PANSS) scores compared to placebo and this improvement was not modified by age.[190] **Abilify Maintena Completed Clinical Trials** • In clinical trials conducted with aripiprazole IM depot, only a very limited number of elderly patients above 65 years of age have been included. The safety and efficacy of aripiprazole IM depot has not been established in patients above 65 years of age. **Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe Completed Clinical Trials** • In clinical trials conducted with aripiprazole IM depot, the safety and efficacy of aripiprazole IM depot has not been established in patients above 65 years of age. **Post-Marketing Safety Data** **Methodology** A review of the Otsuka safety database was performed for all the cases reported with Abilify Maintena cumulatively up to 30 Nov 2021. **Results** 1,796 events (672 cases) were observed in elderly patients above 65 years of age. The most frequently reported PTs included Product use in unapproved indication (n=73), inappropriate schedule of product administration (64), prescribed underdose (n=53), off label use (n=52), no adverse event (n=38), underdose (n=38), drug ineffective (n=30), tremor (n=27), extrapyramidal disorder (n=26) and product use issue (n=25). Out of 672 cases, 502 cases were reported from spontaneous sources, 157 from clinical trials, and 13 from literature. Out of 1,796 events, 434 events were assessed as serious, and 1362 events were assessed as non-serious. There were 1,135 events considered related and 661 events were considered not related. In 80 events, the outcome was reported as fatal. Whereas event outcome was reported as resolved in 181 events, resolved with sequelae in 2 events, resolving in 98 events, not resolved in 259 events, and unknown in 1,176 events.

Table 2.7.3.2-2	**SVII.3.2-2: Details of Missing Information: Use in Elderly Patients Above 65 Years of Age (Abilify Maintena only)**
	Demographics Out of the 672 cases, 408 were female, 236 were male and in 26 cases gender was unknown with ages ranging from 65 to 99 years old. The mean age (standard deviation) reported was 80 (±9.3). The median age (interquartile range) reported was 79.5 (14.5). **Analysis** Evaluation of 1,796 events revealed the most frequently reported system organ classes (SOCs): Injury, poisoning and procedural complications (n=349, 19.43%), General disorders and administration site conditions (n=108, 6.01%) and Nervous system disorders (n=107, 5.96%). The trend has been found that, 19.43% of events reported within the SOC Injury, poisoning and procedural complications included the following PTs: inappropriate schedule of product administration (n=64), incorrect dose administered (n=21), off label use (n=52), prescribed underdose (n=53), product dose omission issue (n=23), product use in unapproved indication (n=73), product use issue (n=25) and underdose (n=38). This is consistent with product labeling as the safety and efficacy of Abilify Maintena in the treatment of schizophrenia for patients 65 years and older has not been established and Abilify Maintena is currently not indicated for the elderly population.

Table 2.7.3.2-2	**SVII.3.2-2: Details of Missing Information: Use in Elderly Patients Above 65 Years of Age (Abilify Maintena only)**
	Out of the 64 events reported for the PT inappropriate schedule of product administration, 39 were from non-interventional trials and majority of the events were reported from Japan (n=26) followed by Canada (n=14). Review of the inappropriate schedule of product administration events identified that there was variability of dosing intervals. Out of the 21 events reported for the PT incorrect dose administered, 2 were from non-interventional trials and majority of the events were reported from United Kingdom (n=8). Out of the 53 events reported for the PT prescribed underdose, 39 were from spontaneous sources and majority of the events were reported from United States (n=14) followed by Canada (n=12). Out of the 38 events reported for the PT underdose, all were from spontaneous sources and majority of the events were reported from Canada (n=11) followed by United States (n=11). The events of incorrect dose administration, underdose and prescribed underdose referred to low drug administration. Out of the 23 events reported for the PT product dose omission issue, 17 were from spontaneous sources and majority of the events were reported from United States (n=19). Out of the 52 events reported for the PT off label use, 45 were from spontaneous sources and majority of the events were from United States (n=13) followed by United Kingdom (n=8). Out of the 72 events reported for the PT product use in unapproved indication, 62 were from spontaneous sources and majority of the events were from United States (n=23) followed by United Kingdom (n=18). Off label use and product use in unapproved indication events of Abilify Maintena were used for the following indications: schizophrenia, schizoaffective disorder, bipolar I disorder, mania, schizoaffective disorder, agitation, Cotard's syndrome, delusional disorder unspecified type, delusion of parasitosis, psychotic disorder, depression, anxiety, affective disorder/mood stabilization, mood swings, delirium, paranoid psychosis with delusions, mental disorder, bipolar disorder, schizophrenia, schizoaffective disorder, major depression, psychotic disorder, post-traumatic stress disorder, affective disorder, and dementia. Out of the 25 events reported for the PT product use issue, 16 were from spontaneous sources and majority of the events were from Canada (n=11). The product use issue events referred to the use of Abilify Maintena in patients ages more than 65 years old which is expected as Abilify Maintena is currently not approved for elderly use.
	Based on the cumulative assessment of the safety information of aripiprazole and safety concerns for the elderly population, the MAH has concluded that the experience from use of Abilify Maintena IM depot in elderly patients above 65 years of age remains limited. Use in elderly patients is addressed in Section 4.2, Section 4.4 and Section 5.2 of the current SmPC, is listed in the Package Leaflet and is included in CCDS Section 5.2.3 Geriatric Use for aripiprazole and no further risk minimization measures are needed. Abilify Maintena use in elderly above 65 years of age remains classified as a safety concern due to missing information.

2.8 Module SVIII: Summary of the Safety Concerns

Aripiprazole has been studied in a comprehensive nonclinical and clinical program and found to have a safety profile similar to that of other atypical antipsychotic agents. The consistency of results across diverse studies and across demographic subpopulations suggests a stable profile that will be broadly applicable to the schizophrenia and bipolar mania populations in the marketplace.

Important identified and potential risks and missing information applicable to aripiprazole oral formulation and aripiprazole solution for injection (IM) are presented in Table 2.8-1.

Table 2.8-1 SVIII-1: Summary of Ongoing Safety Concerns-Abilify	
Important Identified Risks	EPS, including tardive dyskinesia
Important Potential Risks	Orthostatic hypotension
Missing Information	Use in pregnancy and lactation

Important identified and important potential risks and missing information applicable to aripiprazole IM depot are presented in Table 2.8-2.

Table 2.8-2 SVIII-2: Summary of Ongoing Safety Concerns-Abilify Maintena	
Important Identified Risks	EPS, including tardive dyskinesia
Important Potential Risks	Orthostatic hypotension
Missing Information	Use in pregnancy and lactation Use in elderly patients above 65 years of age

Post-marketing data has not identified any additional identified or potential risks after routine evaluation.

Overall, aripiprazole demonstrates a favorable benefit/risk profile in the adult schizophrenia and bipolar mania programs and in the paediatric schizophrenia and bipolar mania programs. Although the safety profile of aripiprazole is favorable, the MAH recognizes the need to continue to manage risks that may occur during the course of treatment with aripiprazole.

3 PART III: PHARMACOVIGILANCE PLAN (Including Postauthorisation Safety Studies)

The MAH maintains systems and standard practices for Routine Pharmacovigilance activities to collect reports of suspected adverse reactions (including spontaneous reports, reports from clinical studies, reports of pregnancy/lactation exposures, overdoses and medication errors); prepare reports for regulatory authorities (e.g., individual case safety reports, periodic safety update reports, etc.), and maintain continuous monitoring of the safety profile of approved products (including signal detection, issue evaluation, updating of labelling, and liaison with regulatory authorities). The MAH maintains a Pharmacovigilance System Master File which contains details of these systems and standard practices.

3.1 III.1: Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

There are no routine PV activities beyond adverse reactions reporting and signal detection for Abilify and Abilify Maintena.

3.2 III.2: Additional Pharmacovigilance Activities

The Sponsor has concluded a long-term safety study (Study 31-10-270) and PASS study 15893N. Information regarding completed studies is included in Annex 2: Tabulated Summary of Planned, Ongoing and Completed Pharmacovigilance Study Programme.

There are no additional pharmacovigilance activities for aripiprazole products Abilify and Abilify Maintena.

3.3 III.3: Summary Table of Additional Pharmacovigilance Activities

There are no ongoing or planned additional pharmacovigilance activities for Abilify and Abilify Maintena.

4 PART IV: PLANS FOR POSTAUTHORISATION EFFICACY STUDIES

There are no postauthorisation efficacy studies planned or ongoing for aripiprazole.

5 PART V: RISK MINIMISATION MEASURES (including evaluation of the effectiveness of risk minimisation activities)

For identified safety concerns, the product label communicates the risk for the approved indications. Risk minimization measures are planned for each important identified or potential risk and missing information as described in tables in Section 5.1.

5.1 V.1: Routine Risk Minimisation Measures

The risk minimization measures for safety concerns are presented in Table 5.1-1 for Abilify and Table 5.1-2 for Abilify Maintena.

Table 5.1-1 V.1-1: Description of Routine Risk Minimisation Measures by Safety Concern for Abilify

Safety Concern	Routine Risk Minimisation Activities
EPS, Including Tardive Dyskinesia	Routine risk communication: - Special warnings and precautions for use, section 4.4 of the SmPC - Undesirable effects, section 4.8 of the SmPC and section 4 of the Package Leaflet - Medicinal product subject to medicinal prescription
Orthostatic Hypotension	Routine risk communication: - Special warnings and precautions for use, section 4.4 of the SmPC - Undesirable effects, section 4.8 of the SmPC and section 4 of the Package Leaflet - Medicinal product subject to medicinal prescription
Use in Pregnancy and Lactation	Routine risk communication: - Fertility, pregnancy and lactation, section 4.6 of the SmPC and section 2 of the Package Leaflet - Medicinal product subject to medicinal prescription

Table 5.1-2 V.1-2: Description of Routine Risk Minimisation Measures by Safety Concern for Abilify Maintena

Safety Concern	Routine Risk Minimisation Activities
EPS, Including Tardive Dyskinesia	Routine risk communication: - Special warnings and precautions for use, section 4.4 of the SmPC - Undesirable effects, section 4.8 of the SmPC and section 4 of the Package Leaflet - Medicinal product subject to medicinal prescription
Orthostatic Hypotension	Routine risk communication: - Undesirable effects, section 4.8 of the SmPC and sections 2 and 4 of the Package Leaflet - Medicinal product subject to medicinal prescription

Table 5.1-2	**V.1-2: Description of Routine Risk Minimisation Measures by Safety Concern for Abilify Maintena**
Safety Concern	**Routine Risk Minimisation Activities**
Use in Pregnancy and Lactation	Routine risk communication: - Fertility, pregnancy and lactation, section 4.6 of the SmPC and section 2 of the Package Leaflet - Medicinal product subject to medicinal prescription
Use in Elderly Patients above 65 Years of Age	Routine risk communication: - Posology and method of administration, section 4.2 of the SmPC - Special warnings and precautions for use, section 4.4 of SmPC and section 2 of the Package Leaflet - Medicinal product subject to medicinal prescription

5.2 V.2: Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Section 5.1 are sufficient to manage the safety concerns of Abilify, and Abilify Maintena.

5.3 V.3: Summary of Risk Minimisation Measures

Table 5.3-1	**V.3-1: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern- Abilify**	
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
EPS, Including Tardive Dyskinesia	Routine risk minimisation measures: - Special warnings and precautions for use, section 4.4 of the SmPC - Undesirable effects, section 4.8 of the SmPC and section 4 of the Package Leaflet - Medicinal product subject to medicinal prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Orthostatic Hypotension	Routine risk minimisation measures: - Special warnings and precautions for use, section 4.4 of the SmPC - Undesirable effects, section 4.8 of the SmPC and section 4 of the Package Leaflet - Medicinal product subject to medicinal prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Use in Pregnancy and Lactation	Routine risk minimisation measures: - Fertility, pregnancy and lactation, section 4.6 of the SmPC - Medicinal product subject to medicinal prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

Table 5.3-2	**V.3-2: Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern- Abilify Maintena**	
Safety Concern	**Risk Minimisation Measures**	**Pharmacovigilance Activities**
EPS, Including Tardive Dyskinesia	Routine risk minimisation measures: - Special warnings and precautions for use, section 4.4 of the SmPC - Undesirable effects, section 4.8 of the SmPC and section 4 of the Package Leaflet - Medicinal product subject to medicinal prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Orthostatic Hypotension	Routine risk minimisation measures: - Undesirable effects, section 4.8 of the SmPC and sections 2 and 4 of the Package Leaflet - Medicinal product subject to medicinal prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Use in Pregnancy and Lactation	Routine risk minimisation measures: - Fertility, pregnancy and lactation, section 4.6 of the SmPC and section 2 of the Package Leaflet - Medicinal product subject to medicinal prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.
Use in Elderly Patients above 65 Years of Age	Routine risk minimisation measures: - Posology and method of administration, section 4.2 of the SmPC - Special warnings and precautions for use, section 4.4 of SmPC and section 2 of the Package Leaflet - Medicinal product subject to medicinal prescription	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None. Additional pharmacovigilance activities: None.

6 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

6.1 VI.1: Summary of the Risk Management Plan for Abilify

This is a summary of the risk management plan (RMP) for Abilify. The RMP details important risks of Abilify, how these risks can be minimised, and how more information will be obtained about Abilify's risks and uncertainties (missing information).

Abilify's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Abilify should be used.

This summary of the RMP for Abilify should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Abilify's RMP.

6.1.1 I: The Medicine and What it is Used for

Aripiprazole (Abilify) is authorised for treatment of schizophrenia in adults and in adolescents aged 15 years and older, treatment of moderate to severe manic episodes in Bipolar I Disorder and the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment, treatment up to 12 weeks of moderate to severe manic episodes in Bipolar I Disorder in adolescents aged 13 years and older and for rapid control of agitation and disturbed behaviours in patients with schizophrenia or in patients with manic episodes in Bipolar I Disorder, when oral therapy is not appropriate (see SmPC for the full indication). It contains aripiprazole as the active substance, and it is given orally or intramuscularly (IM). Forms and strengths are as follows:

Oral use

- Abilify tablets: 5 mg, 10 mg, 15 mg, and 30 mg
- Abilify orodispersible tablets: 10 mg, 15 mg and 30 mg
- Abilify oral solution: 1 mg/mL

Intramuscular use

- Abilify solution for injection: 7.5 mg/mL

Further information about the evaluation of Abilify's benefits can be found in Abilify's EPAR, including in its plain-language summary, available on the European Medicines Agency's (EMA's) website under the medicine's webpage.

6.1.2 II: Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Abilify together with measures to minimise such risks and the proposed studies for learning more about Abilify's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures. In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Abilify is not yet available, it is listed under "missing information" below.

6.1.2.1 II.A: List of Important Risks and Missing Information

Important risks of Abilify are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Abilify. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 6.1.2.1-1 II.A-1: List of Important Risks and Missing Information-Abilify

Important Identified Risks	• EPS, including tardive dyskinesia
Important Potential Risks	• Orthostatic hypotension
Missing Information	• Use in Pregnancy and Lactation

6.1.2.2 II.B: Summary of Important Risks

Table 6.1.2.2-1 II.B-1: Important Identified Risk-EPS, including tardive dyskinesia	
Evidence for linking the risk to the medicine	EPS, including tardive dyskinesia is an important identified risk based upon data from the aripiprazole clinical development program, post-marketing experience, and the therapeutic drug class.
Risk factors and risk groups	***EPS Risk Factors*** Established risk factors for EPS include exposure to antipsychotic treatments (with risk varying according to the agent type and dose), advanced age, male gender, alcohol and substance abuse, use of concomitant medications, and diabetes.[151] ***Tardive Dyskinesia Risk Factors*** Established risk factors for tardive dyskinesia include antipsychotic treatment, the presence or history of EPS, advanced age, cognitive difficulties, alcohol, and substance abuse, use of concomitant medications, and diabetes.[143,152,153,154]
Risk minimisation measures	**Routine risk minimisation measures:** - Special warnings and precautions for use, section 4.4 of the SmPC - Undesirable effects, section 4.8 of the SmPC and section 4 of the Package Leaflet - Medicinal product subject to medicinal prescription **Additional risk minimisation measures:** None.

Table 6.1.2.2-2 II.B-2: Important Potential Risk-Orthostatic hypotension	
Evidence for linking the risk to the medicine	Orthostatic hypotension is an important potential risk based upon data from the aripiprazole clinical development program, and post-marketing experience.
Risk factors and risk groups	Established risk factors for orthostatic hypotension are listed below: • Advanced age Use of psychotropic medications (e.g., dopaminergic drugs, antidepressants, neuroleptic agents)[125] • Use of antianginal drugs or antihypertensive and vasodilator therapy[124] • Medical conditions, including hypovolemia, defects of vasomotor reflexes, and autonomic nervous system dysfunction (as may occur in diabetes and Parkinsonism). Drug-induced orthostatic hypotension remains a concern[125,130]

Table 6.1.2.2-2 II.B-2: Important Potential Risk-Orthostatic hypotension	
	• Prolonged and severe orthostatic hypotension has been associated with stroke and myocardial infarction[131] • Drug-induced orthostatic hypotension and elderly patients: o Orthostatic hypotension is associated with significant morbidity and mortality, especially elderly patients in acute-care settings[124] ranging from mild symptoms (dizziness) to severe symptoms, such as syncope (leading to fractures or other injuries and immobility)[131] o Approximately one third of all falls in nursing homes are attributed to psychotropic drug use.[132]
Risk minimisation measures	**Routine risk minimisation measures:** - Special warnings and precautions for use, section 4.4 of the SmPC - Undesirable effects, section 4.8 of the SmPC and section 4 of the Package Leaflet - Medicinal product subject to medicinal prescription **Additional risk minimisation measures:** None.

Table 6.1.2.2-3 II.B-3: Missing Information: Use in Pregnancy and Lactation	
Risk minimisation measures	**Routine risk minimisation measures:** - Fertility, pregnancy and lactation, section 4.6 of the SmPC - Medicinal product subject to medicinal prescription **Additional risk minimisation measures:** None

6.1.2.3 II.C: Post-authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Abilify.

II.C.2 Other Studies in Post-authorisation Development Plan

There are no ongoing or planned additional studies required for Abilify.

6.2 VI.2: Summary of the Risk Management Plan for Abilify Maintena

This is a summary of the risk management plan (RMP) for Abilify Maintena. The RMP details important risks of Abilify Maintena, how these risks can be minimised, and how more information will be obtained about Abilify Maintena risks and uncertainties (missing information).

Abilify Maintena's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Abilify Maintena should be used.

This summary of the RMP for Abilify Maintena should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Abilify Maintena's RMP.

6.2.1 I: The Medicine and What it is Used for

Aripiprazole (Abilify Maintena) is authorised for maintenance treatment of schizophrenia in adult patients stabilised with oral aripiprazole (see SmPC for the full indication). It contains aripiprazole as the active substance, and it is given intramuscularly in 300 mg/vial or pre-filled dual chamber syringe and 400 mg/vial or pre-filled dual chamber syringe.

Abilify Maintena 720/960 mg prolonged-release suspension for injection in pre-filled syringe, a once every two-month injection, is indicated for maintenance treatment of schizophrenia in adult patients stabilised with aripiprazole. It contains aripiprazole as the active ingredient and is available as a 960 mg prolonged-release suspension for injection in pre-filled syringe and a 720 mg prolonged-release suspension for injection in pre-filled syringe to be administered by gluteal intramuscular injection.

Further information about the evaluation of Abilify Maintena's benefits can be found in Abilify Maintena's EPAR, including in its plain-language summary, available on the European Medicines Agency's (EMA's) website under the medicine's webpage.

6.2.2 II: Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of Abilify Maintena together with measures to minimise such risks and the proposed studies for learning more about Abilify Maintena risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures. In addition to these measures, information about adverse reactions is collected continuously and regulatory analysed so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of Abilify Maintena is not yet available, it is listed under "missing information" below.

6.2.2.1 II.A List of Important Risks and Missing Information

Important risks of Abilify Maintena are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Abilify Maintena. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 6.2.2.1-1 II.A-1: List of Important Risks and Missing Information-Abilify Maintena

Important Identified Risks	• EPS, including tardive dyskinesia
Important Potential Risks	• Orthostatic hypotension
Missing Information	• Use in Pregnancy and Lactation • Use in Elderly Patients above 65 Years of Age

6.2.2.2 II.B Summary of Important Risks

Table 6.2.2.2-1 II.B-1: Important Identified Risk-EPS, including tardive dyskinesia	
Evidence for linking the risk to the medicine	EPS, including tardive dyskinesia is an important identified risk based upon data from the aripiprazole clinical development program, post-marketing experience, and the therapeutic drug class.
Risk factors and risk groups	***EPS Risk Factors*** Established risk factors for EPS include exposure to antipsychotic treatments (with risk varying according to the agent type and dose), advanced age, male gender, alcohol and substance abuse, use of concomitant medications, and diabetes.[151] ***Tardive Dyskinesia Risk Factors*** Established risk factors for tardive dyskinesia include antipsychotic treatment, the presence or history of EPS, advanced age, cognitive difficulties, alcohol, and substance abuse, use of concomitant medications, and diabetes.[143,152,153,154]
Risk minimisation measures	**Routine risk minimisation measures:** - Special warnings and precautions for use, section 4.4 of the SmPC - Undesirable effects, section 4.8 of the SmPC and section 4 of the Package Leaflet - Medicinal product subject to medicinal prescription **Additional risk minimisation measures:** None.

Table 6.2.2.2-2 II.B-2: Important Potential Risk-Orthostatic hypotension	
Evidence for linking the risk to the medicine	Orthostatic hypotension is an important potential risk based upon data from the aripiprazole clinical development program, and post-marketing experience.
Risk factors and risk groups	Established risk factors for orthostatic hypotension are listed below: • Advanced age Use of psychotropic medications (e.g., dopaminergic drugs, antidepressants, neuroleptic agents)[125] • Use of antianginal drugs or antihypertensive and vasodilator therapy[124] • Medical conditions, including hypovolemia, defects of vasomotor reflexes, and autonomic nervous system dysfunction (as may occur in diabetes and Parkinsonism). Drug-induced orthostatic hypotension remains a concern[125,130] • Prolonged and severe orthostatic hypotension has been associated with stroke and myocardial infarction[131] • Drug-induced orthostatic hypotension and elderly patients: o Orthostatic hypotension is associated with significant morbidity and mortality, especially elderly patients in acute-care settings[124] ranging from mild symptoms (dizziness) to severe symptoms, such as syncope (leading to fractures or other injuries and immobility)[131] Approximately one third of all falls in nursing homes are attributed to psychotropic drug use.[132]
Risk minimisation measures	**Routine risk minimisation measures:** - Undesirable effects, section 4.8 of the SmPC and sections 2 and 4 of the Package Leaflet - Medicinal product subject to medicinal prescription **Additional risk minimisation measures:** None.

Table 6.2.2.2-3 II.B-3: Missing Information: Use in Pregnancy and Lactation	
Risk minimisation measures	**Routine risk minimisation measures:** - Fertility, pregnancy and lactation, section 4.6 of the SmPC and section 2 of the Package Leaflet - Medicinal product subject to medicinal prescription **Additional risk minimisation measures:** None

Table 6.2.2.2-4 II.B-4 Missing Information: Use in Elderly Patients above 65 Years of Age	
Risk minimisation measures	**Routine risk minimisation measures:** - Posology and method of administration, section 4.2 of the SmPC - Special warnings and precautions for use, section 4.4 of SmPC and section 2 of the Package Leaflet - Medicinal product subject to medicinal prescription **Additional risk minimisation measures:** None

6.2.2.3 II.C Post-authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Abilify Maintena.

II.C.2 Other Studies in Post-authorisation Development Plan

There are no ongoing or planned additional studies required for Abilify Maintena.

7 PART VII: ANNEXES TO THE RISK MANAGEMENT PLAN

7.4 Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Not Applicable

7.6 Annex 6: Details of Proposed Additional Risk Minimisation Activities (if applicable)

Not Applicable