AstraZeneca

Non-Interventional Study (NIS) Report	
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Prospective, observational study for the maintenance treatment of patients with Bipolar Disorder I and II in Greece: The 'REMINDER' Study

Study dates:	**First Subject In:** 30 September 2010 **Last Subject Last Visit:** 14 November 2011

1. OBJECTIVES

The current study was designed to evaluate the effectiveness of administered maintenance treatments in bipolar disorder I and II, in the real life clinical setting in Greece. Additionally, it aimed at describing the management and outcome of both acute phase and relapse episodes of bipolar disorder as well as assessing the duration of normothymic periods in patients who have been treated with at least one atypical antipsychotic medicine for the mood episode.

1.1 Primary Objective

- Evaluation of the efficacy of administered maintenance treatments in bipolar disorder I and II, defined as the percentage of patients who will experience a relapse episode during the first 9 months after a mood event (manic or depressive).

1.2 Secondary Objectives

- The evaluation of the duration of normothymia in patients with bipolar disorder I and II who have been treated with at least one atypical antipsychotic medicine for the mood episode
- The description of administered treatments for the management of the acute phase of bipolar disorder and the duration of time until the management of a mood episode (manic or depressive)
- The description of management of relapse episodes in patients previously receiving treatment during the maintenance phase.

2. STUDY DESIGN AND SELECTION CRITERIA

2.1 Study Design

This was a 9-month prospective, observational study. In this observational study, 294 outpatients diagnosed with bipolar disorder I or II (as per DSM-IV) were enrolled.

2.2 Selection Criteria

Inclusion criteria

For inclusion in the study subjects had to fulfil all of the following criteria:

- Provision of informed consent prior to study participation

- Outpatients, male and female, aged 18 to 65 years (inclusive)
- Diagnosis of bipolar disorder I or II (as per DSM-IV), with or without rapid cycling
- Subjects who have been treated with at least one atypical antipsychotic for the management of an acute mood event (manic or depressive) as monotherapy or in combination with other medication
- Subjects who experienced the last acute mood episode during the last 2 months and are in normothymic state (YMRS score ≤12 and HAM-D score ≤12) for at least two weeks.

Exclusion criteria

Any of the following was regarded as a criterion for exclusion from the study:

- Subjects fulfilling criteria for diagnosis of any other psychiatric condition (except from bipolar disorder I or II), as per DSM-IV Axis I, concomitant organic mental disorder or mental retardation
- Substance abuse or dependence (with the exception of nicotine dependence), as defined by DSM-IV criteria
- Subjects who have received treatment with a depot during the last month
- Participation in another study
- Inability of subjects to comply with the study protocol.
- Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

3. TARGET PATIENT POPULATION, STUDY DISEASE (IF APPLICABLE) AND SAMPLE SIZE

Overall 294 patients diagnosed with bipolar disorder I or II, fulfilling the study-specific eligibility criteria, were enrolled in the study.

4. CRITERIA FOR EVALUATION (MAIN VARIABLES)

4.1 Primary Outcome Variable

The primary outcome variable in the present study is the proportion of patients (n, %) who experienced a relapse episode (manic, hypomanic, depressive, mixed) during the first 9 months after a mood event (last mood episode prior to enrolment into the study).

4.2 Secondary Outcome Variables

The secondary outcome variables in the present study are the following:

- Duration of normothymic period [mean (+/-SD) days and/or months] (defined as the period that the patient remained in normothymic state or the time to relapse since the last mood

episode) in patients with bipolar disorder I and II who have been treated with at least one atypical antipsychotic medicine for the mood episode

- Description of administered treatments for the management of the acute phase of bipolar disorder [mood stabilizers (n,%), antidepressants (n,%), and antipsychotics (n,%)]
- Description of management of relapse episodes in patients previously receiving treatment during the maintenance phase
- Description of patient baseline sociodemographic and anthropometric characteristics
  - *Gender: male (n,%), female (n,%), male-to-female ratio (male:female)*
  - *Age (mean (+/-SD) yrs)*
  - *Race: white/caucasian (n,%), asian (n,%), black (n,%), other (n,%)*
  - *Education: no education (n,%), primary education (n,%), secondary education (n,%), trietary education (n,%)*
  - *Marital status: single (n,%), married (n,%), divorced (n,%), widowed (n,%)*
  - *Place of residence: urban areas (n,%), semi-urban areas (n,%), rural areas (n,%)*
  - *Employment status: unemployed (n,%), employed (n,%), retired (n,%)*
  - *Height (mean (+/-SD) cm)*
  - *Weight (mean (+/-SD) kg)*
- YMRS total score at baseline and final visit [mean (+/-SD)] and change in score between visits
- HAM-D total score at baseline at baseline and at final visit [mean (+/-SD)] and change in score between visits
- Information regarding bipolar disorder
  - *Age at onset of first mood symptoms [mean (+/-SD) yrs]*
  - *Polarity of first episode [manic (n,%), hypomanic (n,%), depressive (n,%), mixed (n,%)]*
  - *Age at diagnosis and at first treatment administered [mean (+/-SD) yrs]*
  - *Type of bipolar disorder (I or II) (n,%)*
  - *Presence of rapid cycling pattern (n,%)*
  - *Number and length of past hospitalizations (mean +/-SD)*
  - *Number of previous suicide attempts (mean +/-SD)*
  - *Duration (mean +/-SD) and type of last acute mood episode prior to enrolment [manic (n,%), hypomanic (n,%), depressive (n,%), mixed (n,%)]*
  - *Presence of psychotic features during the last mood episode (n,%)*
- Presence of family psychiatric history (n,%)
- Presence of other concomitant diseases (n,%)
- Smoking status: no smoker (n,%), occasional smoker (n,%), previous smoker (n,%), current smoker (n,%), if current smoker: pack-years)
- Alcohol consumption: no (n,%), low (n,%), moderate (n,%), high (n,%).

5. STATISTICAL METHODS

Descriptive statistical analysis has been applied to all study data. All categorical variables are expressed in counts (N) and percentages (%). Continuous variables are summarized with the use of descriptive statistical measures [mean value, standard deviation (SD), median, and extreme values].

The normality of distribution of continuous variables has been examined using the Kolmogorov Smirnov test (K-S test) in order to determine whether or not to use parametric methods for the analysis of the sample data.

For the primary endpoint analysis, the percentage of relapsers in the 'Per Protocol Set' has been calculated and a 95% CI has been estimated according to Clopper-Pearson method.

With regard to secondary endpoint analysis, descriptive statistics have been calculated for all related variables. Furthermore, for the evaluation of the duration of normothymia in patients with bipolar disorder, Kaplan-Meier survival analysis has been performed. Moreover, Wilcoxon Signed-Rank test has been applied in order to investigate potential differences in YMRS and HAM-D scores as well as in weight and BMI between baseline and Visit 3.

Chi-square test has been performed in order to test the association between the relapse occurrence and several categorical variables. Furthermore, t-test or U-Mann-Whitney test were applied in order to investigate any difference between the cohort of relapsers and the cohort of non-relapsers in continuous variables. Finally, in order to investigate potential prognostic factors of relapse occurrence, logistic regression analysis has been performed with baseline anthropometric and clinical characteristics set as independent variables.

All the aforementioned statistical tests were two-sided and performed at a 0.05 significance level. Missing data have not been replaced and data processing and analysis were performed as per the comprehensive study-specific statistical analysis plan (SAP), using the statistical package SPSS v. 20.0.

5.1 Population Analysis Sets

For the purposes of the statistical analysis two population analysis sets have been defined as per the detailed study specific Statistical Analysis Plan: i) the 'Full Analysis Set (FAS)' comprised of all enrolled patients who fulfilled the study specific eligibility criteria and ii) the 'Per Protocol Set (PPS)' which included all patients of the 'Full Analysis Set' who had also completed the study (i.e., performed visit 3 of the study or experienced a relapse episode during the study observational period).

In order to evaluate the primary study objective the 'Per Protocol Set' has been used whereas the analysis of the secondary objectives has been performed in the 'Full Analysis Set'.

5.1.1 Definition of the Target Population

FAS comprised of the total of 294 eligible subjects who were enrolled in the study whereas PPS finally included 293 patients who completed the study *(only 1 patient was excluded from PPS due to loss to follow-up)* [Table 1]. No protocol violations & deviations have been observed and no imputation of missing data has been applied.

Table 1 Overall Subject Disposition in the Study

Subject disposition	N	%
Total Number of Subjects Enrolled in the Study (FAS)	**294**	**100.0**
Number of subjects who completed Visit 2 (4 months after last acute mood episode)	291	99.0
Number of subjects who did not complete Visit 2	3	1.0
Due to relapse occurrence	*3*	*1.0*
Number of subjects who completed visit 3 (9 months after last acute mood episode)	293	99.7
Number of subjects who did not complete Visit 3	1	0.3
Due to loss to follow up	*1*	*0.3*
Total Number of Subjects included in the PPS	**293**	**99.7**

5.2 Statistical Analysis Results

5.2.1 Descriptive Analysis

5.2.1.1 Subject Sociodemographic and Baseline Characteristics

Table 2 Baseline Sociodemographic and Anthropometric Characteristics

Socio-demographic and Anthropometric characteristics (FAS=294)						
	N	**Mean**	**SD**	**Median**	**Min**	**Max**
Age (years)	294	41.5	10.6	41.4	20.0	64.8
Weight (kg)	294	78.3	15.0	76.0	45.0	143.0
Height (cm)	293	170.1	8.2	170.0	149.0	194.0
BMI (kg/m^2)	293	27.0	4.5	26.2	17.8	52.1
Gender			**N**		**%**	
Male			120		40.8	
Female			174		59.2	
Race			**N**		**%**	
Caucasian			291		99.0	
Black			1		0.3	
Other (Latin, Mexican)			2		0.7	
Marital Status			**N**		**%**	
Single			136		46.3	
Married			119		40.5	
Divorced			33		11.2	
Widowed			6		2.0	
Educational Background			**N**		**%**	

Socio-demographic and Anthropometric characteristics (FAS=294)		
Primary	32	10.9
Secondary	166	56.5
Higher	96	32.7
Occupation	**N**	**%**
Employed	145	49.3
Private sector employee	*70*	*23.8*
Public sector employee	*48*	*16.3*
Freelancer	*27*	*9.2*
Unemployed	109	37.1
Retired	34	11.6
Student	6	2.0
Place of Residence	**N**	**%**
Urban	218	74.1
Semi-Urban	54	18.4
Rural	22	7.5

Table 3 Baseline Smoking Status and Alcohol Consumption

Smoking Status and Alcohol Consumption (FAS=294)		
Smoking Status	**N**	**%**
Smokers	151	51.4
Non-Smokers	96	32.7
Occasional Smokers	28	9.5
Ex-Smokers	19	6.5
Duration of smoking cessation > 1 year	*15*	*5.1*
Duration of smoking cessation < 1 year	*4*	*1.4*
Alcohol Consumption	**N**	**%**
None	179	60.9
Low (< 1 glass/ day)	94	32.0
Moderate (1-2 glasses/ day)	17	5.8
High (≥ 3 glasses/ day)	4	1.4

5.2.1.2 Subject Medical History and Concomitant Medications

Table 4 Patient Medical History

Patients' Medical History Except of Bipolar Disorder (FAS=294)	N	%			
Patient with no concomitant medical conditions	**235**	**79.9**			
Patients with at least one concomitant medical condition	**59**	**20.1**			
Disease	**N**	**%**	**Disease**	**N**	**%**
Endocrine Disorders	**24**	**8.2**	**Vascular Disease**	**5**	**1.7**
Present	19	6.5	*Present*	4	1.4
Past	5	1.7	*Past*	1	0.3
Cardiovascular Disease	**15**	**5.1**	**Reproductive System & Breast Disorders**	**4**	**1.4**
Present	14	4.8	*Present*	3	1.0
Past	1	0.3	*Past*	1	0.3
Gastrointestinal Disorders	**13**	**4.4**	**Blood & Lymphatic System Disorders**	**3**	**1.0**
Present	6	2.0	*Present*	3	1.0
Past	7	2.4	*Past*	-	-
Metabolism & Nutrition Disorders	**12**	**4.1**	**Nervous System Disorders**	**2**	**0.7**
Present	12	4.1	*Present*	2	0.7
Past	-	-	*Past*	-	-
Hepatobiliary Disorders	**7**	**2.4**	**Neoplasms Benign, Malignant & Unspecified**	**2**	**0.7**
Present	5	1.7	*Present*	-	-
Past	2	0.7	*Past*	2	0.7
Eye Disorders	**7**	**2.4**	**Skin & Subcutaneous Tissue Disorders**	**1**	**0.3**
Present	7	2.4	*Present*	1	0.3
Past	-	-	*Past*	-	-
Respiratory, Thoracic & Mediastinal Disorders	**7**	**2.4**	**Renal & Urinary Disorders**	**-**	**-**
Present	5	1.7	*Present*	-	-
Past	2	0.7	*Past*	-	-

Subject Family History of Psychiatric Conditions

Table 5 Patients' Family Psychiatric History

Patients' Family Psychiatric History (FAS=294)				**N**	**%**
Patients with no Family Psychiatric History				**205**	**69.7**
Patients with Positive Family Psychiatric History				**89**	**30.3**
Patients with at least one 1st degree relative with psychiatric history *(parents, children)*				**67**	**22.8**
Family Psychiatric Disease PT*	**N**	**%**	**Family Psychiatric Disease PT**	**N**	**%**
Depression/Major depression	29	9.9	Alcoholism/Alcoholic psychosis	6	2.0
Bipolar disorder	20	6.8	Affective disorder	2	0.7
Psychotic disorder/Schizophrenia/ Schizoaffective disorder	10	3.4	Drug dependence	1	0.3
Anxiety disorder	7	2.4	Abnormal behaviour	1	0.3
Patients with at least one 2nd degree relative with psychiatric history *(siblings, grandparents)*				**30**	**10.2**
Family Psychiatric Disease PT	**N**	**%**	**Family Psychiatric Disease PT**	**N**	**%**
Psychotic disorder/Schizophrenia/ Schizoaffective disorder	15	5.1	Alcoholic psychosis	1	0.3
Bipolar disorder	7	2.4	Conversion disorder	1	0.3
Depression/Major depression	4	1.4	Dementia	1	0.3
Generalised anxiety disorder	1	0.3	Not Specified	1	0.3
Paranoid personality disorder	1	0.3			
Patients with at least one 3rd degree relative with psychiatric history *(aunts, uncles)*				**6**	**2.0**
Family Psychiatric Disease PT				**N**	**%**
Major depression				4	1.4
Bipolar disorder				2	0.7

*PT: Preferred Term by MedDRA

5.2.1.3 Bipolar Disorder History

Table 6 Bipolar Disorder History

Bipolar Disorder History (FAS=294)						
	N	**Mean**	**SD**	**Median**	**Min**	**Max**
Age at Onset of 1st Mood Symptoms (years)	293	27.8	7.7	26.0	12.0	62.0
Age at Diagnosis (years)	294	29.6	8.1	28.0	15.0	62.0
Delay between Onset of Symptoms & Diagnosis (years)	293	1.7	3.5	0.0	-15.0	20.0
Total Number of Previous Depression Episodes	289	4.6	5.1	3.0	0.0	60.0
Total Number of Previous Manic/Hypomanic Episodes	290	4.2	5.6	3.0	0.0	70.0
Total Number of Previous Mixed Episodes	285	1.1	2.7	0.0	0.0	20.0
Polarity of 1st episode			**N**		**%**	
Manic			148		50.3	
Depressive			108		36.7	
Hypomanic			24		8.2	
Mixed			14		4.8	
Type of Bipolar Disorder			**N**		**%**	
Type I			195		66.3	
Type II			99		33.7	
Presence of Rapid Cycling Pattern			**N**		**%**	
Yes			26		8.8	
No			268		91.2	
Past Hospitalization due to Bipolar Disorder			**N**		**%**	
Yes			163		55.4	
No of patients with 1 hospitalization in the past			*67*		*22.8*	
No of patients with 2 hospitalizations in the past			*47*		*16.0*	
No of patients with 3 hospitalizations in the past			*29*		*9.9*	
No of patients with ≥4 hospitalizations in the past			*20*		*6.8*	
Number of Past Hospitalizations [mean ± SD; median (range)]			2.3 ± 2.2		2.0 (1.0-16)	
Mean Length of Past Hospitalizations [mean ± SD; median (range)]			30.0 ± 16.2		30.0 (3.0-100.0)	
No			131		44.6	
Suicide Attempt			**N**		**%**	
Yes			42		14.3	
No of patients with 1 suicide attempt in the past			*30*		*10.2*	
No of patients with 2 suicide attempts in the past			*8*		*2.7*	
No of patients with 3 suicide attempts in the past			*4*		*1.4*	
No			252		85.7	

5.2.1.4 Baseline YMRS and HAM-D Scores

Young Mania Rating Scale (YMRS), an eleven-item, multiple-choice diagnostic questionnaire, was used to measure the severity of manic episodes in study participants. The clinicians rated the severity of the symptoms from 0 (no symptoms/normal behaviour) to 4 (extreme deviation) based on the subjective information provided by the patient about the last 48 hours and the clinical observation of behaviour during the interview.

The mean YMRS total score at baseline among the study population was 5.9 ± 3.7.

On the other hand, HAM-D scale was used to assess the severity of depression in patients. The version used in this study contained 23 items, whereas only the first 17 questions (items) have been included in the calculation of the total score. Items were scored from 0 to 4 or from 0 to 2, whereas higher scores indicated more severe depression.

The mean total HAM-D17 score at baseline was 5.6 ± 3.3.

Primary Objective

5.2.1.5 Relapse Rate During the 9-month Follow-up Period

Overall, 4.4% (95% Confidence Interval 2.4-7.5) of the study participants experienced a relapse episode during the 9-month follow-up period after the index mood event.

Among relapsers, 53.8% (7/13) experienced a depressive relapse episode whereas for the rest 46.8% (6/13) the relapse episode was either manic, hypomanic or mixed [Table 7].

Table 7 Relapse Rate During the 9-month Period After the Index Episode

Relapse Rate (PPS= 293)	**N**	**%**
Patients with no Relapse	**280**	**95.6**
Patients who Experienced a Relapse Episode	**13**	**4.4**
Polarity of Relapse Episode	**N**	**%**
Depressive	*7*	*2.4*
Hypomanic	*4*	*1.4*
Manic	*1*	*0.3*
Mixed	*1*	*0.3*

5.2.2 Secondary Objectives

5.2.2.1 Treatment of the Index Episode During the Acute Phase

With regard to the management of the index mood episode during the acute phase, all patients were treated with atypical antipsychotics *(Quetiapine 58.2%; Olanzapine 20.4%; Risperidone 11.6%; Aripiprazole 9.5%; Amisulpride 4.8%; Ziprasidone 1.7% and Paliperidone 1.7%)* as predicted by the protocol, whereas mood stabilizers were also co-administered in 55.4% of patients, antidepressants in 37.1%, anxiolytics in 21.1% and typical antipsychotics in 11.9% of the patients respectively [Table 8].

Table 8 Treatment of the Last Acute Mood Episode

Treatment of the Last Acute Mood Episode (FAS=294)	$N_{patients}$	%
Antipsychotics	**294**	**100.0**
Atypical Antipsychotics	**294**	**100.0**
Quetiapine	171	58.2
Olanzapine	60	20.4
Risperidone	34	11.6
Aripiprazole	28	9.5
Amisulpride	14	4.8
Ziprasidone	5	1.7
Paliperidone	5	1.7
Typical Antipsychotics	**35**	**11.9**
Haloperidol	27	9.2
Zuclopenthixol	5	1.7
Chlorpromazine	2	0.7
Levomepromazine	2	0.7
Sulpiride	1	0.3
Mood Stabilizers	**163**	**55.4**
Valproic Acid	62	21.1
Lithium	42	14.3
Carbamazepine & Oxcabarzepine	30	10.2
Lamotrigine	25	8.5
Topiramate	16	5.4
Other *(Clonazepam, Pregabalin, Gabapentin)*	12	4.1
Antidepressants	**109**	**37.1**
SSRIs (*Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline*)	53	18.0
SNRIs (*Duloxetine, Venlafaxine*)	48	16.3
Other *(Agomelatine, Buproprion, Mirtazapine)*	16	5.4
TCAs (*Amitriptyline, Clomipramine, Imipramin*)	5	1.7
Anxiolytics	**62**	**21.1**
Lorazepam	26	8.8
Alprazolam	16	5.4
Diazepam	10	3.4
Other (*Bromazepam, Clobazam, Potassium Clorazepate, Prazepam, Hydroxyzine*)	10	3.4
Other	**18**	**6.1**
Anticholinergic Agents (*Biperiden*)	11	3.7
Psycholeptics & Psychoanaleptics in Combination (*Amitriptyline & Psychoepileptics*)	3	1.0
Hypnotics and Sedatives (*Zolpidem*)	2	0.7
Psychostimulants, Agents used for ADHD Nootropics Combination (*Modafinil*)	1	0.3
Dopaminergic Agents (*Levodopa & Decarboxylase Inhibitor*)	1	0.3

5.2.2.2 Duration of Normothymia after the Index Episode

The mean duration of normothymic period *(defined as the period that the patient remained in normothymic state or the time to relapse since the last mood episode)* for all study participants was 8.3 ± 1.0 months, while the respective period for relapsers was 5 ± 1.8 months [Table 9].

Based on Kaplan Meier analysis performed, the estimated mean duration of normothymia state for all study population is 10 months [95% CI (9.9-10.2)] [Table 9].

Table 9 Duration of Normothymia after the Index Episode

Duration of Normothymia (PPS= 293)						
	N	**Mean**	**SD**	**Median**	**Min**	**Max**
Duration of Normothymia for all patients (months)	293	8.3	1.0	8.3	2.7	10.3
Duration of Normothymia for relapsers (months)	13	5.0	1.8	5.0	2.7	7.9
Estimation of Normothymia duration (months) by Kaplan Meier	**N**	**Mean**	**St. Error**	**95%CI**		
	293	10.0	0.1	9.9	10.2	

5.2.2.3 Management of Relapse Episodes

With regard to the treatment of the relapse episode, almost all patients (92.3%) apart from one *(who was treated with combination of mood stabilizer and antidepressant)* were administered atypical antipsychotics, whereas antidepressants were administered in 69.2%, mood stabilisers in 53.8%, typical antipsychotics in 15.4%, anxiolytics in 15.4% and other (anticholinergic and hypnotic/sedative) in 7.7% of patients respectively [Table 20].

Furthermore, all patients who relapsed were administered combination psychotropic therapy for the management of the episode; 61.5% were treated with combination of 2 different classes of psychotropic agents, 30.8% with combination of 3 different classes and 7.7% with combination of 5 different classes [Table 10].

Table 10 1 Treatment of Relapse Episode

Treatment of Relapse Episode (n=13)	$N_{patients}$	%
Antipsychotics	**12**	**92.3**
Atypical Antipsychotics	**12**	**92.3**
Quetiapine	8	61.5
Risperidone	4	30.8
Olanzapine	3	23.1
Aripiprazole	1	7.7
Ziprasidone	1	7.7
Typical Antipsychotics	**2**	**15.4**
Haloperidol	2	15.4
Antidepressants	**9**	**69.2**
SSRIs (*Citalopram, Fluoxetine, Paroxetine, Sertraline*)	4	30.8
SNRIs (*Duloxetine, Venlafaxine*)	4	30.8
Other *(Buproprion, Mirtazapine)*	3	23.1
Mood Stabilizers	**7**	**53.8**
Other *(Topiramate, Pregabalin, Gabapentin)*	4	30.8
Lithium	1	7.7
Valproic Acid	1	7.7
Lamotrigine	1	7.7
Carbamazepine	1	7.7
Anxiolytics	**2**	**15.4**
Lorazepam	2	15.4
Other	**1**	**7.7**
Anticholinergic Agents (*Biperiden*)	1	7.7
Hypnotics and Sedatives (*Zolpidem)*	1	7.7

Table 11 Treatment of Relapse Episode per Psychotropic Drug Category

Treatment of the Last Acute Mood Episode (n=13)	$N_{patients}$	%
Combination of 2 different classes of psychotropic agents	**8**	**61.5**
Atypical Antipsychotic & Antidepressant	4	30.8
Atypical Antipsychotic & Mood Stabilizer	2	15.4
Mood Stabilizer & Antidepressant	1	7.7
Atypical Antipsychotic & Anxiolytic	1	7.7
Combination of 3 different classes of psychotropic agents	**4**	**30.8**
Atypical Antipsychotic & Mood Stabilizer & Antidepressant	2	15.4
Atypical Antipsychotic & Mood Stabilizer & Typical Antipsychotic	1	7.7
Atypical Antipsychotic & Anxiolytic & Antidepressant	1	7.7
Combination of 5 different classes of psychotropic agents	**1**	**7.7**
Atypical Antipsychotic & Typical Antipsychotic & Antidepressant & Anticholinergic Agent & Hypnotic and Sedative	1	7.7

5.2.2.4 YMRS and HAM-D Scores at 9 Months after the Index Episode and Change from Baseline

The mean YMRS total score at 9 months after the index episode among the study population was 4.3 ± 4.2

The mean HAM-D17 total score at 9 months after the index episode was 4.2 ± 3.4.

The mean YMRS score change from baseline to 9 months after the acute index episode for all study participants was -1.5 (±3.8) points which was statistically significant ($p<0.001$). It is worth mentioning that YMRS score was significantly reduced from baseline only for the subgroups of patients on maintenance treatment containing quetiapine (-1.7±3.4; $p<0.001$), olanzapine (-1.2±5.6; $p<0.001$), aripiprazole (-1.9±2.9; $p=0.017$), and more than one atypical antipsychotics (-2.7±3.3; $p=0.008$) [Table 12].

Table 12 Change in YMRS Score from Baseline to 4 and 9 Months

Change in YMRS Score		N	Mean	SD	Median	Min	Max	p-value**
All participants irrespective of maintenance treatment patterns								
All Participants	**YMRS Total Score at Visit 1**	294	5.9	3.7	6.0	0.0	12.0	**<0.001***
	YMRS Total Score at Visit 3	293	4.3	4.2	4.0	0.0	43.0	
	Change from Baseline	293	-1.5	3.8	-1.0	-12.0	31.0	

*Statistically Significant, **Wilcoxon Signed Ranks Test

Additionally, HAM-D score was significantly reduced for all study population by -1.4 (±3.2) points from baseline. In particular, the mean reduction in score from baseline to 9 months after the index

episode reached statistical significance only for the subgroups of patients on maintenance treatment containing quetiapine (-1.9±2.7; p<0.001), olanzapine (-0.5±4.4; p=0.039) and amisulpride (-2.7±1.8; p=0.011) [Table 13].

Table 13 Change in HAM-D17 Score from Baseline to 4 and 9 Months

Change in HAM-D17 Score		N	Mean	SD	Median	Min	Max	p-value**
All participants irrespective of maintenance treatment								
All Participants	**HAM-D Total Score at Visit 1**	294	5.6	3.3	6.0	0.0	12.0	**<0.001***
	HAM-D Total Score at Visit 3	293	4.2	3.4	4.0	0.0	20.0	
	Change from Baseline	293	-1.4	3.2	-1.0	-11.0	16.0	

*Statistically Significant, **Wilcoxon Signed Ranks Test

6. SAFETY

NA

7. ETHICS

7.1Ethical conduct of the study

The study has been conducted after the obtainment of the required approvals by the competent IRBs (Scientific Committee/Administrative Council) of the participating coordinating Hospital Sites and the National Organization for Medicines (EOF), and in accordance with the ethical principles that have their origin in the Declaration of Helsinki (ICH-GCP guidelines), all applicable national and E.U. laws and regulations, and AstraZeneca policy on Bioethics.

7.2Subject information and consent

Prior to the conduct of any study-related procedure, investigators ensured that each potential participating patient was provided accurate and adequate oral and written information about the nature, purpose, possible risks and benefits of the present study. Each patient's signed informed consent form (ICF) was obtained in duplicate before his/her enrolment into the study. The original signed and dated ICF was maintained by the investigator at the study file while a copy of the signed ICF was given to the patient.

8. DATE OF THE REPORT SYNOPSIS

03 September 2012