STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT:
ACTIVE INGREDIENT:

Study No: NIS-NFR-XXX-2012/1
Evaluation of subsyndromal symptoms following a stabilized depressive episode in bipolar patients (POLARIS)

Developmental Phase: NA

Study Completion Date: December 2013

Date of Report: Statistical report only: December 2014

OBJECTIVES:

Primary Objective

- To evaluate the prevalence of subsyndromal symptoms after a stabilized depressive episode in BD patients in France, as measured by scoring on YMRS and MADRS scales and the MVAS-BP self-administered questionnaire.

Secondary objectives

- To evaluate the functional impact in subsyndromal symptoms using the FAST scale.

- To assess factors associated with symptomatic and functioning remission in bipolar patients followed up after a stabilized depressive episode.

- To describe daily management patterns associated with the presence and absence of subsyndromal symptoms after a stabilized bipolar depressive episode.

METHODS:

This is a national, longitudinal, 1-year prospective, cohort study conducted in the psychiatric setting (hospital and private practice).

Type of Study

Approximately 100 investigators had to include patients until the total sample size of 600 patients, i.e. approx. 6 patients per investigator

To build the cohort, the inclusion of patients in the study was done in a sequential manner at each site: the first 6 patients seen in the usual consultation context and fulfilling the inclusion/exclusion criteria.

All study scales has been recorded at baseline visit and also at each of the next follow-up visit according to real-life practice: 3 months after baseline (+/- 1 month), 6 months after baseline (+/- 1 month) and 12 months after baseline (+/- 1 month). Regarding Multiple Visual Analogue Scales for Bipolarity (MVAS-BP), a self-administered validated bipolar symptoms assessment scale, it has been recorded on a weekly basis through a validated on-line patient diary. This would allow the study to detect fluctuation on the frequency of appearance. A procedure to limit missing data (paper version for holidays, recall email then call by a third party) was planned.

Rationale for sample size (number of subjects and sites)

Number of patients: the number of patients is based on the precision of the estimates to be made as a function of BD type. The precise percentage of patients presenting sub-syndromal symptoms, the subject of this study, is not known. Calculations were therefore conducted for frequencies from 50 to 85% with a precision of between 5 and 7%.

The formula for calculation of the precision of a percentage yields the following minimum populations:

n	Observed event frequency							
Precision	85%	80%	75%	70%	65%	60%	55%	50%
5%	196	246	288	323	350	369	380	384
6%	136	171	200	224	243	256	264	267
7%	100	125	147	165	178	188	194	196

With an α error of 5%, 196 evaluable cases are necessary in order to measure, in the smallest analysis stratum (40% of patients) an event frequency of 50% with a sampling precision of +/- 7%. The population will be sufficient to measure, at the other extreme, an event frequency of 85% with a sampling precision of +/- 5%. Under these working hypotheses, a total of 490 evaluable cases of all types of BD are necessary. In order to take into account incomplete or non-evaluable cases, a sample of **600 patients** (a mean of 6 patients for each investigating physician over 9 months of recruitment) is required.

Criteria for selection of investigators

Random sampling of French psychiatrists practicing at secondary care (available in CEGEDIM) was performed. Different strata were taken into account considering psychiatrists status (hospital / psychiatric centers / private practice).

During selection of psychiatrists, regular controls were performed in order to reach national representative sample of participants in terms of geographical and male/female distribution.

Selected psychiatrists (a total of 100 estimated) received a letter describing the study together with a reply coupon allowing them to express their agreement or disagreement to participate in the study.

A reminder letter was sent to psychiatrists not returning the reply coupon, and they were then contacted by telephone to ask them whether or not they wish to participate in the study. When the psychiatrist refused to participate, the following psychiatrist on the random list was contacted until the required number of centres was obtained.

Study specific inclusion/exclusion criteria and rationale

Inclusion Criteria	**Rationale**
1. Patient aged 18 years or older	
2. Diagnosis of bipolar disorder according to DSM-IV criteria currently followed up by the investigator in hospital or open-care practice and informed of his/her disease	The most frequent psychiatric diagnostic criteria in real-life
3. Previous episode was a bipolar depression assessed clinically stabilized for at least 4 weeks by the investigator	
4. Patient able to complete the self-assessment diary weekly	To address secondary objectives

Exclusion Criteria	**Rationale**
1. Pregnant women	To avoid patients out of the scope of daily clinical practice
2. Patient included in a clinical trial on an investigational drug or having received an investigational drug in the preceding 30 days	To avoid patients out of the scope of daily clinical practice
3. Person deprived of freedom or subject to a guardianship (or ward) order.	
4. Unable to undergo medical monitoring for geographical, social or psychological reasons	

RESULTS:

The planned analysis could not be performed due to premature end of the study: inclusion rate was too low. After 9 months, only 126 patients were included instead of 600. Following this, descriptive statistic has been performed.

A total of 126 patients were included in the study by 29 investigators. Follow-up was available for 93 patients at 3 months and for 53 patients at 6 months, due to the premature stop of the study. All the patients fulfilled the inclusion / exclusion criteria except one patient who was 15 years old. Demographics and baseline characteristics are shown in the table 1.

Table 1. Demographics and baseline characteristics

Characteristics	Included patients (N = 126)
Sex, n (%), male (n=124)	37 (29.8)
Age, mean (SD), years (n=124)	45.3 (11.2)
BMI, mean (SD), kg/m² (n=122)	26.2 (5.5)
Bipolar disorder, n (%), (n=124)	
• Type I	71 (57.3)
• Type II	51 (41.1)
• Other	2 (1.6)
Disease dominant polarity, n (%), (n=68)	
• Depressive type	53 (77.9)
• Manic type	15 (22.1)
Duration of disease, years, (n=111)	
• mean (SD)	6.54 (6.99)
• median	3.8
Duration of untreated period, years, (n=108)	
• mean (SD)	9.25 (8.70)
• median	6.5

Concerning the disease management, at inclusion, 96.0% of patients received a pharmacological treatment (table 2), 28.2% had psychoeducation, 15.3% had cognitive reeducation and 65.3% followed psychotherapy.

Table 2. Pharmacological treatment

	Total (N = 119)
Unknown	1
Antidepressants	80 (67.8%)
Other mood stabilizers	58 (49.2%)
Anxiolytics, Sedative-Hypnotics	52 (44.1%)
Atypical Antipsychotics	50 (42.4%)
Typical Antipsychotics	15 (12.7%)
Lithium	12 (10.2%)
Antiparkinsonian agents	3 (2.5%)
Thyroid treatment	3 (2.5%)
ECT	1 (0.8%)
Other	2 (1.7%)

NB: each patient could received more than one treatment

Primary and secondary objectives of the study couldn't be analysed. Descriptive score analysis for the different scales has been performed (table 3 to 5).

Table 3. MADRS scale

MADRS score	Inclusion (N=126)	3 months (N=93)	6 months (N=53)
n	123	93	53
Mean ± SD	12.3 ± 10.4	11.5 ± 10.2	13.0 ± 10.4
Median	12	8	10
Range	0 - 42	0 - 46	0 - 38

Table 4. YMRS scale

YMRS score	Inclusion (N=126)	3 months (N=93)	6 months (N=53)
n	123	93	53
Mean ± SD	4.2 ± 5.0	4.7 ± 5.3	5.5 ± 6.2
Median	2	3	3
Range	0 - 22	0 - 28	0 - 24

Table 5. Hamilton anxiety scale

Hamilton score	Inclusion (N=126)	3 months (N=93)	6 months (N=53)
n	123	93	53
Mean ± SD	10.0 ± 9.2	9.3 ± 10.0	10.6 ± 9.9
Median	8	6	8
Range	0 - 41	0 - 47	0 - 39

Table 6. FAST scale

FAST score	Inclusion (N=126)	3 months (N=93)	6 months (N=53)
n	123	93	53
Mean ± SD	18.8 ± 15.1	18.2 ± 16.0	18.6 ± 15.7
Median	14	16	16
Range	0 - 63	0 - 61	0 - 52